PERCEPTION OF PROGNOSTIC RISK IN MULTIPLE SCLEROSIS

Cecile Janssens

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Voor mijn ouders
Ter nagedachtenis aan mijn moeder

CONTENTS

Publications/manuscripts based on the studies described in this thesis

ACJW Janssens, W Reedeker, JB de Boer, NF Kalkers, J Passchier, PA van Doorn, RQ Hintzen. Patients with multiple sclerosis prefer early diagnosis. *Submitted*.

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ACJW Janssens, PA van Doorn, JB de Boer, NF Kalkers, FGA van der Meché, J Passchier, RQ Hintzen. Anxiety and depression influence the relation between disability status and quality of life in multiple sclerosis. *Mult Scler. In press.*

ACJW Janssens, JB de Boer, PA van Doorn, HM van der Ploeg, FGA van der Meché, J Passchier, RQ Hintzen. Expectations of wheelchair dependence in recently diagnosed patients with multiple sclerosis and their partners. *Eur J Neurol. In press.*

ACJW Janssens, PA van Doorn, JB de Boer, FGA van der Meché, J Passchier, RQ Hintzen. Perception of prognostic risk in patients with multiple sclerosis: the relationship with anxiety, depression and disease-related distress. *J Clin Epidemiol. In press.*

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ACJW Janssens, JB de Boer, PA van Doorn, HM van der Ploeg, FGA van der Meché, RQ Hintzen, J Passchier. Individual differences in perception of prognostic risk: the role of neuroticism and pessimism. *Submitted*.

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ACJW Janssens, PA van Doorn, JB de Boer, D Buljevac, FGA van der Meché, J Passchier, RQ Hintzen. The association between perception of prognostic risk and anxiety, depression and distress in recently diagnosed multiple sclerosis: a 2-year follow-up study. *Prepared for submission.*

1

INTRODUCTION

"A diagnosis of MS can create havoc and confusion in many aspects of your life. It is normal to experience a roller coaster of emotions including fear, shock, frustration, sadness, anger, and the feeling that "this isn't happening to me". Perhaps diagnosis brings relief - finally there is an explanation for the symptoms you've been experiencing. The diagnosis of MS is unsettling for both you and your family. You may feel isolated from family and close friends, despite their good intentions to support you. Your family will also struggle with coming to terms with the diagnosis. Naturally, you are all concerned about the future and the impact that MS will have on your lives. It is important to know that you can successfully move through these difficult emotions, adjust to the changes and resume the pursuit of your goals."

Multiple Sclerosis Society of Australia @ www.multiple-wa.asn.au

Multiple sclerosis (MS) is a chronic neurological disease, affecting young individuals in the prime of their lives. The quote above illustrates the far-reaching impact of the disease on the lives of patients and their families. It shows that in the early phase, the burden of MS is characterized not by physical limitations but rather by psychological distress. Since the course of MS is highly variable and unpredictable,[1-3] the uncertainty about the disease progression is a key problem for patients and their families. In the absence of clinical information about the course of disease, personal expectations about disease progression, or, perception of prognostic risks, will play a major role in the psychological well-being. Despite

the vast literature on the psychological burden of MS, we know nothing about perceptions of prognostic risk of patients and their relatives.

This thesis is motivated by our lack of knowledge of perceptions of prognostic risk in MS patients and by the view that these perceptions may be potentially modifiable determinants of psychological well-being. The three main questions targeted are: (1) How do patients and their partners perceive prognostic risks? (2) How do these perceptions relate to psychological well-being? (3) What are the determinants of perception of prognostic risks? These questions are addressed from a quantitative angle in cross-sectional and longitudinal studies in patients recently diagnosed with MS. To come to a better understanding of how patients come to their perceptions, also a qualitative study in which patients explained their perception of risk and seriousness was included. In this chapter, the current status of our knowledge of MS and its psychosocial consequences is reviewed.

Clinical aspects of multiple sclerosis

Pathology and epidemiology

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS). The disease is characterized by inflammations of the myelin sheath – the insulation of the nerves. These inflammations disrupt transmission of neural information and thereby cause loss of bodily functions. Inflammations come and go, but they can leave damaged nerves, neurons and axons. This damage is considered important in the development of irreversible disability.[5] The pathogenesis of MS is unknown, but there is strong evidence that the disease is caused by the interaction of multiple genes and environmental factors.[5]

The prevalence of MS in Western countries is estimated to be about 1 in 1000,[8] with an incidence of 2-6 per 100.000 person years.[10] For the Netherlands, this means that approximately 16.000 people suffer from MS and about 600 are newly diagnosed with the disease each year. MS generally affects young adults between 20 and 40 years of age[12] and is more frequent among women than men.[10]

Clinical features and diagnosis

MS is characterized by a wide variety of symptoms, including fatigue, sensory disturbances, optic neuritis, diplopia, limb weakness, cognitive impairment, spasticity, sexual dysfunction, clumsiness, bladder and bowel problems.[10] The severity of these symptoms ranges from mild to severely disabling.

The diagnosis of MS is primarily based on clinical and paraclinical evidence of typical CNS lesions disseminated in time and place.[12,16,17] This evidence is

formulated in a set of diagnostic criteria – known as the Poser criteria[16] – that have been the gold standard for almost two decades. Based on these criteria patients with definite and probable MS can be distinguished. The advances in MRI diagnostics and CSF technology and the emerging possibilities of early treatment have recently induced an update of the Poser criteria, known as the McDonald criteria.[20] Through the extensive use of MRI as a diagnostic tool these new criteria allow for a definite diagnosis of MS within only a few months after the first presentation of suspected symptoms. This may be particular of benefit to those patients and neurologists who would opt for treatment in the earliest phase of the disease. First findings on the clinical application of these criteria have been promising.[21]

Despite the higher accuracy of diagnosis, the benefits of the new McDonald criteria are still subject to discussion. Argument against the use of these criteria is the higher risk of misdiagnosis due to the reliance on MRI findings that are not properly validated prospectively.[22] Further, in the new criteria there is a decreased role for clinical history and dissemination of lesions and events in time. This may lead to a diagnosis and treatment of patients with mild benign forms of MS who would not have developed further symptoms for years anyway.[17]

The present debate on the timing of diagnosis builds upon earlier discussions on whether to disclose the diagnosis at the presentation of first symptoms.[23-28] This debate is for a large part determined by the (lack of) clinical knowledge of the course of disease, the (lack of) possibilities of treatment in an early phase, and the anticipated burden for patients of knowing (or not knowing) the diagnosis. It is not known whether patients themselves would prefer an earlier diagnosis.

Clinical course and prognosis

The course of disease is diverse, ranging from a benign course with minimal disability to a rapid progressive course leading to significant disability or death within a relatively short time after disease onset.[1] The most frequent courses of symptoms are illustrated in Figure 1. In approximately 10-15% of the patients, the disease has a course that is progressive from onset (Figure 1a).[5] In the majority of patients (80-85%) the disease presents with a relapsing-remitting form (Figure 1b), in which the presence (relapse) and absence (remission) of signs and symptoms alternate.[5,10,29] A relapse of symptoms typically evolves over a couple of days, stabilizes and then often improves, spontaneously or in response to medication, within weeks. This recovery of function can be complete or partial, i.e., leaving some degree of symptoms. A next relapse may occur, within weeks, months or years. The relapsing-remitting course can develop into progressive clinical

disability, with or without superimposed relapses and remissions (Figure 1c).[1,2] Finally, when patients have a relapsing-remitting course with long phases of remission and have not reached a score of 3.0 on the Expanded Disability Status Scale (EDSS) in ten years, the course is referred to as benign (Figure 1d).[30] The distinction between the courses is not always clear: patients can gradually progress to more severe forms, but not vice versa. It is important to note that a reliable diagnosis of benign MS can only be made in retrospect, since also patients who initially met these criteria may develop more severe disability later in life.[30]

For individual MS patients prognosis is largely unpredictable. Prognostic studies have aimed to define risks of EDSS endpoints and to identify factors that predict a benign or progressive course of disease. Based on epidemiological data (Figure 2), it is estimated that within ten years after the onset of disease 30% of the patients will require aids to walk about 20-100 meters, as indicated by a score of 6.0 on the Disability Status Scale (DSS).[2] The lifetime risk of wheelchair dependence without being able to walk a few steps (DSS = 8.0) is about 50%.[2]

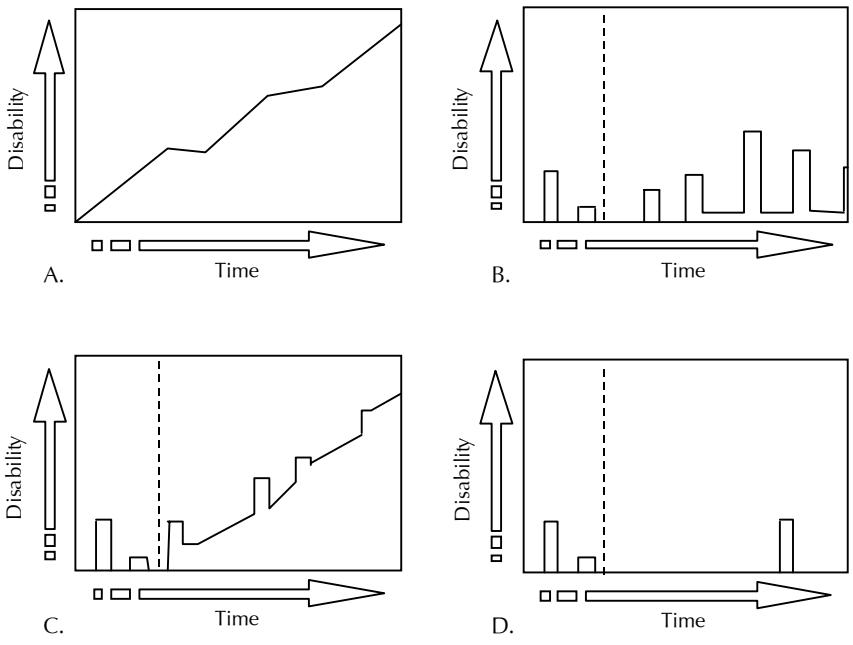

Figure 1 Possible courses of MS

A. Primary progressive MS; B. Relapsing-remitting MS; C. Secondary progressive MS, D. Benign MS (adapted from Lublin[1]). The dashed lines in Figure B-D demonstrate that the same disease history (two relapses – left to the line) can lead to a diverse course.

Factors that predict a more progressive course include a high relapse rate in the early years of disease, motor or cerebellar signs at onset, older age at onset, incomplete remission after first relapses, early disability, male sex, short interval between initial and second attack and high lesion load detected by early MRI of the brain.[31-34] Yet, the predictive value of these prognostic factors is limited.[30]

Treatment

At present, there is no therapy that can halt the accumulation of disability,[10] but several treatment strategies that have a favorable effect on the natural course of disease have been developed. The main options are corticosteroids for the treatment of acute exacerbations and immunomodulatory drugs for the long-term slowdown of disease progression.[29] Corticosteroids are often used to treat clinically significant relapses in order to speed up recovery, and prevent permanent damage of the nerves. At present there is no consensus about the optimal form, dose, route (oral or injection) or duration of corticosteroid therapy.[10] Immunomodulatory drugs, such as interferon β, aim to reduce the frequency and severity of relapses and to prevent or postpone the onset of the progressive phase of disease.[29]

The optimal treatment of patients after a first clinical episode of possible MS remains uncertain. Two recent trials indicate that early interferon treatment may

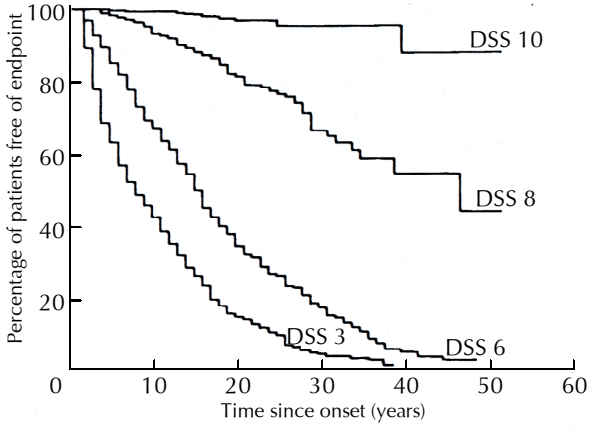

Figure 2 Actuarial analysis of disability from onset in a population of 1100 MS patients[2]

DSS = Disability Status Scale, which is the precursor of the Expanded Disability Status Scale (EDSS) used in this study. The EDSS distinguishes within one step of the DSS, e.g. EDSS scores of 6.0 and 6.5 are identical with a DSS value of 6.[3]

delay the development of a second relapse.[35,36] These findings may influence patients' and physicians' decisions towards an early start of interferon therapy. In contrast, the treatment-related side effects, inconvenience, costs, and lack of evidence of an important long-term benefit of interferon will deter others from treatment early in the disease course.[10,37] In addition, the optimal dose and duration of interferon treatment and the possible teratogenic effects on the developing fetus in pregnant patients are unknown.[38]

In summary, the clinical expression of MS is highly variable in type, duration, intensity and consequences of symptoms. The course of disease is unpredictable and, at present, insufficiently controllable by medication. The increasing functional limitations and the prognostic uncertainty may have a significant influence on psychological well-being and quality of life of patients and their families. These consequences are reviewed in the next section.

Psychological aspects of multiple sclerosis

Diagnostic and prognostic uncertainty

As a consequence of the unpredictable and uncontrollable course of MS, uncertainty is a predominant feature of MS with major effects on psychological well-being. Patients with MS merely have to wait and see what consequences will happen to them. Uncertainty has been rated the second most stressful aspect of MS by patients, following fatigue but preceding the inability to walk.[39]

For many patients the burden of uncertainty starts with a long period of vague unexplained symptoms before diagnosis. Symptoms are not always recognized as early signs of MS by patients themselves or by their general practitioners. For some patients, a prolonged diagnostic period may occur even when referred to a neurologist because they do not meet the criteria for definite MS at their initial visit and only learn about MS when a second or later episode occurs.[12,25] The burden of uncertainty in the phase prior to diagnosis has only been studied retrospectively in comparison to the uncertainty after diagnosis. To date, three studies have examined the impact of the diagnosis of MS on illness uncertainty in patients with MS.[40-42] In two studies, patients reported significantly lower uncertainty[40,41] and distress over physical symptoms after diagnosis than before,[40] whereas in another study the decrease in uncertainty, anxiety and worries was only moderate.[42] As expected, learning that the diagnosis was MS significantly reduced uncertainty about the diagnosis, but did not reduce uncertainty about the future course of disease.[41] Several studies in advanced phases of the disease demonstrated that increased feelings of uncertainty sustained after diagnosis.[43-45] In patients with

relapsing-remitting MS, exacerbations heightened patients' feelings of uncertainty which in turn increased their symptoms of depression.[44] Other studies have also demonstrated that perceived uncertainty was an important determinant of depression,[43,45] also after adjustment for disability status.[45]

Health-related quality of life

Health-related quality of life is a multi-dimensional concept that refers to the patients' evaluation of their physical, mental and social functioning. Many studies have demonstrated that patients with multiple sclerosis (MS) report poorer quality of life (QoL) than persons from the general population.[46-51] A major impact of the disease was found for both the physical health and mental health dimensions of QoL.[46-50] In patients with MS, QoL is for a large part determined by the presence of physical limitations. Higher disability status, as assessed by the EDSS is primarily associated with poorer QoL of physical health,[46-54] whereas only a few studies also reported a negative effect on mental health.[46-48] Other factors that have been found as determinants of poorer QoL in patients with MS include depression, anxiety and fatigue.[54-56]

Studies on QoL in MS have generally been conducted in patients who were ill for a long period: the average duration of illness of the studies conducted to date was longer than eight years.[46-54] QoL in advanced stages of MS may for a large part be determined by the progression of disease resulting in more disability. In contrast, in the early period after diagnosis most patients face relatively good health and their need for care and assistance in daily activities is limited. QoL of patients may then be more affected by the burden of the diagnosis, rather than the presence of physical symptoms. To date, no studies have addressed QoL of patients in the early phase of disease specifically. This is an important period from a psychological perspective as in this period patients will be coping with the diagnosis of MS.

Depression and anxiety

Depression is a common feature in MS.[57,58] Depression is more prevalent in MS patients than in healthy controls.[59-61] Although some studies reported a higher frequency of depression in patients with more physical limitations,[55,59,62] others failed to replicate this finding.[61,63,64] The origin of depression is not clear. Several studies have found that symptoms of depression were strongly correlated to MRI lesions.[59,62,65,66] These findings suggest that brain lesions play a causative role in the pathogenesis of depression. Arguing against this hypothesis is that others found no relation between MRI abnormalities and depression,[67] or found that depression

mainly resulted from feelings of uncertainty.[44] Also, one can argue that MRI lesions correlate to disability status, which may consequently influence the mood of patients. These findings suggest that to some extend depressive symptoms may also have a psychological origin.[58]

Patients with MS also demonstrate high levels of anxiety.[59,63,64,68] In contrast to depression, anxiety is thought to be of psychological origin – as a result of the accumulation of stressful events.[59,63] So far, studies of anxiety and depression have been conducted in patients with advanced stages of disease; the mean duration of disease in the aforementioned studies was longer than eight years.[59,62,64,68] The prevalence of anxiety and depression in earlier phases has not been studied. This early period may be crucial as high levels of anxiety and depression in patients may hamper the process of coping with the diagnosis. The success of coping may consequently determine whether psychosocial problems sustain.

Psychological burden for partners

Compared to other chronic diseases, the burden of MS for partners and caregivers is not extensively studied.[69] Only a few studies have addressed the consequences on quality of life and emotional well-being of partners.[56,70-72] These studies found that partners of patients with more physical limitations had higher levels of anxiety and depression, lower mood and poorer quality of life.[56,70,72] QoL of partners was poorer compared to persons from the general population.[56] Perceived illness uncertainty was associated with poorer emotional wel-being among partners.[72] In addition, partners also experienced considerable problems in social relationships and work.[70,71,73]

In summary, the uncontrollable and unpredictable nature of the disease implies that patients have little opportunity to anticipate or prevent future disease progression. The prognostic uncertainty plays a crucial role in psychological well-being of patients with MS and their partners. It is an important determinant of depression and anxiety and may consequently lower QoL. In the absence of unambiguous clinical information, patients' expectations about their future course of disease – whether realistic or not – may play a crucial role in their decisions about treatment, family planning, relationships, career and housing. Expectations can be regarded as a psychological strategy to reduce feelings of (prognostic) uncertainty[74] and may therefore influence psychological well-being. For example, patients who expect that their disease will progress within a short time may be more anxious and distressed than patients who expect that the severity of their condition will remain unchanged. In the next part, we will discuss relevant

literature on perception of prognostic risk, which is an alternative way to study expectations about particular prognostic outcomes.

Perception of prognostic risk

What is risk perception?

Risk is defined as the probability of an adverse event to happen within a certain period of time.[76] The subjective judgment of individuals about the height of the risk is referred to as perception of risk. Within the context of chronic diseases, examples of adverse events are disease progression, functional disability, handicap, side-effects of treatment, and mortality. It is obvious that the evaluation whether an event is adverse is highly subjective. For that reason, perception of seriousness of an outcome is often measured together with perception of risk. Perceived risk and seriousness of adverse health outcomes are considered important determinants of health-related behavior such as treatment uptake and compliance. For that reason, perception of the risk and seriousness have developed into key concepts in many health behavior theories.[77-79]

The first study of risk perception in a medical context dates from 1975 and reports about determinants of participation in a genetic screening program.[80] In that study, persons who considered themselves at higher risk of being a mutation carrier of Tay-Sachs disease (perceived susceptibility) and those who perceived the impact of learning about the carrier status as being low (perceived seriousness) were more likely to participate in the screening program. To date, risk perception has primarily been studied with regard to the risk of disease in healthy individuals, particularly among those at high risk of a specific disease. A large number of studies have addressed perception of disease risk in relation to behavior change and preventive strategies. Examples include the risk of HIV/AIDS in relation to safe sex, the risk of cardiovascular disease in relation to diet, exercise and smoking, the risk of cancer in relation to smoking, sun-bathing and screening for disease, and the risk of congenital anomalies (e.g. Down syndrome or spina bifida) in offspring in relation to prenatal testing.[81-86] Perception of these risks and in particular their impact on psychosocial well-being may essentially differ from so-called 'embodied' risks[87] that are not easily preventable, such as genetic and prognostic risks. To date, no studies have investigated the impact of perception of prognostic risk on psychological well-being. For that reason, the selection of determinants of perceived risk and psychological consequences in this study will mainly be based on previous research in the area of genetic (embodied) risks. In the remaining part of this chapter, we will review these and previous findings on expectations of future consequences in MS and other chronic disorders.

Studies on perception of genetic risk

Perception of genetic risk has been studied extensively in persons at high risk of hereditary diseases such as Huntington's disease, prostate cancer, breast cancer and ovarian cancer. These studies have focused on various topics including the accuracy of risk perception compared to actual risks, the impact of risk perception on psychological well-being and the determinants of perceived risk. With regard to the accuracy, it has been demonstrated that perception of risk is often inaccurate: high-risk individuals were found to overestimate[88-91] or underestimate[92-94] their risks of disease. High perception of risk was associated with increased worry, disease-related distress, anxiety and depression in some studies,[89,92,93,95-97] but not in others.[88,93,98] Studies on determinants of risk perception have demonstrated that higher perception or overestimation of risk was associated with higher actual risk,[92] higher number of affected relatives,[89,99] closer family relation to the patient with the hereditary disorder,[100] higher severity of illness of the affected relative,[101,102] younger age,[98,100-103] lower education,[102] and prior disease experience (e.g. biopsies or benign breast disease).[100] Findings on the importance of these determinants differed between studies: some did not find a significant association between risk perception and previous disease experience,[104] the number of affected first-degree relatives,[104] age[89] and education.[89,100,104]

When we translate these findings to perception of prognostic risk of patients with MS, we may expect that higher perception of risk may also have a significant impact on psychological well-being of patients. Also, we expect patients' beliefs about their illness and personality factors to influence perceptions of risk. Patients may have expectations about the course of disease that may not be evidently anticipated given their present health condition, i.e. they may over- or under-estimate their risks of complications.

Studies on perception of prognostic risk and expectations about prognosis

A major difference in the perception of genetic and prognostic risks is that prognostic risks are faced by individuals who may already experience symptoms of the disease. These symptoms may be interpreted as signs of favorable or unfavorable prognosis and are for that reason potentially important determinants of perception of risk of patients and partners. There has been limited research on perception of prognostic risk or expectations about prognosis.[4,6,7,9,11,13-15,18,19] Table 1 shows an overview of studies on expectations of specific health outcomes and general health status in patients with chronic diseases. The majority of these studies were conducted in relation to decisions about surgery or pharmacological treatment. These studies demonstrate that patients tend to overestimate their

Table 1 Overview of studies on expectations of prognosis in chronic diseases

Patient population	Expectations of	Major findings	Reference
Descriptive studies on expectations			
Cancer (during palliative radiotherapy)	Cure of disease and disease duration	Overestimation of the benefits of radiotherapy	Chow et al., 2001[4] Doyle et al., 2001[6]
TIA and stroke patients	Risk of stroke, risk of surgery and benefit of surgery	Overestimation of the risks and the benefits of surgery (carotid endarterectomy)	Lloyd et al., 2001[7]
Diabetes	Risk of blindness, end-state renal disease and lower-leg amputation	Overestimation of the prognostic risks and benefits of treatment effects	Meltzer et al., 2000[9]
Studies of expectations in relation to health outcomes			
Arthroplasty patients (before and after total hip revision)	Future pain and walking ability	Pre-operative unrealistic optimistic expectations contributed to greater post-operative dissatisfaction	Eisler et al., 2002[11]
Asthma	Future health status	*A priori* expectations of cure from asthma were associated with poorer QoL at follow-up.	Mancuso et al., 2001[13]
Epilepsy (before and after surgery)	Frequency of seizures	More realistic *a priori* expectations were related to higher satisfaction with post-operative functioning.	Wheelock et al., 1998[14]
HIV/AIDS	Risk of complications if treatment is not taken	Higher perceptions of risk were related to stronger treatment adherence.	Gao et al., 2000[15]
Multiple sclerosis	Risk of recurrent attacks and improvement in health status	Unrealistic optimistic expectations of improvement in health status were related to higher risk to discontinue therapy in 6 months	Mohr et al., 1996[18]
Rheumatoid arthritis	Health status within the next years	Pessimistic expectations were significantly correlated with poorer clinical and self-perceived health status, but not with neuroticism	Radanov et al, 1997[19]

prognostic risks,[7] and are too optimistic about the possibilities for treatment.[4,6,7] Furthermore, patients who had unrealistic *a priori* expectations were more likely to discontinue treatment [15,18] and had poorer QoL.[13] None of the previous studies addressed expectations about prognosis in partners of chronically ill patients.

Despite the high levels of uncertainty, patients' expectations about future disease status in MS have not been studied extensively. Only one previous study on expectations about prognosis has been conducted in MS. Mohr et al.

investigated patients' expectations about the effectiveness of treatment, and found that 57% of the patients who started interferon β treatment had unrealistic expectations about the risk of recurrent attacks and 34% about the improvement in health status.[18] Patients who had unrealistic positive expectations about the benefits of treatment were more likely to discontinue treatment within the first six months.[18] The only other study in MS that relates to expectations of future disease was conducted by Fournier et al. They demonstrated that MS patients who generally hold a positive outlook on life reported less symptoms of depression.[105] However, this study did not provide insight whether these patients also had favorable expectations about their prognosis.[105]

In summary, the studies on expectations about prognosis in chronic diseases conducted so far demonstrate that being too optimistic or too pessimistic may both negatively affect psychological well-being: being too optimistic may lead to later disappointment, whereas being too pessimistic may be accompanied by increased worry. To date, there are no studies that investigated what MS patients expect with regard to their future course of disease and how these expectations relate to psychological well-being.

Scope of this thesis

This study aims to get insight in the expectations of prognosis of patients recently diagnosed with MS and their partners. Of all possible consequences of MS, we focus on the risk of future wheelchair dependence. This prognostic outcome was selected for several reasons: (1) it is the best-known consequence of disease, so it is unlikely that patients will be confronted with new information; (2) it is a frequent consequence with a lifetime risk of wheelchair dependence of 70-80%;[2] (3) we expect that the majority of patients will consider this a serious consequence of their disease; (4) wheelchair dependence can be clearly defined following descriptions of wheelchair dependence of the EDSS; (5) by following these descriptions, perceptions of patients and partners can be compared with data from epidemiological studies that have used this scale as an outcome measure.

An overview of the study design, patient population and the instruments is presented in Chapter 2. In Chapter 3, as an indication of the burden of uncertainty before diagnosis, the preference with regard to the timing of diagnosis of patients is described and related to the duration of the diagnostic work-up. Chapter 4 presents the psychological well-being and quality of life of patients and their partners in the early phase after diagnosis. Where possible, these data are compared with that of general population controls. Next, Chapter 5 discusses the influence of anxiety and

depression on the relationship between disability status and quality of life. In Chapter 6, the expectations of risk and seriousness of future wheelchair dependence of patients and partners are described. Chapter 7 addresses the question whether perception of risk and seriousness of wheelchair dependence relate to higher levels of anxiety, depression and distress. In Chapter 8 to 10, the factors associated with perception of risk and seriousness are investigated. The role of illness beliefs and personality characteristics are described in Chapter 8 and 9, respectively. Chapter 10 reports on the results of the qualitative study in which patients explained their perception of risk and seriousness.

In the last part of the thesis, confirmation of the findings of the cross-sectional analyses on perception of risk and seriousness is sought in follow-up assessments. Using follow-up measurements, we examined whether changes in determinants found to be of importance in the cross-sectional analyses in Chapter 6 to 9 were associated with changes in perception of risk and seriousness (Chapter 11), and whether changes in perception of risk and seriousness were associated with changes in anxiety, depression and disease-related distress (Chapter 12). The findings of this study are summarized and discussed in Chapter 13.

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2

METHODS

Design of the study

This study on perception of risk of MS (PROMS) is a longitudinal study comprising four time points in two years at which patients underwent neurological and neuropsychological examinations and completed psychological questionnaires. An overview of the study is presented in Table 1.

Participants

The PROMS study was conducted among recently diagnosed MS patients and their partners. Patients were recruited through the Departments of Neurology of the Erasmus MC, three hospitals within the region of this academic hospital, and the VU Medical Center in the period of March 1999 – December 2000. Patients were eligible if they had a definite or probable diagnosis of MS,[1] were diagnosed within two years before study entry, were between 18 and 55 years old and had signed informed consent. The diagnoses were verified by senior neurologists of the academic hospitals. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Partners were eligible if they had sufficient understanding of the Dutch language.

Part of this study was conducted in collaboration with the FUPRO-MS study of the department of rehabilitation of the VU Medical Center (Amsterdam), a large-scale study on the clinimetric evaluation and determinants of functional prognosis. The PROMS and FUPRO-MS studies had different research questions but a comparable schedule of measurements and a considerable overlap in the

Table 1 Overview of assessments in the PROMS study

Measurement	1	2	3	4
Follow-up in years	0	½	1	2
Patients				
General characteristics	X			
Disease characteristics				
MRI*	X			
MS-related medical history	X			
Neurological examination	X	X		X
Neuropsychological examination*	X	X		X
Personality traits				
Optimism, neuroticism	X			
Psychological outcome variables				
Perception of risk and seriousness, health-related quality of life, anxiety, depression, disease-related distress, illness representations, uncertainty	X	X	X	X
Psychological interview	X			
Partners				
Psychological outcome variables				
Perception of risk and seriousness, health-related quality of life, anxiety, depression, disease-related distress, illness representations, uncertainty	X		X	X
Psychological interview	X			

* The MRI and neuropsychological examinations were conducted to study the predictive value of cognitive function on progression of disease. This research question is outside the scope of this thesis.

examinations and questionnaires. The inclusion criteria of the FUPRO-MS study were limited to patients with definite MS who were diagnosed no longer than six months before study entry. Patients with definite MS who were diagnosed between 6-24 months and those with probable MS were eligible for the PROMS study only. Patients who met the criteria for both studies were invited to participate in both.

Of the 120 patients who met the inclusion criteria, 101 agreed to participate in the study. Patients who declined participation further mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine patients declined without additional comments and four never responded to our reminders. Ninety of 101 (89%) had a partner of whom 78 did participate. Others were excluded due to insufficient understanding of the Dutch language (n = 2), were not living together and for that reason not invited by the patient (n = 6) or declined for unknown reasons (n = 4).

Fifty-nine patients were recruited through the Erasmus MC, 32 through the VU Medical Center and 10 through hospitals within the region of the Erasmus MC.

Half of the patients (57/101) participated in the PROMS-study only, and the other half (54/101) participated in both the PROMS- and FUPRO-MS study.

Of the 101 patients who started, two declined further participation after the first measurement and one after the second (Table 2). Reasons for withdrawing were the high emotional burden (n = 1), problems with disability payment procedures (n = 1), loss to follow-up (n = 1). Patients who missed one assessment often did not respond to several reminders or repeatedly postponed visits. Loss of follow-up in partners was mainly explained by the non-participation of patients (n = 5) and broken relationships (n = 3).

Procedure

Patients were informed about the study by their treating physician. When they showed interest, patients were given an information letter and a reply form. The letter included additional information about the study, as well as explanations on the protection of privacy and the non-interference of study participation with their treatment by the neurologist. At the same time and with permission of the patient, the neurologist completed a form with general and clinical characteristics of the patient, which was returned to the investigators. Patients were asked to return the reply form within two weeks. Those who did not respond were phoned by the investigator to hear their decision.

Patients who agreed to participate were scheduled for a neurological and neuropsychological examination and an interview. These appointments were planned one week apart with the examinations preceding the interview. Patients participating in both studies were visited at home for the neurological and

Table 2 Participation at follow-up measurements

	Time point	Resigned (cumulative)	Missing assessments at one time point	Available data
Patients	1	-	-	101
	2	2	1	98
	3	3	1	97
	4	9 *	-	72 *
Partners	1	-	-	78
	3	3	3	72
	4	11 *	-	55 *

* Measurement 4 was scheduled to finish in March 2003. Numbers are based on available data by December 2002. At that time, 81 patients and 66 partners had been scheduled for measurement 4.

neuropsychological examinations, whereas PROMS participants were invited to visit the hospital. All interviews were held at home by the same psychologist (CJ). One week before the examinations, questionnaires for the patients were sent by mail. These had to be completed one week after the examination and handed in before the interview. Partners were given their questionnaires prior to the patient's interview and were asked to complete these in another room during the patient's interview. After the patient's interview, the partner was interviewed in absence of the patient. At follow-up, all questionnaires were sent to the patients and partners by mail with an explicit request to complete the questionnaires on their own. The questionnaires could be handed in at the neurological examinations or returned by mail. If necessary, repeated phone calls were made to remind participants of returning their questionnaires. The study protocol was approved by the medical ethical committees of the participating hospitals.

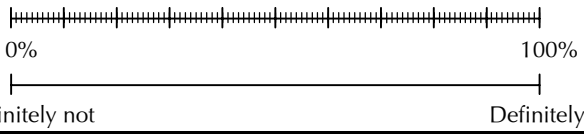
Instruments

Description of instruments

Perception of risk and seriousness – Expectations about prognosis were operationalized as perception of prognostic risk and perceived seriousness of prognosis. There is no widely-used instrument or gold standard for the assessment of risk perception. Instead, researchers have developed their own instruments, which differ considerably from one another. It is known that different assessments yield different impressions of perceptions of risk, implying that the choice of measurement has a significant impact on the findings of the study.[2-5] For example, women at increased risk of breast cancer appeared to have more accurate perceptions of their risks when these were measured as comparative risks than when measured as absolute risks.[5] Table 3 provides an overview of aspects that define measurements of risk perception. These aspects can be categorized as three major decisions: the definition of the prognostic outcome, the choice of the risk format, and the choice of scale or answer format.

In this study, wheelchair dependence was selected as the prognostic outcome because it is a well-known consequence of MS (see previous chapter). Wheelchair dependence was defined as the inability to walk beyond five meters, equaling a score of 7.0 on the EDSS. Because we were interested in the expectations of patients for the near and far future, we investigated the short (2-year), medium (10-year) and long term (lifetime) risk of wheelchair dependence. Risk perception was measured as an absolute and relative risk. In the relative risk, patients were asked to evaluate their risk compared to other patients of their age and sex who have similar limitations due to the disease. Since many patients reported problems of

Table 3 Definition and measurement of perception of risk

Definition of outcome	
Choice of outcome	Progressive course, wheelchair dependence, use of walking aids, blindness, cognitive decline, dying due to MS
Operationalization	Wheelchair dependence for distances over 5 meters, 100 meters, 1 kilometer
Time span	Wheelchair dependence within two years, ten years, lifetime
Definition of risk format	
Absolute versus relative risk	What do you think is your risk of wheelchair dependence? Compared to other women of your age and sex, what do you think is your risk of wheelchair dependence?
Unconditional versus conditional risk	What do you think is your risk of wheelchair dependence? Suppose you take interferon, what do you think is your risk of wheelchair dependence?
Definition of scale	
Dichotomous	Yes / No, Likely / Unlikely, Definitely / Definitely not
Percentage	1%, 20%, 50%
Frequency	1 in 100, 20 in 100, 50 in 100
Odds	1 to 100, 1 to 5, 1 to 2
Likert scale	3-, 5-, 7-, 9-, 11-point scale, e.g.: 5-point: No chance, unlikely, moderate, likely, certain to occur. 7-point: No chance, very unlikely, unlikely, 50/50 chance, likely, very likely, certain to occur.
Visual analogue scale	

Based on references[5-11]

understanding this relative risk format (see also Chapter 10), these questions are not discussed in the thesis.

The basic choice in response modes is that between numerical and verbal (non-numerical) scales.[6,12-16] This classification is in line with the two basic systems of reasoning: associative, intuitive and automatic processes versus rule-based, deliberative, controlled processes:[16,17] verbal assessments may be preferred in non-rational processes, and numerical in rule-based processes. Because we were interested in the impact of perceived risk on emotional well-being, we opted for verbal – or non-numerical – assessment of risk perception. A second, practical, reason is that we expected a high number of missing values with a numerical assessment, as patients emphasized in the pilot study that prognostic risks are

unknown. Therefore, we aimed to reduce any associations with numbers or counting in order to assess beliefs or ideas rather than knowledge about risks. We chose for blank visual analogue scales with verbally labeled end-points. Thus, patients were asked to what extent they thought they would become wheelchair-dependent for distances over five meters within two years, ten years and lifetime (see Appendix A). Answers had to be given by marking a blank 100mm visual analogue scale (VAS), which ends were anchored at 'Definitely not' and 'Definitely'. Marks on the scale were measured in millimeters from the left end of the scale. Answers ranged from 0 (definitely not) to 100 (definitely).

Perceived seriousness of wheelchair dependence was assessed in a similar way. Patients were asked for each of these periods how serious they thought it would be to be wheelchair-dependent by that time. Again, answers had to be given on a VAS anchored at 'Not serious at all' and 'The most serious thing I can imagine', with a possible range from 0 to 100, respectively.

Health-related quality of life – Quality of life was assessed using the SF-36.[18] The SF-36 comprises four physical health (physical functioning, role-physical functioning, bodily pain and general health) and four mental health scales (vitality, social functioning, role-emotional functioning and mental health). Items are summed per scale and transformed into scores between 0 (poor health) and 100 (optimal health).[18] For the bodily pain scale, higher scores mean less pain. The SF-36 was validated in a Dutch population and norm values were available.[19]

Anxiety and depression – Anxiety and depression were assessed by two 7-item scales of the Hospital Anxiety and Depression Scale (HADS).[20,21] Scale scores can vary from 0-21 with high scores indicating higher levels of anxiety and depression. This instrument was chosen because the HADS is relatively free of interference by coexisting general medical conditions.[22] Scores between 8 and 10 are considered clinically borderline and 11 or higher clinically definite levels of anxiety and depression.[20,21] Norm scores of the general population were available.[23]

Disease-related distress – Specific MS-related distress was assessed using the Impact of Event Scale.[24,25] This questionnaire addresses the psychological distress of having MS by focusing on the impact of thoughts and feelings. One scale measures being overwhelmed by thoughts and feelings about having MS (intrusion) and the other evaluates the tendency to avoid these thoughts and feelings (avoidance). The intrusion scale ranges from 0 to 35 with high scores indicating more intrusive thoughts and feelings. The avoidance scale ranges from 0 to 40 with high scores indicating a greater tendency to avoid MS-related feelings and thoughts. A total distress score was obtained by summing intrusion and avoidance scores. Scores of 26 and higher on the total scale indicate levels of severe distress.

Illness representations – Illness representations are the core determinant of coping behavior in the self-regulation theory of illness.[26] Illness representations were assessed using the Illness Perception Questionnaire (IPQ).[27] The illness identity, cause and timeline (cyclical) scales were derived from the revised version (IPQ-R).[28] Also, the coherence scale from the revised version was included to assess whether patients believe they have a clear understanding of their illness.

Optimism – Dispositional optimism, a generalized tendency to believe in positive outcome expectancies was assessed using the Life Orientation Test (LOT).[29,30] The scale consists of four positively formulated items (optimism), four negatively formulated items (pessimism) and four filler items. The optimism and pessimism sub-scales are summed into a total score, with a possible range from 8 to 40, with higher values indicating greater dispositional optimism and pessimism. Good validity has been demonstrated in a Dutch population sample.[30]

Neuroticism – Neuroticism refers to a stable dimension of personality consisting of negative emotions such as anxiety and anger, and cognitive and behavioral characteristics such as low self-esteem, preoccupation and insecurity.[31] Patients completed the 12-item neuroticism scale of the Eysenck Personality Questionnaire (EPQ).[32,33] The scale ranges from 0 – 12, with high scores indicating high neuroticism.

Illness uncertainty – The Mishel Uncertainty in Illness Scale (MUIS) was used to measure the patient's feelings of uncertainty about symptoms, diagnosis, treatment, relationships with caregivers and future plans.[34] The questionnaire comprises 33 items with 5-point Likert answer formats (strongly agree – strongly disagree). Items are summed into four scales: inconsistency, unpredictability, complexity and ambiguity with high scores indicating greater uncertainty.

MS-related disease history – Date of first symptoms, type of first symptoms and use of immunomodulatory drugs were registered at the neurological examination. Initial date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the treating physicians and the medical records. The diagnoses were confirmed at study entry by neurologists of the participating academic hospitals.

Disability status – Physical limitations were assessed by physicians of the academic hospitals following a standardized research protocol. Level of disability was rated on the widely-used Expanded Disability Status Scale (EDSS).[35] This scale ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS).

Psychological interview – A semi-structured interview was conducted to address experiences with the disease before and after diagnosis. Topics included the symptom history, disclosure of the diagnosis, uncertainty and worries about prognosis, beliefs about MS, expectations of prognosis, doctor-patient relationship,

and information needs. In this thesis, we will report about patients' explanations of their perceptions of risk and seriousness of wheelchair dependence. Patients were asked to elucidate their VAS scores (see perception of risk and seriousness). To prevent priming of the answers, questions were framed without interpreting the location of the mark on the VAS. For example, we asked 'can you explain why you put your mark *on that point of the line'* instead of '*in the middle'* or '*nearly at the end of the line'*. Explanations were recorded on audiotapes and transcribed verbatim.

Psychometric properties of instruments

Psychometric properties of the instruments used in this study are summarized in Table 4. We examined the following statistics:

Reliability – Reliability concerns the extent to which measurements are stable over a variety of conditions in which the same results should be obtained. We calculated Coefficient α as a measure of internal consistency which is based on the average inter-item correlation. When α is 0.80, at least 80% of the total score variance is due to true score variance.[36] For research purposes Coefficient α is acceptable at about 0.70 or higher, whereas for diagnostic purposes 0.90-0.95 may not even be high enough.[37] Reliabilities of the scales are calculated using the baseline data of patients. Based on these criteria, coefficient α of the IPQ cyclical timeline and personal control scales, the EPQ Neuroticism and the MUIS complexity and predictability scales were insufficient. The reliability of the IPQ cyclical timeline scale increased after items with the weakest item-total correlation were excluded. Since the remaining items ('My symptoms come and go in cycles' and 'I go through cycles in which my illness get better and worse') are most relevant in MS, it was decided to use the 2-item scale in further analyses. The low reliability of the personal control scale was not caused by errors in recoding of the items, but due to low inverse correlations between the items. Coefficient α of the EPQ Neuroticism scale increased to 0.74 when the scale was reduced by one item and to 0.80 when the two 'weakest' items were removed. Yet, the correlation coefficients of these scales with the original 12-item scale were 0.99 and 0.97, respectively. As this indicates that scale reduction will not yield different results, we decided to use the original scale.

Factor analysis – We performed principal component analysis with Varimax rotation to *screen* whether the original groupings of items (scales) were replicated in our study. The results of the factor analyses of the scales were compared with the original structure. When for a given scale, all (++) or all but one (+) of its items loaded on the same factor, we considered the original scale to be confirmed.

Table 4 Psychometric properties of the psychological instruments in this study

Questionnaire	Scale	Number of items	Reliability[1]	Factor analysis[2]	Skewness[3]
Perceived risk	2 years	1	NA	NA	1.17
	10 years	1	NA	NA	0.20
	Lifetime	1	NA	NA	-0.26
Perceived seriousness	2 years	1	NA	NA	-1.69
	10 years	1	NA	NA	-1.39
	Lifetime	1	NA	NA	-1.29
Health-related	Physical functioning	10	0.94	++	-0.81
quality of life	Role-physical functioning	4	0.84	++	0.05
– SF-36	Bodily pain	2	0.89	++	-0.61
	General health	5	0.77	++	-0.10
	Vitality	4	0.78	+	-0.11
	Social functioning	2	0.80	++	-0.81
	Role-emotional functioning	3	0.74	++	-0.94
	Mental health	5	0.82	+/-	-0.62
Anxiety / depression	Anxiety	7	0.83	++	1.03
– HADS	Depression	7	0.81	++	1.14
Disease-related	Avoidance	7	0.75	++	0.67
distress – IES	Intrusion	7	0.82	++	0.81
Illness representations	Causes	19	NA	NA	NA
– IPQ	Coherence	5	0.82	++	0.16
	Consequences	7	0.72	++	-0.07
	Chronic timeline	3	0.82	++	0.49
	Cyclical timeline	5	0.32	-	-0.03
		2	0.72	++	-0.74
	Personal control	3	0.00	+	0.14
	Treatment control	3	0.66	+	-0.10
	Identity	23	0.87	NA	0.93
Optimism – LOT	Optimism	4	0.72	++	-0.13
	Pessimism	4	0.68	++	-0.39
Neuroticism – EPQ	Neuroticism	12	0.64	++	-0.02
		11	0.74	++	-0.07
Illness uncertainty	Inconsistency	7	0.78	+	0.82
– MUIS	Unpredictability	5	0.28	+	-0.38
	Complexity	7	0.56	-	1.05
	Ambiguity	13	0.63	-	0.43

[1] Coefficient α; [2] ++ All items load on 1 factor, + all but 1 item load on one factor, +/- most items load on 1 factor, - items are divided over factors. NA = not applicable; [3] SE = 0.24.

When most of its items loaded on one factor (+/-) confirmation was considered moderate. When items of the original scale were dispersed over several factors (-), we considered the structure not confirmed. In our study, factor analyses could not reproduce the IPQ cyclical timeline scale and the MUIS ambiguity and complexity scales. Since the 2-item cyclical timeline scale of the IPQ loaded on one factor, this scale was used.

Normality – Although statistical tests generally require that data are normally distributed, it is tempting to conclude that most tests are robust for deviations from normal distributions.[38] For example, in multivariate regression analyses it is not required that individual variables are normally distributed, but that the residuals (unexplained variance) of analyses demonstrate a normal distribution. Yet, it is adviced to use transformations of variables to improve their normality unless there is some compelling reason not to.[38] One reason may be that results of transformed data are far more difficult to interpret from a clinical perspective. Therefore, we limited transformation to those analyses in which transformation of skewed variables yielded different conclusions. To examine which variables *might* need transformation, we evaluated normality by examination of the skewness of the distributions. As a rule of thumb, distributions are considered to deviate from normality when the skewness is higher than twice its standard error (SE). The distribution of perceived risk and seriousness, SF-36 quality of life, HAD anxiety and depression and IES intrusion and avoidance were all skewed. To examine whether these variables *do* need transformation, we inspected the normal probability plots of the residuals.

Based on inspection of the internal consistency reliability and factor analysis, it was decided that the psychometric properties of the illness uncertainty scale (MUIS) and the IPQ personal control scale were insufficient. These scales were not used in the analyses. The distributions of most SF-36 scales, the HADS, IES and perceptions of risk and seriousness were skewed. All analyses including these variables will be inspected on adverse effects of skewness.

Missing data handling

The percentage of missing data of the main follow-up variables (perception of risk and seriousness, quality of life, anxiety and depression and disease related distress) in patients was 0-3% at measurement 1, 0-3% at measurement 2, 0-5% at measurement 3, and 0-2% at measurement 4. In partners, the percentage of missing values was 0-5% at measurement 1, 0-7% at measurement 3, and 0-2% at measurement 4. Exception was perceived 2-year risk and seriousness, which were included later in the study and therefore missing at measurement 1 in thirteen

patients and eleven partners. Compared to those who did complete these questions, we found no differences in perceived 10-year and lifetime risk and seriousness. Thus, missing values were considered 'at random'. For the cross-sectional analyses, missing data of the perceived 2-year risk were imputed using the iterative expectation-maximization method based on their perceived 10-year and lifetime risk and seriousness.[39]

Statistical analysis

Statistical analyses were performed using SPSS 9.0-11.0 for Windows (SPSS Inc., www.spss.com) and SAS 8.0 for Windows (SAS Institute Inc., www.sas.com). All data were inspected for coding errors, outliers and extreme values. All multivariate analyses were inspected for multicollinearity and normality of the residuals. P-values (2-sided) lower than 0.05 were considered statistically significant.

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3

PATIENTS WITH MULTIPLE SCLEROSIS PREFER EARLY DIAGNOSIS

Abstract

The new diagnostic criteria for multiple sclerosis (MS) allow for a definite diagnosis in earlier stages of disease. Yet, clinicians may be hesitant to pursue a diagnosis of MS at the presentation of first symptoms as they consider the benefit for the patients limited. We studied satisfaction with the timing of diagnosis in patients recently diagnosed with MS and found that 70% of the patients were satisfied with the timing, whereas 24% favoured an earlier, and 6% a later disclosure. Patients who preferred an earlier diagnosis had a significantly longer interval between their first visit to the neurologist and the disclosure of diagnosis ($p < 0.001$). The probability of satisfaction did not substantially decrease in the year following the first visit to the neurologist, meaning the neurologist has ample opportunity for a thorough evaluation of the early clinical course.

Introduction

The introduction of MRI in the diagnostic criteria for multiple sclerosis (MS) allow for a definite diagnosis of MS in an early phase of the disease.[1] The benefits of an early diagnosis are subject for debate, because the effectiveness of early treatment for the long term prognosis is not certain[2] and the possibilities for prediction of prognosis are limited.[3] In addition, early diagnosis of MS could bring along a higher frequency of misdiagnoses.[4] For these clinical reasons, physicians may hesitate to discuss the possibility of MS at the presentation of first symptoms and may defer further diagnostic investigations to prevent psychological harm to patients.[5,6] It is not known whether patients themselves prefer an early diagnosis. We examined satisfaction with the timing of diagnosis in recently diagnosed MS patients and related their preferences to the duration of their diagnostic work-up.

Methods

The study sample consisted of 95 recently diagnosed MS patients, who participated in an ongoing follow-up study of early MS. Mean age of the patients was 38.7 years (SD 9.4), 71% were female, 91% were diagnosed as definite MS, mean time *since* diagnosis was 1.7 years (SD 0.8) and the median score on the Expanded Disability Status Scale (EDSS) was 2.5 (range 0.0 - 7.0). In a short questionnaire, patients were asked to summarise their MS-related medical history including the date of first visit to a general practitioner (GP), date of first visit to a neurologist and date of diagnosis. These dates divide the diagnostic period into two phases: duration of the diagnostic workup within the primary health care and at the neurological clinics. Further, patients were asked whether they were satisfied with the timing of their diagnosis or whether they would have preferred – if possible – to be diagnosed earlier or later. Patients were asked to elucidate their preferences in their own words.

Results

Seventy percent of the patients were satisfied with the timing of diagnosis, whereas 24% preferred an earlier and 6% a later diagnosis. Patients who were satisfied had a shorter time interval between their first visit to a GP and their diagnosis (median 5 months, inter-quartile range [IQR 2-17]) compared to those who preferred an earlier (31 months [9-87]) or later diagnosis (25 months [3-74], Kruskal-Wallis test $p < 0.001$). Further analyses demonstrated that these differences were particularly significant for the duration at the neurological clinics ($p < 0.001$) and not at the GP ($p = 0.59$); median duration at the neurological clinics was 1 month [1-5] in those who were satisfied compared to 9 months [3-45] in patients preferring an earlier

and 4 months [2-7] in patients preferring a later diagnosis. Figure 1 shows that the predicted probability of satisfaction was lower when the time between the first consultation with the neurologist and the diagnosis was longer. Of all patients who were diagnosed within 6 months after the first visit with the neurologist , 82% (54/66) were satisfied with the timing of diagnosis, compared to 41% (12/29) of the patients whose diagnostic workup took more than six months. These results remained significant after adjustment for EDSS, time since diagnosis, age and sex ($p = 0.03$).

The main reasons for favouring an earlier diagnosis were the high burden of uncertainty (n = 8), lack of understanding of family and friends (n = 4) and the possibility of having missed options for early treatment (n = 4). Patients who preferred a later diagnosis favoured diagnostic uncertainty over a definite diagnosis (n = 3) or did not experience any further symptoms (n = 2).

Conclusions

Our study shows that 70% of the MS patients were satisfied with the timing of their diagnosis and 24% had preferred an earlier diagnosis – if this had been possible. The probability of patients' satisfaction particularly decreased with a longer duration of the work-up after their first visit to the neurologist. The duration of the

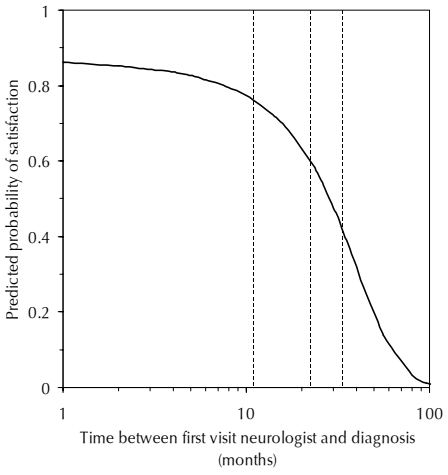

Figure 1 Predicted probability of patient satisfaction by duration of diagnostic work-up at the neurological clinics

Predicted values were obtained from logistic regression analyses with duration as independent variable. Vertical lines indicate 1-, 2- and 3-year period. Time is presented on a logarithmic scale.

neurological work-up may be important to the patient because a referral to a medical specialist indicates that the severity of their symptoms apparently warrants further examination at the hospital. From that moment, patients may start worrying about the origin of their complaints.

A potential shortcoming of the study is that patients evaluated satisfaction with the timing of diagnosis *after* they were diagnosed. Preferably one would study these preferences at the presentation of first symptoms, when patients are not yet informed about the possibility of MS. It is questionable whether studying the satisfaction with a future diagnosis of MS in patients who did not yet receive their diagnosis is feasible and ethical. Our retrospective approach may have biased the conclusions in two ways. First, patients may be more inclined to be dissatisfied because they are in general dissatisfied with the fact they were diagnosed with MS. It is difficult to see that this explains the significant association between satisfaction and duration of the diagnostic workup that we observed. More likely, this would also have led to higher levels of dissatisfaction in those with a short diagnostic workup. Moreover, the lack of a relationship between satisfaction and duration of the workup by the GP argues against the view this bias had occurred. Second, bias may have occurred due to the fact that the study population only included patients who were sooner or later diagnosed with MS, but not subjects with suspected symptoms who were never diagnosed. Most likely these patients will be comfortable with the fact that they were not informed about their (possible) diagnosis of MS. The clinical dilemma is that this group cannot be identified at the presentation of first symptoms but only with hindsight. An important question to be answered in future studies is how many patients do not progress. However, another point of consideration will be to examine the influence of the rapid developments at the Internet. When patients with major MS related symptoms such as optic neuritis search at the Internet for more information, they will easily learn about the possibility of MS (see also Appendix B).[7] Not discussing the possibility with the patient in neurological practice may lead to unanticipated findings of patients at the Internet. Needless to say there also is a high risk that patients will (mis)diagnose themselves.

A last issue to be discussed is that a long duration may be indicative of a difficult diagnostic workup, which may in turn explain the dissatisfaction of patients. The retrospective study design does not provide information whether earlier disclosure of the diagnosis in our patients with a long workup had been possible. There could have been medical reasons for the prolonged diagnostic period, such as discrepancies between clinical findings, MRI and CSF test results. In these instances, time itself may be the decisive factor. However, a point of

consideration in this scenario is the fact that patients may be dissatisfied with such lengthy procedures because they did not understand why the workup took that long. This implies a need for more explanation on the diagnostic procedures by the neurologist.

Since the majority of MS patients was satisfied with a disclosure of diagnosis within 6 months, our data suggest that there appears to be no reason to delay diagnostic procedures. It is important to note that satisfaction did not substantially decrease in the months following the first visit to the neurologist, leaving ample time for a prudent diagnostic work-up. In line with the present findings, we argue that further diagnostic testing at the presentation of first symptoms may benefit to all patients either because the disease is diagnosed early in those who do suffer from MS or is ruled out in those who do not suffer MS. Finally, satisfaction with the timing of diagnosis will obviously not be determined by time alone, but is most likely influenced by adequate and transparent diagnostic procedures that are clearly communicated with patients. The knowledge that their symptoms are taken seriously and efforts are made to find out the causes of symptoms may outweigh the effect of time in determining patients' satisfaction.

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4

IMPACT OF RECENTLY DIAGNOSED MULTIPLE SCLEROSIS ON QUALITY OF LIFE, ANXIETY, DEPRESSION AND DISTRESS OF PATIENTS AND PARTNERS

Abstract

Objectives: Studies demonstrating reduced quality of life and psychological well-being in MS have typically investigated patients within more advanced stages of disease. The aim of the present paper was to evaluate the emotional burden and quality of life of recently diagnosed MS patients and their partners. **Methods:** Data on health-related quality of life (SF-36), anxiety and depression (HADS) and disease-related distress (IES) were obtained in 101 patients and their partners (n=78). **Results:** On average eight months after diagnosis (range 0 – 24 months), 34% of the patients and 40% of the partners had clinically high levels of anxiety, and 36% of the patients and 24% of the partners had levels of severe distress. Scores of anxiety, depression and distress were higher in patients with more functional limitations (EDSS ≥ 3.0). Quality of life was significantly poorer in patients compared to controls, particularly among those with higher disability. **Conclusions:** Both patients and their partners demonstrated high levels of anxiety and distress in the early period after the diagnosis. These findings indicate careful attention by health care professionals to identify those who may benefit from further psychological support.

Introduction

Multiple sclerosis (MS) has a major impact on the lives of patients and their partners. In patients, the disease substantially interferes with daily activities and family, social and working life, disturbs emotional well-being, and reduces quality of life.[1-8] Similar negative consequences on well-being, quality of life and employment have also been found in partners of MS patients.[9-11] This psychosocial impact of the disease in patients and partners was found to be significantly associated with the patients' severity of disability.[2-6,8,9,11]

Studies on quality of life and psychological well-being in MS have mainly been conducted among patients who were at more advanced stages of disease. In the above-mentioned studies, the average illness duration varied between 8 and 16 years and median scores on the Expanded Disability Status Scale (EDSS) varied between 3.5 and 5.0.[1-11] The impact of the disease on quality of life and psychological outcomes of patients and their partners in earlier phases of disease has not been examined. In the early period after diagnosis, patients and their partners may still have to cope with the uncertainty and the prospect of potential serious disability. Also, the uncertainty about unexplained symptoms that had evoked anxiety and distress before the diagnosis may prolong in the period thereafter. On the other hand, at an early stage most patients may still face relatively good health with limited need for care and assistance in daily activities. This would predict that quality of life of patients and their partners may not be reduced in an early phase of disease.

The aim of the present study was to investigate the emotional burden of MS in patients and partners in order to determine the need for psychological support in the early period of disease. For this purpose, we assessed health-related quality of life, anxiety, depression and distress (i.e. the intrusion and avoidance of thoughts and feelings that relate to MS) in recently diagnosed patients and their partners. Psychological outcomes were related to disability status (EDSS) and compared with scores from a general population sample. Finally, we examined differences in psychological well-being between patients and their partners within couples.

Methods

Participants and procedures

In the period of March 1999 – December 2000, consecutive patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam). Patients were eligible if they were diagnosed as having definite or probable MS[12] no longer than two years before study entry, were

between 18 and 55 years old and had given informed consent. Patients with serious comorbidity of other neurological or systemic diseases or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the inclusion criteria, 101 agreed to participate in the study. Patients who declined participation mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine others declined without additional comments and four never responded to our reminders. Ninety of them (89%) had a partner, of whom 78 (87%) did participate. Two partners were excluded due to insufficient understanding of the Dutch language, six were not living with the patient and for that reason not invited by the patient, and four refused for unknown reasons.

Patients underwent a neurological examination, participated in an interview and filled out questionnaires. The questionnaires were sent one week before the neurological examination and had to be given back one week later, before the at-home interview. At that time, partners were given their questionnaires, and requested to complete these in another room during the interview with the patient. Functional limitations were assessed by a physician and rated on the EDSS.[13] As the present population of recently diagnosed patients is relatively homogeneous with regard to time since first symptoms, EDSS can be regarded as an indicator of disease progression.[13] The study protocol was approved by the medical ethical committees of the participating hospitals.

Instruments

Patients and partners were asked to evaluate their health-related quality of life during the week prior to the examinations using the SF-36.[14] The SF-36 is a validated and commonly used instrument for the self-evaluation of physical and mental health. The questionnaire comprises four physical health scales (physical functioning, role-physical functioning, bodily pain and general health) and four mental health scales (vitality, social functioning, role-emotional functioning and mental health). A shortcoming of the SF-36 is its insensitivity to change and the significant floor and ceiling effects in several dimensions.[15] For this study, both the insensitivity to change and the ceiling effects imply that minor differences in QoL between patients, partners and general population controls may not be detected. Items are summed per scale and transformed into scores between 0 (poor health) and 100 (optimal health).[14] In our study, Coefficient α ranged from 0.74 to 0.94, indicating good reliability of the scales. Quality of life scores of healthy controls were obtained from a nationwide, population-based study that was conducted to provide Dutch normative data for the SF-36.[16] Original data on quality of life, age and sex were available for analysis (n = 1742).

The intensity of feelings of anxiety and depression during the past seven days was measured by the Hospital Anxiety and Depression Scale (HADS).[17] Both scales include seven items that are summed into a total score with a possible range of 0-21. High scores indicate higher levels of anxiety and depression. Scores between 8 and 10 are considered clinically borderline and 11 or higher are considered clinically definite levels of anxiety and depression.[17] Internal consistency reliability in this study was good: Coefficient α was 0.83 for the anxiety and 0.81 for the depression scale. Data on anxiety and depression of a general population sample were derived from published results of a Dutch validation study of the HADS.[18] Mean age of this population sample (n = 199) was 39.9 years and 54% were women.

Disease-related psychological distress was measured using the Impact of Event Scale (IES).[19] This questionnaire addresses the psychological distress of having MS by focusing on the intensity of thoughts and feelings that relate to the disease within the past seven days. The questionnaire includes two scales: a 7-item intrusion scale (range 0 – 35) and an 8-item avoidance scale (0 – 40). Intrusion refers to the degree of being overwhelmed by thoughts and feelings about MS. Items include e.g. 'Any reminder brought back feelings about it' and 'I had dreams about it'. Avoidance refers to the tendency to keep off these thoughts and feelings, and is measured by items such as 'I tried not to think about it' and 'I stayed away from any reminders of it'. Answers were given on a 4-point scale with 0 = not at all, 1 = rarely, 3 = sometimes and 5 = often. In this study, Coefficient α was 0.82 for the intrusion scale and 0.75 for the avoidance scale. Intrusion and avoidance are positively correlated.[20] Although this seems paradoxical, avoidance can be thought of as a way of coping with high levels of intrusive thoughts: if thoughts and feelings are too disturbing, patients may restore emotional equilibrium by avoidance. This co-occurrence of intrusion and avoidance is expressed in a total distress score obtained by summation of the intrusion and avoidance scores.[19] Total scores of 26 and higher indicate a high risk of developing a stress disorder.[21] Since intrusion and avoidance are relevant only in subjects who are confronted with the disease, no comparisons were made to general population controls.

Statistical analysis

To test overall differences in quality of life (SF-36) between patients, partners and controls, we performed univariate analysis of variance with age and sex as covariates. Similar analyses were performed to compare quality of life in two groups of disability status (EDSS) for patients and partners separately. EDSS 3.0 was taken as a cut-off score to distinguish between no to minimal disability (0 - 2.5)

and moderate to severe disability (3.0 - 10.0).[13] Student's t-tests were performed to compare psychological well-being between high and low EDSS groups for patients and partners separately. Differences in psychological well-being between patients and partners were compared using paired t-tests. A p-value lower than 0.05 was considered statistically significant.

Results

Characteristics of patients and partners

General and clinical characteristics of patients and partners are presented in Table 1. Fifty-nine patients were recruited through the Erasmus MC, 32 through the VU medical center and 10 through local hospitals within the region of the academic centers. Thirty-seven percent of the patients had EDSS scores ≥ 3.0. Higher EDSS scores were found among male patients (median EDSS 3.0 versus 2.0 in females; $p = 0.05$), in older patients (correlation coefficient $\rho = 0.22$; $p = 0.03$) and in those with definite MS (2.5 versus 2.0 in probable MS; $p = 0.02$). EDSS tended to be higher in patients with a longer time since first symptoms ($\rho = 0.19$; $p = 0.06$). Time since diagnosis ranged from 0 to 24 months (mean 7.8 months), and was not significantly related to EDSS ($\rho = -0.06$; $p = 0.58$).

Quality of life

Overall, recently diagnosed MS patients reported significantly poorer quality of life on all SF-36 scales compared to controls from the general population ($p < 0.05$),

Table 1 General characteristics of MS patients and their partners

	Patients (n = 101)	Partners (n = 78)
Age (years; mean ± SD)	37.5 ± 9.5	39.3 ± 8.7
Sex (women)	70%	36%
Diagnosis		
Definite MS	90%	
Probable MS	10%	
EDSS (median; range)	2.5 [0.0 – 7.0]	
EDSS < 3.0	63%	58%*
EDSS ≥ 3.0	37%	42%*
Time since first symptoms (years; mean ± SD)	3.7 ± 4.6 (median 2.1)	
Time since diagnosis (months; mean ± SD)	7.8 ± 6.5 (median 5.1)	

* Categorization based on EDSS score of patient.

except for the SF-36 bodily pain scale (p = 0.67). SF-36 scores of patients were significantly correlated to their level of disability as measured by the EDSS (p < 0.001).

Figure 1 shows mean SF-36 scores of MS patients and controls from the general population. The center of the graph indicates poorest possible health status, representing lowest scores (0) on all scales. Differences between the three groups were significant at all scales (p < 0.001). Post-hoc analyses of between-group differences demonstrated that patients with high EDSS scores (≥ 3.0) evaluated their mental and physical health significantly poorer on all SF-36 scales compared with controls. Yet, also patients with low disability (EDSS < 3.0) had significantly poorer SF-36 general health (p < 0.001), role-physical functioning (p < 0.001), vitality (p < 0.001) and physical functioning (p = 0.01) than controls. Disease duration from first symptoms was related to two out of eight SF-36 scales: patients with a longer time since their first symptoms reported significantly more

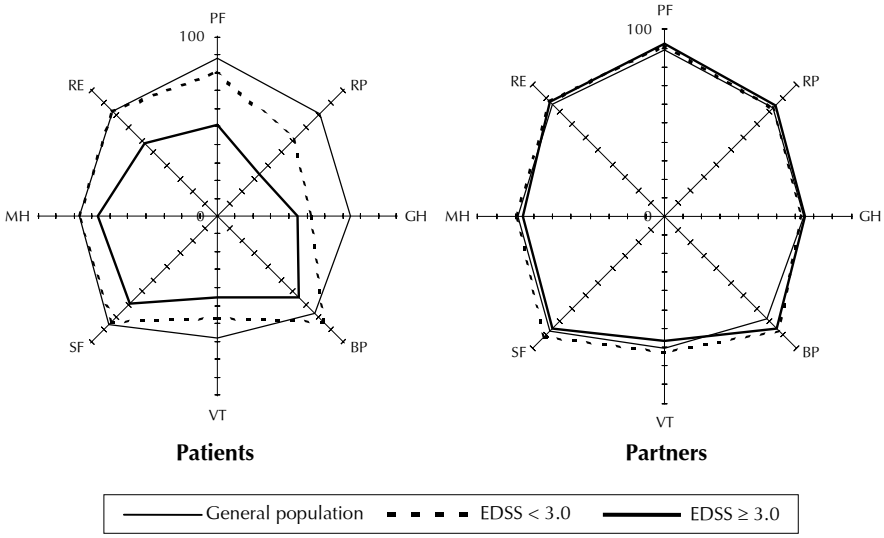

Figure 1 Quality of life of MS patients and partners related to severity of disability (EDSS)

Values are mean scores of SF-36 scales. PF = physical functioning, RP = role-physical functioning, GH = general health, BP = bodily pain, VT = vitality, SF = social functioning, MH = mental health, RE = role-emotional functioning. The center of the graph represents the lowest possible score on each scale. Grouping of partners was based on the patient's EDSS score. Differences between the three groups were tested by univariate ANOVA. In patients, the differences were significant at all scales (p < 0.001). In partners, none of the differences were significant, except bodily pain (p = 0.003).

pain (ρ = -0.32, p = 0.002) and tended to report poorer physical functioning (ρ = -0.19, p = 0.06). SF-36 quality of life was not significantly related to time since diagnosis. Partners did not differ significantly in mean SF-36 scores from general population controls, except that they reported less pain (p = 0.001). Their SF-36 scores were not related to patients' status of functional disability as measured by the EDSS (Figure 1).

Anxiety, depression and psychological distress.

Both patients and partners had significantly higher levels of anxiety than controls from a Dutch population sample (mean score of anxiety in patients 6.6 versus 5.1 in controls; p = 0.003; mean score of partners 6.4 versus 5.1, p = 0.012).[18] Thirty-four percent of the patients and 40% of the partners had clinically relevant levels of anxiety (score $\geq$ 8). Patients and partners did not differ from controls in their mean scores of depression (mean score in patients 3.8 versus 3.4 in controls; p = 0.41; mean score of partners 3.7 versus 3.4; p = 0.56). Figure 2 shows mean scores of anxiety and depression of patients and partners in two groups divided by the patients' EDSS scores. The figure shows that patients with more functional limitations (EDSS $\geq$ 3.0) had significantly higher levels of anxiety (p = 0.05) and depression (p < 0.001) compared to patients with fewer limitations. In a stratified analysis, patients with a high EDSS score were found more anxious (p = 0.001) and depressed (p < 0.001) than controls. Yet, patients with fewer functional limitations (EDSS < 3.0) did not significantly differ from controls in their levels of anxiety (p = 0.20) and depression (p = 0.14). In partners, anxiety and depression were not significantly related to the patient's severity of disability (Figure 2).

Figure 2 also demonstrates mean scores of intrusion and avoidance of thoughts and negative feelings about MS. Again, intrusion (p = 0.01) as well as avoidance (p = 0.02) were significantly related to disability status in patients, but not in partners. Severe distress (defined as the sum of intrusion and avoidance scores > 25) was found in 36% of patients and 24% of the partners. In total, 48% of the patients and 46% of the partners had clinically relevant levels either of anxiety, depression or distress. Neither in patients nor in partners were anxiety, depression and distress associated with time since first symptoms or time since diagnosis.

Comparison between patients and partners

Overall, patients demonstrated a greater tendency to avoid MS-related feelings and thoughts than partners (mean score of avoidance 11.1 versus 7.1; p < 0.001), but they did not differ significantly in their levels of anxiety (means 6.6 versus 6.4; p = 0.76), depression (3.8 versus 3.7; p = 0.76) and intrusion (10.3 versus 9.9;

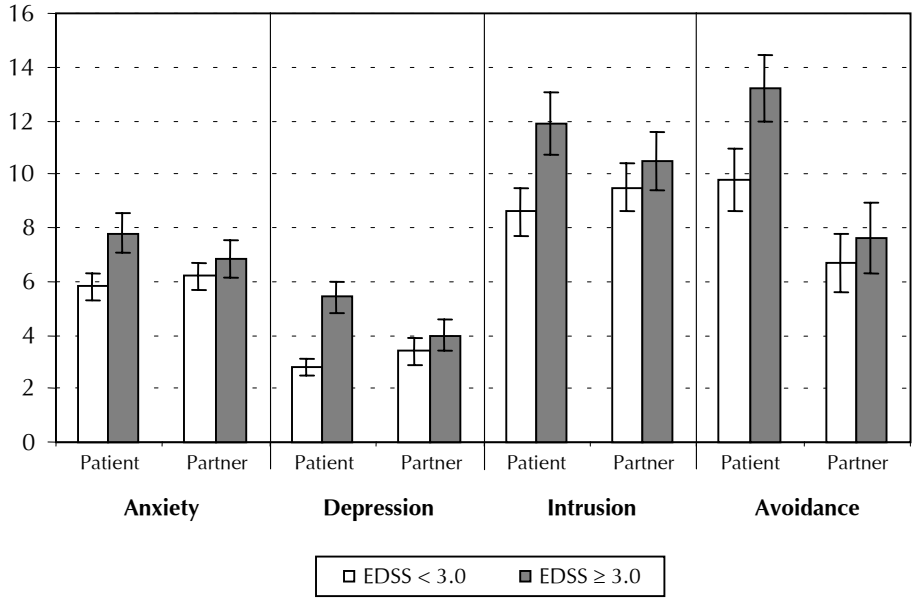

Figure 2 Anxiety, depression, intrusion and avoidance of patients and partners

Bars represent mean values (± standard errors) of the Hospital Anxiety and Depression scale and the Impact of Event scale (intrusion and avoidance).

p = 0.67). Given these similarities in overall mean scores of psychological well-being, correlations between scores of patients and partners were moderate (anxiety r = 0.31, p = 0.006; depression r = 0.36, p = 0.001; intrusion r = 0.10, p = 0.37 and avoidance r = 0.27, p = 0.02). This suggests that there were substantial differences within couples, with patients having poorer psychological well-being than partners in some couples, and better in others.

Discussion

In the early phase after diagnosis of MS, patients and their partners experienced a substantial emotional burden of the disease: approximately 50% of the patients and partners had clinically relevant levels of either anxiety or distress. Compared to general population controls, SF-36 scores were significantly lower in patients, also in those with no to minimal disability (EDSS < 3.0). Disturbances in psychological well-being and quality of life were more prevalent among patients with more disability (EDSS ≥ 3.0). In partners, psychological well-being and SF-36 quality of life were not related to the patients' EDSS scores.

Previous studies demonstrating that psychological well-being and quality of life are reduced in MS patients and inversely related to disability status, have typically investigated MS patients within the more advanced stages of disease.[2-8] Our data show that a major impact of the disease on the quality of both physical and mental health was also found in recently diagnosed patients. Compared to SF-36 scores of patients with an average disease duration of 10-15 years,[2,4] our patients generally reported equal or better quality of life, except that our patients had substantially *lower* scores on the general health scale. Various reasons may explain the poorer quality of life and high emotional burden in this early phase of disease. First, quality of life may be reduced because patients already experienced practical consequences of their disability, as indicated by the lower SF-36 scores of patients with higher disability. Second, in judging the quality of their current physical health condition, patients may still compare their health status with their condition before they became ill.[22] That is, in the evaluation of their health status, patients with a recent diagnosis may focus more on the *loss* in functional ability, rather than on the functional ability itself. This may explain the poorer quality of life of patients with relatively mild limitations (EDSS < 3.0) as well as the poorer evaluations of general health. Finally, patients may feel more uncertain and bothered about the implications of these early limitations for their future disability. The latter may be most prominent for those with more functional limitations and particularly contribute to their high emotional burden. In partners, psychological well-being and quality of life were not related to the level of functional limitations of the patient. This suggests that emotional problems in partners, at least in early phases of the disease, were not due to the burden of care. Instead, the high levels of anxiety and intrusion of partners may reflect their worry about the patient's future disability and the possible impact of the disease for *their* lives.

The origin of anxiety and depression in MS patients is still unclear, but psychosocial, i.e. a response to the burden of having an invalidating disease, and pathogenic, i.e. related to the cerebral pathology, causes are considered.[23,24] Compared to general population controls, we found significantly increased levels of anxiety but not of depression. Patients did not differ from partners in their levels of anxiety, suggesting that anxiety is a reactive response on the disclosure of diagnosis.[24,25] In line with previous studies in later phases of disease,[6,24,26] we also found more symptoms of depression among patients with higher disability in our population of recently diagnosed patients. Yet, the fact that both levels of anxiety and depression were similar in patients and partners argues in favor of the view that, at least in an early phase of disease, depression is a result of the accumulated burden of adverse stressful experiences.[27]

Quality of life scales are widely considered as broader measurements of the impact of disease as compared to the EDSS.[2,28,29] The widely-used SF-36 may not be sufficient in studies that also aim to address the emotional burden of disease.[15] In this study, scores on the SF-36 mental health scale were not substantially reduced compared to controls, whereas patients and partners did report significantly more symptoms of anxiety than controls, and had high levels of intrusion and avoidance. Although the mental health scale of the SF-36 was related to anxiety ($r = -.57$, $p < 0.001$), depression ($r = -.60$, $p < 0.001$), intrusion ($r=-43$, $p < 0.001$) and avoidance ($r=-.47$, $p < 0.001$), the SF-36 failed to indicate the considerable disturbances in emotional well-being that we found in our population. Therefore, we advocate the use of specific screening scales for the assessment of symptoms of anxiety, depression or distress as they prove to have additive value over generic quality of life instruments.

Further follow-up studies are needed to elucidate the course of anxiety and distress in patients and partners in the early period after diagnosis. This will be necessary to identify those who will remain anxious and distressed for a longer period and who may need further psychological support. Another issue that deserves further investigation is the finding of considerable differences in psychological well-being within couples. Although it may be advantageous for a couple when at least one of the spouses is not profoundly distressed, these discrepancies may also hamper mutual support in the adaptation to the disease and potentially threaten the relationship between spouses.

In conclusion, this study demonstrates that MS patients as well as their partners experience a substantial emotional burden in the early phase after diagnosis. About half of the patients and partners had clinically high levels of anxiety and distress. These clinically high levels of anxiety and distress of patients *and* partners ask for attention of health care professionals, to observe those who may need further psychological support.

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5

ANXIETY AND DEPRESSION INFLUENCE THE RELATION BETWEEN DISABILITY STATUS AND QUALITY OF LIFE IN MULTIPLE SCLEROSIS

Abstract

Disability status, depression and anxiety are important determinants of quality of life (QoL) in patients with multiple sclerosis (MS). We investigated whether anxiety and depression influence the relation between disability status and QoL in our cohort of recently diagnosed patients. Disability status (EDSS), anxiety and depression (HADS), and QoL (SF-36) were prospectively obtained in 101 MS patients. The relation between EDSS and SF-36 scales was examined using regression analyses, without and with adjustment for anxiety and depression. Interaction effects were investigated by comparing the relation between EDSS and QoL in patients with high and low anxiety and depression. In the unadjusted analyses, EDSS was significantly related to all SF-36 physical and mental health scales. After adjustment for anxiety and depression, EDSS was significantly related only to the SF-36 physical functioning, role-physical functioning and bodily pain scales. The relation between EDSS and these SF-36 scales was consistently higher in patients with more symptoms of anxiety or depression, suggesting that anxiety and depression strengthened the association of EDSS with these SF-36 physical health scales. After adjustment for anxiety and depression, EDSS was not significantly related to the SF-36 mental health scales and the general health scale. This finding is compatible with the hypothesis that anxiety and depression are intermediate factors in the association of EDSS with these SF-36 scales. Screening for symptoms of anxiety and depression is recommended in studies that use QoL as an outcome measure of treatment or intervention efficacy.

Introduction

A large number of studies have demonstrated that patients with multiple sclerosis (MS) have poorer quality of life (QoL) than persons from the general population.[1-6] The disease has negative effects on both the physical and mental health dimensions of QoL.[1-5] This reduction of QoL in patients with MS is for a large part explained by the severity of their neurological symptoms. As expected, patients with more physical limitations generally report poorer QoL on the physical health dimensions than those with fewer limitations.[1-10] In addition, several studies have demonstrated a negative effect of disability status also on mental health,[1-3] but this was not confirmed by others.[4-10]

In MS, only two studies have investigated the association of depression and anxiety with health-related QoL. These studies showed that MS patients with more symptoms of depression or anxiety reported poorer QoL.[9,11] Moreover, depression was an important predictor of both the physical and mental health dimensions of QoL, independent of clinically-assessed disability status.[11] In these studies, the relation between depression and QoL was stronger than the association between clinical disability, as measured by the Expanded Disability Status Scale (EDSS), and QoL. Further, patients with higher disability were found to be more anxious and depressed.[10-14] These findings combined led to the hypothesis that higher disability is associated with higher levels of anxiety or depression in patients with MS, which in consequence may affect QoL. This hypothetical model, in which anxiety and depression are intermediate factors in the relationship between disability status (EDSS) and QoL, as measured by the SF-36, is depicted in Figure 1.

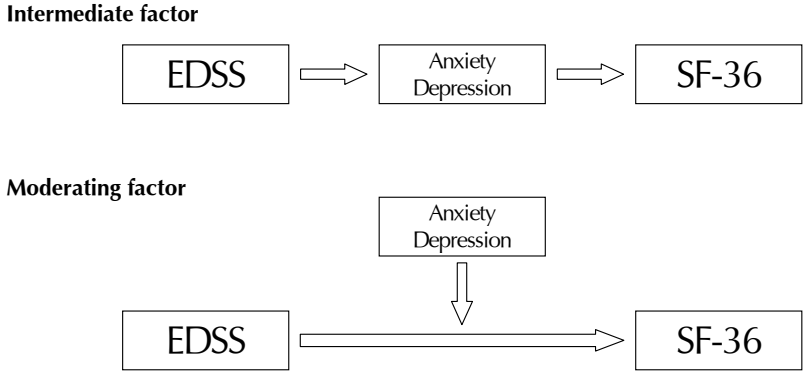

Figure 1 Schematic presentation of anxiety and depression as intermediate or moderating factors of the relation between disability status (EDSS) and quality of life (SF-36).

On the other hand, it can be argued that disability status may have a stronger impact on QoL when patients are anxious or depressed. In this alternative hypothesis, anxiety and depression moderate the relationship between disability status and QoL (Figure1). As QoL is increasingly recommended as an outcome measure in clinical trials and intervention studies,[1,3,4,8,9,15] it is important to understand the role of factors that may strengthen the impact of physical limitations on QoL. In our cohort of recently diagnosed patients with MS, we investigated whether anxiety and depression alter the relationship between disability status and health-related QoL.

Methods

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam) in the period of March 1999 – December 2000. Patients were eligible if they were diagnosed with definite or probable MS based on the criteria of Poser[16] within two years before study entry, were between 18 and 55 years old and had signed informed consent. Diagnoses were verified by senior neurologists of the academic hospitals. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate in the study. Patients who declined participation mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine patients declined without additional comments and four never responded to our reminders. Patients underwent a neurological examination and filled out questionnaires. The study protocol was approved by the medical ethical committees of the participating hospitals.

Measurements

Functional limitations were assessed by trained physicians of the Erasmus MC and VU Medical Center following a standardized research protocol. Functional limitations were rated on the Expanded Disability Status Scale (EDSS). The EDSS ranges from 0.0 (no disability) to 10.0 (death due to MS).[17] None of the patients were hospitalized at the time of data collection. Assessments of the EDSS were postponed when patients experienced a relapse at the scheduled examination.

Health-related QoL was assessed using the SF-36.[18] The SF-36 is a commonly used and well-validated instrument comprising four physical health (physical functioning, role-physical functioning, bodily pain and general health) and four mental health scales (vitality, social functioning, role-emotional functioning and

mental health). In the SF-36, role-physical functioning refers to the interference of physical limitations with daily activities and work and role-emotional functioning refers to the interference of emotional problems on activities of daily life. The general health scale assesses the overall evaluation of the patient's health status. For each SF-36 scale, the items are summed and transformed into scores between 0 (poor health) and 100 (optimal health). Patients returned their questionnaires at the neurological examinations where they were asked to fill in missing values, if any. Therefore, the percentage of missing values at individual scales was low (< 3%). In this population, internal consistency reliability of the SF-36 scales was high[19] with Coefficient α ranging from 0.74 to 0.94.

Anxiety and depression were assessed by the two 7-item scales of the Hospital Anxiety and Depression Scale (HADS).[20,21] The HADS is a validated self-report screening scale developed for use in medical settings that indicates the presence of anxious or depressed states. The anxiety and depression scales range from 0-21 with high scores reflecting more symptoms of anxiety or depression. A total HADS score is obtained by summation of the anxiety and depression scores. Scores between 8 and 10 are considered clinically borderline and 11 or higher are considered clinically definite levels of anxiety and depression.[20] In this study, internal consistency reliability for the HADS was high: Coefficient α was 0.83 for the anxiety and 0.81 for the depression scale. Depression and anxiety were strongly correlated ($r = 0.66$, $p < 0.001$).

Statistical analysis

Mean scores of the SF-36 and median score of EDSS were compared between patients with high and low levels of anxiety and depression. These groups were defined by the median score of the total HADS. Differences between patients with lower (total HADS < 8) and higher (HADS ≥ 8) anxiety and depression were tested using t-test (SF-36) and Mann-Whitney U test (EDSS).

Next, we performed a series of regression analyses to investigate the role of EDSS, anxiety and depression as well as their interaction in relation to QoL (SF-36). 'Unadjusted' coefficients were calculated by separate regression analyses of EDSS, anxiety and depression with each SF-36 scale, including only age and sex in the model. Adjusted coefficients were obtained by simultaneous analysis of EDSS, anxiety and depression. In these analyses, anxiety and depression were included as continuous variables. Then, two strategies were followed to determine whether anxiety and depression alter the relationship between EDSS and QoL. First, we examined whether anxiety and depression were an intermediate step in the relation between EDSS and QoL. This was evaluated by comparing the unadjusted

and adjusted regression coefficients of EDSS. When regression coefficients for EDSS are no longer significant after adjustment, anxiety or depression are likely intermediate factors in the relationship between disability status and QoL. Second, we examined whether depression and anxiety modify the relationship of EDSS and QoL. For this purpose, we evaluated interaction effects by comparing the strength of association between EDSS and SF-36 in patients with high and low levels of anxiety and depression. These groups were defined by median split of the total HADS scores. Further, differences in the strength of the associations were tested for significance by adding interaction effects in the models specified above. P-values of 0.05 and lower were considered statistically significant.

Results

The mean age of the patients was 37.5 years (SD 9.5) and 70% were women. Ninety percent of the patients were diagnosed with definite MS and 10% with probable MS. The mean time since diagnosis was 7.8 months (median 5.1, SD 6.5) and the mean time since first symptoms was 3.7 years (median 2.1, SD 4.6). EDSS scores ranged from 0.0 to 7.0 (median 2.5). The majority of the patients (75%)

Table 1 Comparison of quality of life, depression, anxiety and EDSS between patients with low and high levels of anxiety and depression

		Anxiety and depression		
	Total (n = 98)	Low (n = 42)	High (n = 56)	p
Quality of life (SF-36)				
Physical health				
Physical functioning	68.8 (25.9)	80.6 (18.2)	59.6 (27.3)	< 0.001
Role-physical functioning	49.2 (41.3)	69.1 (35.7)	34.4 (39.2)	< 0.001
Bodily pain	75.4 (23.0)	84.4 (19.4)	68.7 (23.3)	< 0.001
General health	49.1 (19.4)	56.1 (16.6)	43.9 (19.8)	0.002
Mental health				
Vitality	52.5 (18.2)	60.2 (15.4)	46.6 (18.0)	< 0.001
Social functioning	77.2 (23.3)	86.9 (18.3)	69.9 (24.1)	< 0.001
Role-emotional functioning	73.0 (35.9)	86.9 (25.4)	62.5 (39.2)	< 0.001
Mental health	72.7 (16.2)	81.5 (11.4)	66.1 (16.2)	< 0.001
Depression (HADS)	3.7 (3.2)	1.2 (0.8)	5.6 (3.1)	-†
Anxiety (HADS)	6.6 (4.1)	3.4 (1.5)	8.8 (3.9)	-†
EDSS (median)	2.5	2.5	3.0	0.002

Values are means (SD) unless otherwise indicated. P-values are based on t-test or Mann-Whitney U (EDSS). High and low anxiety and depression are defined by a median split of the total HADS score (see Methods). † Not relevant.

were still employed. Ten patients were on interferon treatment and one patient was treated for depression. Table 1 presents mean scores of QoL, depression and anxiety. QoL was significantly poorer among patients who reported more symptoms of anxiety or depression. These patients also had significantly higher EDSS scores than patients with low anxiety and depression scores (median 2.5 versus 2.0, $p = 0.002$). Thirty-four percent of the patients had clinically relevant levels of anxiety (scores ≥ 8) and 10% of depression. SF-36 QoL, anxiety, depression and EDSS did not differ between patients recruited through the three different hospitals ($p > 0.20$). Patients who used interferon treatment had similar anxiety, depression and SF-36 scores compared to patients who did not use medication, except that they reported poorer role-physical functioning (mean 15.0 versus 53.1, $p < 0.001$).

Table 2 shows the relation of EDSS, anxiety and depression with QoL as assessed by the physical health scales of the SF-36. The negative coefficients indicate that a higher EDSS and more symptoms of depression and anxiety were associated with poorer QoL. In the unadjusted analyses, EDSS, depression and anxiety were significantly correlated to all four SF-36 physical health scales ($p < 0.01$). When including EDSS, anxiety and depression simultaneously in the model, EDSS remained significantly related to physical functioning ($\beta = -0.64$, $p < 0.001$), role-physical functioning ($\beta = -0.24$, $p = 0.03$) and bodily pain ($\beta = -0.33$, $p = 0.002$), but was no longer associated with general health ($\beta = -0.09$, $p = 0.40$). Depression was the only significant determinant of general health, and was further associated with role physical functioning and bodily pain.

EDSS, depression and anxiety were also significantly associated with each of the SF-36 mental health scales in the unadjusted analyses (Table 3). When including all three predictors simultaneously in the model, EDSS was not

Table 2 Relationship between EDSS, depression, anxiety and SF-36 physical health scales

	SF-36 Physical health							
	Physical functioning		Role-physical functioning		Bodily pain		General health	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
EDSS	-0.70***	-0.64***	-0.43***	-0.24*	-0.46***	-0.33**	-0.26**	-0.09
Depression	-0.45***	-0.11	-0.53***	-0.38**	-0.43***	-0.21*	-0.41***	-0.24*
Anxiety	-0.31***	-0.05	-0.35***	-0.05	-0.31***	-0.09	-0.35***	-0.17

Values are standardized regression coefficients (β). In the 'unadjusted' analyses, each variable was entered separately, with adjustment for age and sex only. In the 'adjusted' analyses, EDSS, depression, anxiety, age and sex were entered simultaneously. Negative β's indicate that higher EDSS and more symptoms of depression or anxiety are related to poorer QoL or more (bodily) pain. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3 Relationship between EDSS, depression, anxiety and SF-36 mental health scales

	SF-36 mental health							
	Vitality		Social functioning		Role-emotional functioning		Mental health	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
EDSS	-0.34***	-0.14	-0.37***	-0.13	-0.32**	-0.14	-0.37***	-0.09
Depression	-0.51***	-0.37**	-0.57***	-0.39**	-0.45***	-0.15	-0.64***	-0.41***
Anxiety	-0.37***	-0.12	-0.43***	-0.18	-0.43***	-0.32**	-0.53***	-0.28**

Values are standardized regression coefficients (β). In the 'unadjusted' analyses, each variable was entered separately, with adjustment for age and sex only. In the adjusted analyses, EDSS, depression, anxiety, age and sex were entered simultaneously. Negative β's indicate that higher EDSS and more symptoms of depression or anxiety are related to poorer QoL. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

significantly associated to the mental health dimensions of QoL (see adjusted analysis in Table 3). This finding suggests that the relation between EDSS and the SF-36 mental health scales, observed in the unadjusted analyses, was for a large part explained by the relation of EDSS with anxiety and/or depression. In the adjusted analyses, depression remained significantly associated to three SF-36 mental health scales (vitality, social functioning and mental health), while anxiety remained significantly associated to two scales (role emotional functioning and mental health).

Although the association between EDSS and SF-36 physical health scales was independent of anxiety and depression, these factors may still modify the relationship between EDSS and these SF-36 scales. Therefore, we compared the relationship of EDSS and SF-36 between patients with high and low levels of anxiety and depression. Figure 2 shows that the relationship between EDSS and SF-36 physical functioning, role-physical functioning and bodily pain was stronger in patients with higher scores of anxiety or depression. Moreover, the relation of EDSS with SF-36 role-physical functioning and bodily pain was significant only in patients with high total HADS scores ($p < 0.001$), but was not significant in those with lower levels of anxiety and depression. This suggests that more feelings of anxiety and depression strengthen the association between disability status and these SF-36 physical health scales. When testing for the statistical significance of the interaction effects only the relation between EDSS and the SF-36 physical functioning scale differed significantly between patients with high and low total HADS scores (β for interaction term = -0.59, $p = 0.05$). The standardized regression coefficients for the interaction terms for SF-36 role-physical functioning (β interaction = -0.43, $p = 0.32$) and bodily pain (β interaction = -0.65, $p = 0.13$)

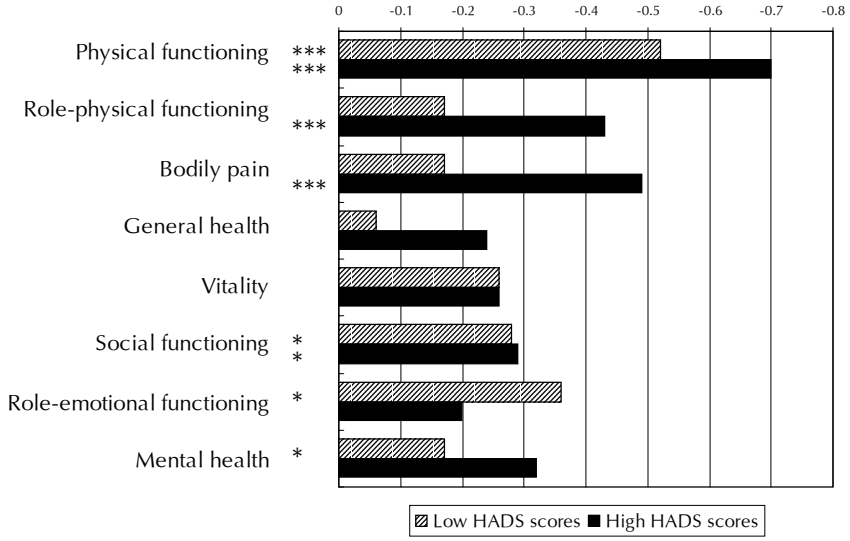

Figure 2. The relation between EDSS and SF-36 scores in groups with low and high levels of anxiety and depression

Values are standardized regression coefficients (β), adjusted for age and sex. High and low anxiety and depression are defined by median split of the total HADS scores (see Methods).

scale were not statistically significant. Further, as patients with high levels of anxiety or depression also had higher EDSS (Table 1), it is important to rule out that a difference between these two groups could be explained by a non-linear relationship of EDSS with the SF-36. Examination of the residuals scatterplots of EDSS with each of the SF-scales did not show evidence for a non-linear relationship (data not shown). This means that the regression coefficients of the high and low anxiety and depression groups would have been equal when there was no effect modification.

Discussion

In this cohort of patients with a recent diagnosis of MS, we found that disability status (EDSS), depression and anxiety were significantly associated with all SF-36 scales. Yet, after adjustment for anxiety and depression, we found that EDSS was only significantly related to the SF-36 physical functioning, role-physical functioning and bodily pain scales. The association of EDSS with these SF-36 scales was higher among patients who reported more symptoms of anxiety or depression. EDSS was not significantly associated with the mental health scales after adjustment for anxiety and depression.

Before interpreting the results, three methodological issues need to be discussed. The first point concerns the overlap in the measurement of several study variables. In our study, there was a high correlation between EDSS and the SF-36 physical functioning scale (r = -0.73). This means that EDSS explained much (54%) but not all of the variance of the scale suggesting that other determinants were involved. An important difference between the instruments is that the EDSS aims to assess the objective clinical status, whereas the SF-36 is a subjective evaluation of physical functioning by the patient. The latter is also determined by other factors such as illness intrusiveness[10] and mood [9,11]. A similar point concerns the overlap between the assessment of anxiety and depression and the SF-36 mental health scale. This SF-36 scale comprises questions that may reflect anxious and depressed mood. In line with previous findings,[22] we found that the correlation of the SF-36 mental health scale with depression (r = -0.60) and anxiety (r = -0.57) was substantial. But again, anxiety and depression did not entirely explain the variance in this SF-36 mental health score (42%), suggesting that other factors played a role.

The second point concerns our study of interaction effects between EDSS and total HADS scores. We only found evidence for a significant interaction effect for the SF-36 physical functioning scale. Although the standardized regression coefficients (β) of the other interaction effects were comparable and were higher than the coefficients of the main effects included in the model, they were not statistically significant. This suggests that the study may have been too small to demonstrate significant interaction effects. This is likely because large studies are needed to examine interaction effects with sufficient statistical power.[23] However, due to the small sample size, we can also not exclude a false positive interaction effect in SF-36 physical functioning. Our findings on the moderating effect of anxiety and depression remain to be replicated in future studies.

A third methodological issue is the cross-sectional design of this study, which limits the interpretation of relationships in terms of causality. Together with theoretical considerations and findings of previous studies, cross-sectional studies can only point to causal pathways, but not prove them. In previous studies, disability status has generally been modeled as a predictor of emotional well-being[10-14] and QoL.[1-10] Also, anxiety and depression have been analyzed as determinants of QoL,[9,11] rather than vice versa. The view that anxiety and depression depend on disability status and determine QoL has led us to examine whether anxiety and depression mediate or moderate the relationship between disability status and QoL (see Figure 2).

Our study differs in two aspects from those previously conducted on health-related QoL in patients with MS. First, we have studied the interrelation between

disability status, anxiety and depression as well as their joint and independent effects on QoL. Second, we have only included patients who were diagnosed with MS no longer than two years before study entry. These patients have relatively mild disability and will still be coping with the diagnosis of this chronic unpredictable disease. In this cohort, we found that patients with more physical limitations reported poorer QoL on all SF-36 scales, including those assessing mental health. These findings are in line with several previous studies,[1-3] but in contrast with studies that only found a significant relation of EDSS with the physical dimensions of QoL and not with mental health dimensions.[4-6,8,9]

The two important findings of this study result from the simultaneous analysis of EDSS, anxiety and depression. The first finding is that the associations of EDSS with the SF-36 mental health scales and the general health scale were not significant after adjustment for anxiety and depression. This is compatible with the hypothesis that anxiety and depression are intermediate factors in the relation between EDSS and these SF-36 scales. That is, higher levels of disability lead to increased feelings of anxiety and depression, which subsequently lower the self-reported quality of mental health. An important question, still to be answered, is whether anxiety and depression actually lower QoL or bias the evaluation of QoL in that depressed patients perceived themselves as more disabled.

The second important finding is that our study suggests that anxiety and depression modify the negative effect of disability status on three out of four physical health scales of the SF-36. The relationship of EDSS with physical functioning, role-physical functioning and bodily pain was stronger in patients with more symptoms of anxiety or depression, albeit that the interaction effects reached statistical significance for only one scale. Although findings remain to be confirmed, our study suggests that in patients with more symptoms of anxiety and depression, physical limitations may have a greater impact on the quality of physical health as assessed by the SF-36. A possible explanation is that anxiety and depression impede coping with physical limitations and therefore result in a diminished QoL on these scales.

In this study, we did not consider the role of fatigue. As several studies have demonstrated significant associations of fatigue with EDSS, depression and QoL in MS,[9,24-26] fatigue could represent another intermediate factor in the relationship between disability status and QoL. In our patients, we assessed the frequency of fatigue symptoms on a four-point scale (often, frequently, seldom, never). Although the scale was not validated, we explored a possible confounding role by repeating the analyses presented in Tables 2 and 3 including fatigue in the model. There were no major changes in the association of EDSS, anxiety and depression with

QoL, except that the strength of the relationship between depression and SF-36 vitality was markedly lower (B = 0.24, p = 0.05). Fatigue significantly added to the prediction of SF-36 role-physical functioning and general health scores, but not in the other scales. These findings suggest that fatigue does not explain the relationship between EDSS, anxiety and depression on the one hand, and QoL on the other.

In conclusion, we found that disability status as measured by the EDSS is an important determinant of QoL in patients with a recent diagnosis of MS. Our data were compatible with the hypothesis that anxiety and depression are intermediate factors in the relation of EDSS with the SF-36 mental health scales and the general health scale, and may moderate the relation between EDSS and the SF-36 physical health scales. Improvement in QoL in therapeutic studies may depend on the patient's level of anxiety and depression. It is therefore important to assess symptoms of anxiety and depression when studying QoL as an outcome measure in clinical trials or other intervention studies.

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6

EXPECTATIONS OF WHEELCHAIR DEPENDENCE IN RECENTLY DIAGNOSED PATIENTS WITH MULTIPLE SCLEROSIS AND THEIR PARTNERS

Abstract

The aim of the present paper was to quantify expectations of wheelchair dependence in patients recently diagnosed with MS (n=101) and their partners (n=78). Expectations focused on the risk and seriousness of becoming wheelchair-dependent in two years, ten years or lifetime. Expectations were compared with natural history data, compared between patients and their partners, and related to clinical characteristics. Our results show that patients overestimated their 2-year and 10-year risks of wheelchair dependence, but underestimated their lifetime risks. A large number of patients were uncertain about their 2-year risk, even those with no or only minimal disability (EDSS < 3.0). One-third of the patients perceived the 10-year and lifetime risk to be 50%, which, as they explained in the interviews, reflected their uncertainty: they did not know what to expect – it might happen or it might not. Patients with more functional limitations had higher perceptions of risk, but lower perceptions of seriousness. Concordance in perceived risk and seriousness between patients and partners was moderate. The overestimation of the short-term risks and the substantial differences in expectations within couples warrant further research on the impact of expectations on their treatment decisions and psychological well-being.

Introduction

Patients with multiple sclerosis (MS) face enormous prognostic uncertainty as the disease is characterized by an unpredictable variation in symptoms, severity and progression.[1] While aware of the serious consequences of their disease, patients cannot be informed about their personal prognosis. This uncertainty may disrupt their psychological well-being,[2-4] and may particularly be a problem for newly diagnosed patients.[5] MS affects young individuals between 20 and 40 years of age. At these ages, people are making decisions about relationships, family planning and career that have important implications for their lives. As these decisions cannot be based on clinical prognostic information, patients' expectations of disease progression will play a major role.

Expectations of the risk of future health states have frequently been studied in other medical areas, such as prenatal testing,[6] presymptomatic genetic testing,[7,8] surgery,[9] and preventive medicine.[10,11] However, studies on expectations of prognosis, or perception of *prognostic* risk, are still scarce. We know of one study that described perceived risk of major consequences of type 1 diabetes mellitus. This study showed that patients considerably overestimated their 20-year risks of end state renal disease, amputation and blindness.[12] In MS, patients' expectations have only been studied with regard to the benefits of treatment. This study demonstrated that patients who had unrealistic expectations about the possible improvement in functional status showed poorer adherence to treatment.[13]

The aim of our study was to quantify expectations of prognosis in patients recently diagnosed with MS and their partners. We focused on the risk of wheelchair dependence, as this is one of the major and most recognized consequences of the disease by patients. We intended to answer the following questions: (1) Do recently diagnosed MS patients expect to become wheelchair-dependent in the short, medium or long term? (2) How serious do they consider it is to become wheelchair-dependent? (3) Do expectations differ between patients and their partners? (4) Are expectations about the risk and seriousness of wheelchair dependence related to clinical characteristics?

Methods

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam) in the period of March 1999 – December 2002. Patients were eligible if they were diagnosed with definite or probable MS[14] within two years before entry in the study, were between 18 and 55 years old, and

had given informed consent. Patients with serious comorbidity of other neurological or systemic diseases, or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate. Patients who declined participation mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine others declined without additional comments and four never responded to our reminders. Ninety out of 101 patients had a partner, of whom 78 (87%) did participate. Two partners did not speak Dutch, six were not living with the patient and for that reason not invited by the patient, and four refused for unknown reasons.

Patients underwent a neurological examination, filled out questionnaires and were interviewed. The questionnaires were sent one week before the neurological examination and had to be completed before the interview, which was scheduled one week after the examination. Interviews were carried out by the first author at the patient's home. Partners received their questionnaires before the patient's interview and were asked to complete these in another room. This procedure was chosen to control separate completion of the questionnaires by patients and partners in order to assess their expectations independently. The study protocol was approved by the medical ethical committees of the participating hospitals.

Measurements

Expectations. We assessed patients' expectations with regard to the risk and seriousness of becoming wheelchair-dependent as a consequence of the disease.[15] Wheelchair dependence was defined as the inability to walk beyond five meters. This definition equals a score of 7.0 on the Expanded Disability Status Scale (EDSS).[16] The risk of wheelchair dependence was measured for the short (two years), medium (ten years) and long term (lifetime). Perception of risk was assessed using a 100mm visual analogue scale (VAS) which ends were anchored at 'Definitely not' (0%) and 'Definitely' (100%). The VAS is a widely-used instrument for the quantification of subjective phenomena including attitudes, pain, discomfort and perception of risk.[17,18] Actual risks were derived from epidemiological data and estimated to be 5-10% for the 2-year risk, 20-25% for the 10-year risk and 70-80% for the lifetime risk.[19] In a population of 800 patients the 10-year risk was calculated 24% (G.C. Ebers, MD, PhD, unpublished data, 2001), which confirmed our estimation. Further, patients were asked for each time period how serious they think it is to be wheelchair-dependent by that time. Answers were given on a VAS anchored at 'Not serious at all' (0) and 'The most serious thing I can imagine' (100). Partners completed the same questions. In the interview, patients were asked to explain their perception of the 10-year risk. These

explanations were transcribed verbatim and independently evaluated by two psychologists (CJ and JdB). Similar explanations were grouped together in categories, and categories were labeled. Differences between the categorizations of the two psychologists were discussed with a third (JP), until a final categorization was reached by consensus. To determine differences in the use of specific explanations between groups, we created a variable for each category. This variable was coded 1 when an explanation of the patient was assigned to the category, and 0 if not. Patients could give multiple explanations. Interview data were available for 80 out of 101 patients.

Clinical data. The neurological examinations were assessed by physicians from the academic hospitals following a standardized research protocol. Functional limitations were rated on the EDSS,[16] which ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS). Date of first symptoms was assessed during the neurological examination. Date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the medical records.

Statistical analysis

Differences in means of perceived risk and seriousness between patients and partners were analyzed using the paired t-test. To determine the degree of concordance in perception of risk and seriousness *within* pairs, we calculated the absolute differences between patient and partner scores. Perceptions of patients and partners were considered concordant when the absolute difference between the VAS scores was lower than 20, partially discordant when the difference was between 20 and 39, and fully discordant when the difference was 40 or higher. To determine the relationship with clinical characteristics, we calculated Spearman's rank correlations between perceived risk and seriousness, time since diagnosis, time since first symptoms and EDSS. The relationship of perceived risk and seriousness with EDSS was further investigated by comparing two groups and tested using the independent samples t-test. These groups were defined by the patient's EDSS score, combining no to minimal disability (EDSS < 3.0) and moderate to severe disability (EDSS ≥ 3.0).[16] Frequencies of coded explanations of the perceived 10-year risk were compared between subgroups using Fisher's exact test.

Results

Description of subjects

Mean age of the patients was 37.5 years (SD 9.5) and 70% were women. Ninety percent was diagnosed with definite and 10% with probable MS. Mean time since

diagnosis was 7.8 months (SD 6.5) and mean time since first symptoms 3.7 years (SD 4.6; median 2.1). EDSS scores ranged from 0.0 to 7.0. Median EDSS score was 2.5. Mean age of the partners was 39.3 years (SD 8.7) and 64% were men.

Perceived risk and seriousness of wheelchair dependence of patients

Mean perception of the 2-year risk of wheelchair dependence was 22.5% (SD 21.2), of the 10-year risk 38.7% (SD 25.5) and of the lifetime risk 54.0% (SD 24.6). These means were higher than the actual 2-year (actual risk 5-10%) and 10-year risks (actual 20-25%) and lower than the actual lifetime risk (actual 70-80%). The distributions of the perceived 2-year, 10-year and lifetime risk of wheelchair dependence are presented in Figure 1. Figure 1a shows that the majority of patients (82%) thought the risk to become wheelchair-dependent within two years was lower than 50% (VAS-scores 0-45). Twenty-eight percent thought it highly unlikely that they would need a wheelchair within two years (VAS 0-5), while 54% was less certain about this (VAS 6-45). Figure 1b shows that half of the patients (48%) thought the risk to become wheelchair-dependent within a period of ten years less than 50%. One-third of the patients perceived the 10-year risk to be about 50% (VAS 46-55). This group stands out as a major isolated peak. Similar results were found for the perceived lifetime risk (Figure 1c), albeit that a smaller group (28%) thought the lifetime risk to be lower than 50% (VAS 0-45).

As was shown in Figure 1, one third of the patients perceived their 10-year or lifetime risk to be about 50% (VAS 46-55). When examining the interviews, these

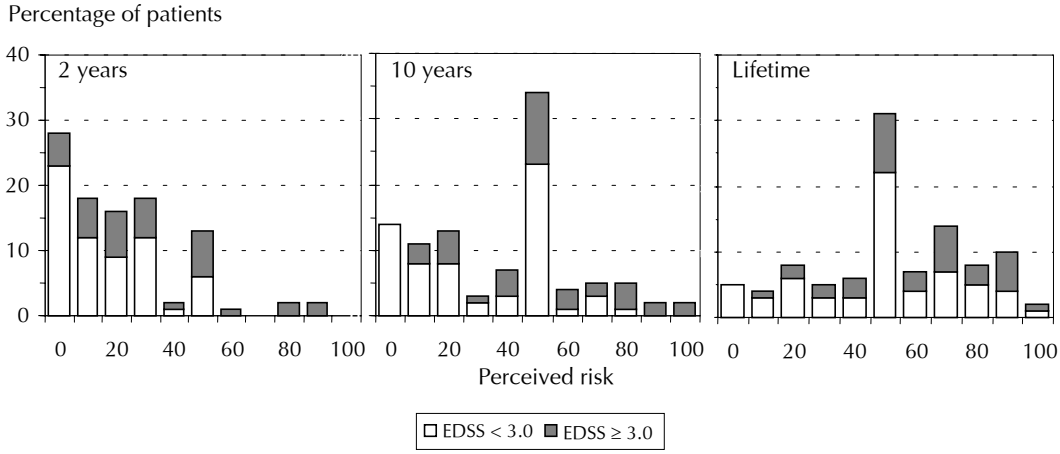

Figure 1 Perceived risk of wheelchair dependence of patients

Perceptions of risk (mm VAS) were recoded into 11 categories: 0-5 into 0, 6-15 into 10, and so on.

Table 1 Common explanations on perceived 10-year risk of 50%-responders in comparison with other patients

Explanation on perceived risk	Perceived 10-year risk		Relative frequency (95% CI)	p Value
	50% (n=30)	Other (n=50)		
"I don't know"	23 (77%)	10 (20%)	3.8 (2.1-6.9)	<0.001
"It might happen or not"	18 (60%)	1 (2%)	30.0 (4.2-213.4)	<0.001
Physical condition	10 (33%)	17 (34%)	1.0 (0.5-1.9)	0.95

Frequencies were compared between patients who gave a 50%-response and those who did not. A 50%-response was defined as a VAS-score between 46-55, whereas 'other' included patients with VAS-scores lower than 46 or higher than 55. Values indicate the number (%) of patients that mentioned the explanation in the interview. Multiple explanations were allowed. * Fisher's exact.

50%-responders significantly more often stressed their uncertainty. With regard to the 10-year risk (Table 1), explanations like "I don't know" (3.8 fold increase compared to others, $p < 0.001$) and "It might happen or might not happen" (30 fold increase compared to others, $p < 0.001$) were significantly more often used by 50%-responders. Peaks at 50% were found among patients with high and low EDSS and among partners (data not shown). Means of perceived risk were still higher than actual risks when 50%-responses (VAS 46-55) were excluded.

Mean perception of seriousness was slightly higher for the 2-year risk of wheelchair dependence (82.5, SD 19.7) than for the 10-year (74.5, SD 22.9) and lifetime risk (71.6, SD 24.0). These findings indicate that patients considered wheelchair dependence a serious consequence of their disease, particularly when it would happen within two years.

Differences between patients and partners

Mean perceptions of risk of partners did not significantly differ from that of patients ($p > 0.05$). Partners considered wheelchair dependence to be less serious than patients, but within-pair differences were significant only for the 2-year period (mean 73.6% versus 82.5%; p=0.05). Although differences in means were not significant, inspection of the data did show substantial differences within pairs at all time points: that is, patients had higher perceptions than partners in some couples, but lower in others. Analyses of absolute differences demonstrated that in approximately half of couples the differences in perceptions of risk and seriousness of patients and partners were less than 20 points on the VAS scales (Table 2). Fully discordant perceptions of risk (differences in VAS ≥ 40) were found in 14% of the couples and fully discordant perceptions of seriousness in 21%.

Table 2 Differences in perceived risk and seriousness of wheelchair dependence between patients and partners (n = 77 couples)

	Concordance (%)	Discordance (%)	
		Partial	Full
Difference in VAS scores:	0 - 19	20-39	≥ 40
Perceived absolute risk			
2-year	55	31	14
10-year	59	27	14
Lifetime	57	27	16
Perceived seriousness			
2-year	57	22	21
10-year	49	31	20
Lifetime	54	25	21

Correlation with clinical characteristics

Patients with more functional limitations perceived themselves to be at higher risk of wheelchair dependence (Figure 2). The relation between perceived risk and EDSS was stronger for the shorter periods than for the lifetime risk: the correlation of EDSS with perceived 2-year risk was 0.48 ($p < 0.001$), perceived 10-year risk 0.50 ($p < 0.001$) and perceived lifetime risk 0.26 ($p = 0.01$). Perceptions of risk were also significantly higher among partners of patients with more functional limitations compared to partners of patients with EDSS < 3.0 ($p < 0.04$; Figure 2). Perceived seriousness of wheelchair dependence was inversely related to EDSS only in patients: patients with *more* functional limitations evaluated wheelchair dependence to be less serious ($p < 0.01$). No relation between perceived seriousness and EDSS was seen in partners. Neither in patients nor partners, perceptions of risk and seriousness were related to sex, age, diagnostic certainty (definite versus probable MS), time since diagnosis and time since first symptoms (data not shown).

Discussion

Our study demonstrated that patients recently diagnosed with MS overestimated their 2-year and 10-year risks of wheelchair dependence, and underestimated their lifetime risks. A large number of patients were uncertain about their 2-year risk, even those with no or minimal disability. This uncertainty was even more predominant in medium- and long-term expectations. Patients with more functional limitations had higher perceptions of risk, but lower perceptions of

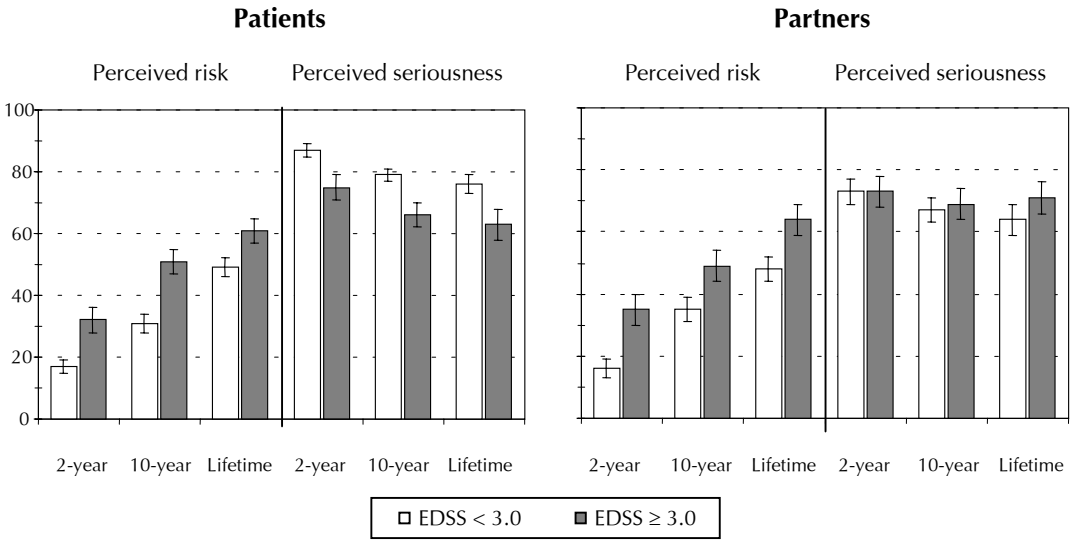

Figure 2 Means (SE) of perceived risk and seriousness of wheelchair dependence by EDSS

seriousness. Concordance in perceived risk and seriousness between patients and partners was moderate.

Before interpreting the data from a clinical perspective, three issues remain to be elucidated. First, we found that perceived risks were not related to clinical parameters such as time since diagnosis, time since onset of symptoms and diagnostic certainty (definite or probable MS). A point of consideration is that all patients were diagnosed within two years prior to inclusion. This means that there was limited variation in the time since diagnosis and time since first symptoms of our patients. Further, we intended to include patients with definite and probable MS to investigate the impact of diagnostic certainty, but could include only ten patients with probable MS. This small number implies that the findings of this study are primarily generalizable to patients recently diagnosed with definite MS.

Second, for studying differences between patients and partners, it is important that they completed their questionnaires separately. We arranged this by asking partners to fill in their questionnaires while the patients were interviewed. Nevertheless, we cannot completely rule out that partners had discussed and retained the patients' results prior to completion of their own questionnaires. If partner responses had been biased, differences in expectations between patients and partners were more likely underestimated rather than overestimated.

Third, up to one-third of the participants perceived their 10-year and lifetime risk about 50%. Our interview data confirmed that these 50%-responses primarily

reflected patients' uncertainty about prognosis, rather than their belief that the risk was about 50%.[20] The question that remains to be answered is *why* uncertainty elicits 50%-responses. First of all, participants who have absolutely no idea what to expect may perceive the risk of wheelchair dependence to be equal to the risk of not becoming wheelchair-dependent, as explained in the interview as 'it might happen or it might not'. Second, 50% is a neutral response that will be justifiable whatever happens.[21] Patients who do not expect to become wheelchair-dependent may prefer this neutral answer to prevent future disappointment, whereas for those who do expect to become wheelchair-dependent, it is the most optimistic answer that is not yet unrealistic. Finally, the 50%-response may be an escape for whom thinking about consequences of MS is too threatening. From a clinical point of view, it may be relevant to distinguish between these underlying motivations, because they are informative on how patients deal with uncertain future consequences.

Patients with more functional limitations evaluated their risks of wheelchair dependence to be higher than did patients with fewer limitations, while at the same time, they considered wheelchair dependence as less serious. The first results suggest that patients extrapolate present functional limitations into expectations of future disease progression. This may be justified for expectations of short-term disease progression, but less so for the long term. The unpredictable and uncertain course of MS implies that this early period after diagnosis is not representative for the long-term disease course. Second, the fact that patients with higher disability evaluated wheelchair dependence to be less serious may be explained by the fact that differences in disability status alter the need and significance of a wheelchair, and hence change the criteria to evaluate its seriousness.[22,23] Patients who are limited in walking may value the need of a wheelchair as an increase of mobility, whereas others who are fully ambulant view wheelchair dependence as a major step backwards. This shift in criteria is characteristic for accommodative coping processes, which enable patients to maintain positive outlooks in situations of increasing functional limitations.[24,25]

Comparison of mean perceptions of risk and seriousness revealed no significant differences between patients and partners. However, we found considerable discordance in perceptions within couples, which implies that patients had higher perceptions than their partners in some couples, but lower in others. Previous studies have also demonstrated poor agreement between spouses in the judgment of quality of life of patients with metastatic cancer[26] and in the assessment of behavioral risk factors of healthy workers.[27] Further research is needed to investigate the consequences of discordant expectations for the

relationship between patients and partners focusing on their communication, mutual support, future plans and well-being.

Natural history data showed that the 'actual' 2-year risk of EDSS 7.0 after diagnosis is approximately 5-10%.[19] In our study, this was overestimated by patients (mean VAS score 23%) and their partners (mean 25%). They also overestimated the 10-year risk ('actual' risk 20-25%), but underestimated the lifetime risk ('actual' risk 70-80%) as compared with natural history data.[19] These biases in perceptions were found in patients with low EDSS (< 3.0) and high EDSS (≥ 3.0). These findings raise the question whether and how their perceptions of prognostic risks can be improved in a clinical setting. For this purpose, it is important to know what factors influence perception of risk. The present study showed that perception of risk was related to disability status, suggesting that patients' expectations were determined by their experience of symptoms. This means that for patients it is important to learn the difference between common symptoms and MS-related symptoms, which may not be easy in the early phase. Another factor that will determine patients' expectations is the information they receive about MS. Particularly in uncertain and unpredictable diseases as MS, patients may rely on the information that is provided by neurologists and other health professionals. A point of consideration is that information is also increasingly obtained from the Internet. Notwithstanding that this is a valuable source of facts and figures about the disease, patients may not be able to judge what certain information means for their particular situation. To help in this interpretation, it is important that neurologists discuss expectations of future disease progression, treatment benefits and other MS-related issues in the clinical consultation with patients and partners.

To our knowledge, this is the first paper on expectations of prognosis in patients with MS and their partners. Overall, patients overestimated their short-term risks of wheelchair dependence and underestimated the long-term risk, even those with low EDSS. Further research is needed to understand the impact of uncertainty and unfavorable perceptions of prognostic risk on psychological well-being, and the consequences of discordant expectations for the relationship between patients and their partners.

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7

PERCEPTION OF PROGNOSTIC RISK IN PATIENTS WITH MULTIPLE SCLEROSIS: THE RELATIONSHIP WITH ANXIETY, DEPRESSION AND DISEASE-RELATED DISTRESS

Abstract

Objectives: The aim of the study was to investigate the impact of perception of prognostic risk on anxiety, depression and disease-related distress in patients with multiple sclerosis (MS). **Method:** Perceived risk and perceived seriousness of the 2-year, 10-year and lifetime prognosis of wheelchair dependence, disability status (EDSS), disease-related distress (IES) and anxiety and depression (HADS) were assessed in 101 patients. **Results:** Patients with higher perceptions of 2-year, 10-year or lifetime risk were bothered by more intrusion of MS-related thoughts and feelings ($p < 0.01$). Only higher perception of the 2-year risk of wheelchair dependence was significantly related with higher levels of anxiety, depression and avoidance. Similarly, higher perception of the seriousness of wheelchair dependence was consistently associated with more intrusion and avoidance (IES), but only perceived seriousness of the 2-year prospect of wheelchair dependence was significantly correlated with anxiety and depression. All relations were independent of clinically assessed disability status. **Conclusions:** Perceptions of the *short-term* risk and seriousness of wheelchair dependence were significantly related to anxiety, depression and disease-related distress in patients with MS. These findings underscore the importance of informing patients with chronic disorders, such as MS, about the short-term prognosis of important long-term consequences of disease.

Introduction

Patients with multiple sclerosis (MS) experience considerable prognostic uncertainty.[1-4] The course of the disease is variable and unpredictable and can lead to serious consequences such as wheelchair dependence and cognitive decline. Patients often are aware of these disease prospects, but cannot be informed about what complications they themselves will develop. How patients perceive their risks of major disease complications may determine their decisions about treatment and future planning, and also affect their mental health. Studies in cancer and cardiovascular diseases showed that patients' expectations about treatment outcome and their general health condition – whether realistic or not – may enhance mental health when expectations are positive, but may have adverse effects when they are negative.[5-9] In MS, it has been demonstrated that patients who generally hold positive expectations in life reported less symptoms of depression.[6] The relation between expectations about *specific* disease consequences and mental health has not yet been studied in MS or in other chronic diseases. From a clinical perspective, this may be more relevant because health care professionals can discuss these specific consequences with patients, in order to adjust apparent unrealistic expectations. This may be particularly important in the early phase after diagnosis, when patients are in the need for information about the disease.

The aim of the present paper is to investigate the impact of perception of prognostic risk and seriousness on mental health, as assessed by anxiety, depression and disease-related distress in patients diagnosed with MS no longer than two years before study entry. We particularly focused on perception of the risk of wheelchair dependence, as this is one of the major and most recognized consequences of MS by patients. Since the impact of expectations on psychological outcomes may differ for prospects about the near or far future, we examined perception of the short (two years), medium (ten years) and long-term (lifetime) risk of wheelchair dependence.

Methods

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam) in the period of March 1999 – December 2000. Patients were eligible to participate in the study if they were diagnosed as having definite or probable MS[10] within two years before study entry, were explicitly informed about the diagnosis, were between 18 and 55 years old and had signed

informed consent. Diagnoses were verified by senior neurologists of the academic hospitals. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate in the study. Patients who declined participation mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine patients declined without additional comments and four never responded to our reminders. Patients underwent a neurological examination and filled out questionnaires. The questionnaires were sent one week before the neurological examination and had to be completed one week after the examination. The study protocol was approved by the medical ethical committees of the participating hospitals.

Measurements

Patients underwent a neurological examination following a standardized research protocol. Functional limitations were assessed by a trained physician, and rated on the Expanded Disability Status Scale (EDSS).[11] This scale ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS). None of the patients were hospitalized at the time of data collection. Assessments of the EDSS were postponed when patients experienced a relapse at the time of the scheduled examination. Date of first symptoms was registered together with the neurological examination, whereas date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the medical records.

Perception of prognostic risk was assessed for the short (2-year), medium (10-year) and long-term (lifetime) risk of wheelchair dependence. Wheelchair dependence was defined as the inability to walk beyond five meters, which equals a score of 7.0 on the EDSS.[11] Patients were asked to what extent they expected to become wheelchair-dependent for this distance within two years, ten years and lifetime. Perception of risk was assessed by marking a 100mm visual analogue scale (VAS)[12,13] from 'Definitely not' (0%) and 'Definitely' (100%). Next, patients were asked for each prognosis how serious they considered being wheelchair-dependent by that time. Perception of seriousness was scored on a VAS anchored at ‘Not serious at all’ (0) and ‘The most serious thing I can imagine’ (100).

Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS).[14] This scale has been reviewed as a reliable and valid instrument for assessing anxiety and depression in patients with various diseases.[15] The anxiety and depression scales range from 0-21 with high scores indicating higher levels of anxiety and depression. Internal consistency reliability was high in our study:[16] coefficient α was 0.83 for the anxiety and 0.81 for the depression scale. Scale scores of 8 and higher indicate a high risk of anxiety and depressive

disorder.[14] Disease-related distress was assessed using the Impact of Event Scale (IES).[17] This questionnaire addresses psychological distress by focusing on the intensity of thoughts and feelings that relate to specific negative events or concerns, in this study being diagnosed with MS. Though designed to assess the impact of traumatic events, the scale has been also used to assess the psychological burden of being at high risk of hereditary prostate cancer and breast cancer.[18-20] The questionnaire comprises two scales: intrusion (range 0 – 35) and avoidance (0 – 40). Intrusion refers to the degree of being overwhelmed by thoughts and feelings about MS. Items include 'Any reminder brought back feelings about it' and 'I had dreams about it'. Avoidance refers to tendency to keep off these thoughts and feelings and is measured by items such as 'I tried not to think about it' and 'I stayed away from any reminders of it'. In our study, coefficient α was 0.82 for the intrusion scale and 0.75 for the avoidance scale. Intrusion and avoidance are positively correlated.[21] Although this seems paradoxical, avoidance can be thought of as a way of coping with high levels of intrusive thoughts: if disease-related thoughts and feelings are too disturbing, patients may restore emotional equilibrium by avoidance.

Statistical analysis

Spearman correlations were computed to examine the crude association of disability status (EDSS) with psychological outcomes and perceived of risk and seriousness of wheelchair dependence. Differences in perceived risk, perceived seriousness and mental health between the two academic hospitals and the non-academic hospitals were tested using ANOVA. To investigate the relationship of perceived risk and seriousness with psychological outcomes, we performed a series of multiple regression analyses with adjustment for disability status (EDSS), time since diagnosis, time since first symptoms, age and sex. These analyses were conducted for the 2-year, 10-year and lifetime prognosis separately. Results are presented as regression coefficients (B) with 95% confidence intervals. The correlation (ρ) between time since diagnosis and time since first symptoms was 0.19 so no problems of collinearity between these time variables were expected. Descriptive statistics demonstrated that the distributions of the main study variables were skewed. For multivariate regression analyses this does not need to be a problem if it can be assumed that the residuals of the analyses are normally distributed.[22] This is indicated by straight diagonals in the normal-probability plots. For all regression analyses, these scatterplots produced reasonably straight lines, so there was no compelling need to transform the distributions of the study variables. Finally, the relationship of perceived risk and perceived seriousness with

psychological outcomes were compared between groups with a high and low disability by evaluation of their interaction effects. These groups were defined by an EDSS cut-off score of 3.0 to make a distinction between no to minimal disability (EDSS 0-2.5) and moderate to severe disability (EDSS 3.0-10.0).[11] P-values lower than 0.05 were considered statistically significant.

Results

Characteristics of patients

Mean age of the patients was 37.5 years (SD 9.5) and 70% were women. Patients were diagnosed with definite MS (90%) or probable MS (10%), on average 7.8 months (median 5.1, inter-quartile range IRQ [2.4, 12.2]) before entry in the study. The median time since first symptoms was 2.1 years (IQR [1.1, 4.5], mean 3.7). EDSS-scores ranged from 0.0 to 7.0 (median 2.5). Fifty-nine patients were recruited through the Erasmus MC, 32 through the VU medical center and 10 through non-academic hospitals. Patients with more physical limitations had significantly higher perception of the 2-year, 10-year and lifetime risk of wheelchair dependence ($p < 0.05$), but considered wheelchair dependence to be less serious ($p < 0.007$; Table 1). Patients with higher disability reported significantly more symptoms of anxiety ($\rho = 0.24$, $p = 0.02$) and depression ($\rho = 0.43$, $p < 0.001$). Thirty-four percent of the patients had clinically relevant levels of anxiety and 10% of depression (HADS scores ≥ 8). They were also significantly more distressed, as indicated by the positive correlations of EDSS with intrusion ($\rho = 0.27$, $p = 0.006$) and avoidance ($\rho = 0.28$, $p = 0.005$). No significant differences in perceived risk, perceived seriousness and psychological well-being were observed between patients from the two academic centers and the hospitals within the region.

Expectations about wheelchair dependence and psychological distress

Table 2 shows regression coefficients (B) of the relationship between patients' perception of the risk and seriousness of wheelchair dependence and their levels of disease-related distress. After adjustment for disability status (EDSS), time since first symptoms, time since diagnosis, age and sex, we found that patients with higher perception of risk were bothered by more intrusion of MS-related thoughts and feelings ($p < 0.01$). This relationship was found for the 2-year, 10-year and lifetime risks of wheelchair dependence. In contrast, only higher perception of the 2-year risk was significantly associated with avoidance of MS-related thoughts and feelings ($B = 1.00$, $p = 0.03$). Patients who considered wheelchair dependence as more serious had higher levels of intrusion and avoidance ($p < 0.05$), irrespective whether this concerns the 2-year, 10-year or lifetime prognosis.

Table 1 Perception of risk and seriousness of wheelchair dependence and psychological outcomes: means and correlations with disability status (EDSS)

		Median [IQR]	Correlation with EDSS	
			ρ	p-Value
Prognosis of wheelchair dependence:				
Short-term expectations				
Perceived 2-year risk		20 [4, 33]	0.39	< 0.001
Perceived 2-year seriousness		90 [78, 97]	-0.32	0.001
Medium-term expectations				
Perceived 10-year risk		46 [16, 52]	0.42	< 0.001
Perceived 10-year seriousness		79 [66, 92]	-0.29	0.004
Long-term expectations				
Perceived lifetime risk		52 [44, 73]	0.20	0.05
Perceived lifetime seriousness		77 [66, 88]	-0.27	0.007
Psychological outcomes:				
Anxiety		5 [4, 9]	0.24	0.02
Depression		2 [1, 6]	0.43	< 0.001
MS-related distress:	Intrusion	8 [4, 15]	0.27	0.006
	Avoidance	9 [4, 17]	0.28	0.005

IQR = inter-quartile range; ρ = Spearman correlations.

Expectations about wheelchair dependence and anxiety and depression

Patients who thought it more likely to become wheelchair-dependent within two years showed increased levels of anxiety (B = 0.78, p < 0.001) and depression (B = 0.45, p = 0.007; Table 2), after adjustment for neurological status (EDSS), time since diagnosis, time since first symptoms, age and sex. Higher perception of the 10-year and lifetime risk was not significantly associated with more symptoms of anxiety or depression. Similarly, patients who considered wheelchair dependence within two years as more serious reported more symptoms of anxiety (B = 0.53, p = 0.02) and depression (B = 0.37, p = 0.02). Perceived seriousness of the 10-year and lifetime prognosis of wheelchair dependence was not significantly associated with these psychological variables. The findings on the relationships of perceived risk and seriousness with psychological well-being remained unchanged when only patients with definite MS were included in the analyses.

Comparison between high and low disability groups

To examine the differences between patients with high and low disability, mental health scores were plotted against perception of the 2-year risk (Figure 1) and seriousness of wheelchair dependence. Although patients with more physical

Table 2 Perceived risk and seriousness of wheelchair dependence in relation to disease-related distress, anxiety and depression

	Intrusion	Avoidance	Anxiety	Depression
Short-term expectations				
Perceived 2-year risk	1.16 **	1.00 *	0.78 ***	0.45 **
	[0.38, 1.94]	[0.05, 1.94]	[0.33, 1.23]	[0.12, 0.77]
Perceived 2-year seriousness	1.09 **	1.61 ***	0.53 *	0.37 *
	[0.32, 1.87]	[0.68, 2.55]	[0.08, 0.98]	[0.05, 0.69]
Medium-term expectations				
Perceived 10-year risk	1.04 ***	0.26	0.09	0.10
	[0.43, 1.64]	[-0.49, 1.00]	[-0.28, 0.47]	[-0.16, 0.36]
Perceived 10-year seriousness	0.76 *	1.31 ***	0.31	0.20
	[0.16, 1.37]	[0.58, 2.06]	[-0.07, 0.68]	[-0.06, 0.47]
Long-term expectations				
Perceived lifetime risk	0.78 **	0.00	-0.11	0.03
	[0.21, 1.35]	[-0.70, 0.70]	[-0.46, 0.24]	[-0.22, 0.27]
Perceived lifetime seriousness	1.02 ***	1.32 ***	0.32	0.21
	[0.44, 1.60]	[0.61, 2.03]	[-0.03, 0.68]	[-0.04, 0.46]

Intrusion refers to the degree of being overwhelmed by thoughts and feelings about MS, and avoidance to tendency to keep off these thoughts and feelings. Values are regression coefficients [95% confidence interval] representing the changes in scores per 10 points on the visual analogue scale. Coefficients are adjusted for disability status, time since first symptoms, time since diagnosis, age and sex. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

limitations had higher scores of all four mental health indicators, the difference was only significant for depression ($p = 0.002$). None of the interaction effects for perceived risk and seriousness with EDSS was statistically significant in the regression analyses ($p > 0.50$).

Discussion

This study demonstrates that patients with higher perception of the risk and seriousness of wheelchair dependence had higher levels of MS-related distress. This relation was found for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Yet, only perception of the 2-year risk and seriousness were related to anxiety and depression. All associations were independent of clinically assessed disability status.

Before interpreting the data from a clinical perspective, two issues are to be elucidated. First, perceived seriousness was assessed for each prognosis separately, because we hypothesized that patients would consider wheelchair dependence more serious when occurring in the near future. Although perceived seriousness was higher for the 2-year prognosis, the three assessments of perceived seriousness

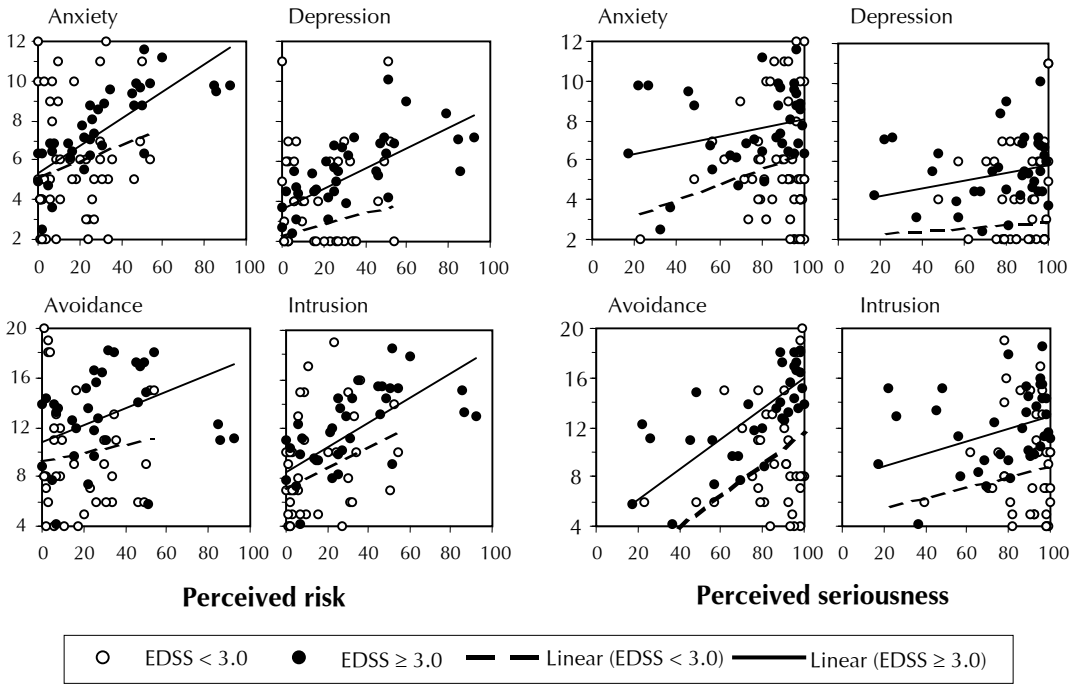

Figure 1 Mental health scores by perceived 2-year risk and seriousness of wheelchair dependence in patients with high and low disability

were highly correlated ($0.72 < r < 0.89$, $p < 0.001$). This suggests that patients perceived wheelchair dependence a serious consequence of their disease, no matter when it would happen. The consistency in the relationships between perceived seriousness and distress (intrusion and avoidance) for each prognosis may therefore be explained by a similar evaluation of seriousness for each period.

Second, the results of this study should be viewed within the limitations of a cross-sectional study design: we cannot prove whether higher perception of risk and seriousness increase distress, anxiety and depression, or vice versa. Nevertheless, our data may be indicative for the direction of the relationship. It can be argued that, if distress, anxiety or depression had determined perception of risk, this would have affected the short- as well as long-term risk perception. Following this reasoning, the significant relationship with intrusion for each prognosis is consistent with the hypothesis that risk perception is in part determined by intrusive thoughts and feelings about the disease. On the contrary, avoidance, anxiety and depression were significantly related only to the perceived two-year risk. This would imply that anxiety, depression and avoidance are more likely

determined by risk perception, than vice versa. Yet, these hypotheses are to be confirmed in experimental follow-up studies.

To our knowledge, this is the first study that addressed perception of prognostic risk in relation to mental health in chronically ill patients. Nevertheless, the findings of our study may be compared to those that have investigated risk of disease in healthy subjects, because both groups face uncertain adverse health prospects. In persons at high-risk of developing breast cancer, prostate cancer or diabetes, higher perception of risk was associated with more psychological distress, as was found in the present study.[18,23,24]

The most important finding of this study is that perception of the 2-year risk was strongly related to anxiety and depression while perception of the 10-year and lifetime risk were not. This may be explained by the fact that short-term disability may have a more disruptive impact on family life, work, and leisure activities than disability occurring in the remote future. In that light, our findings are in line with earlier studies reporting that patients who perceived MS as a major threat had higher levels of distress, more feelings of depression, poorer subjective health status and poorer social adjustment.[25,26] Further, as in previous studies,[27-30] we found that patients with more physical limitations were significantly more anxious and depressed than patients with fewer limitations. However, the association of perceived 2-year risk and seriousness of wheelchair dependence with psychological outcomes was independent of the patients' disability status.

The finding that perceived short-term risk influenced feelings of anxiety, depression and distress may have implications for the clinical care of patients. It can be argued that informing recently diagnosed patients about the low probability of wheelchair dependence within the short term – or about other consequences they consider important – may decrease their feelings of anxiety and depression. This will be particularly relevant, because in our study patients overestimated their short-term risks (Chapter 6): mean perception of the 2-year risk of wheelchair dependence was 22.4% compared to an actual risk of 5-10% based on epidemiological studies.[31] The challenge for future research will be to investigate whether it is feasible to communicate low probabilities of short-term prognosis to patients without raising false hope for the long-term prospects of the disease.

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8

ILLNESS BELIEFS AND PERCEPTION OF PROGNOSTIC RISK IN PATIENTS RECENTLY DIAGNOSED WITH MULTIPLE SCLEROSIS

Abstract

Objective: Patients' beliefs about their illness may affect their expectations about future disease progression. The aim of this study was to investigate the relation between illness beliefs and perception of *prognostic* risk in patients recently diagnosed with multiple sclerosis (MS). **Methods:** Hundred and one patients were included. Illness beliefs were measured using the Illness Perception Questionnaire (IPQ). Perceived risk and seriousness were assessed for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Clinical disability status was assessed by a physician. **Results:** Patients who reported a higher intensity of disease-attributed symptoms (IPQ illness identity) had higher perception of the 2-year (regression coefficient B = 0.58, p = 0.02) and 10-year risk of wheelchair dependence (B = 0.76, p = 0.009), after adjustment for clinical disability status. IPQ coherence was significantly associated with perceived seriousness: patients who believed they had a clearer understanding of their illness, considered future wheelchair dependence less serious (B = -1.10, p = 0.03). None of the other IPQ scales were significantly related to perceived risk and seriousness of wheelchair dependence. **Conclusions:** Perceived symptoms were significantly related with short- and medium-term expectations of disease progression. Implications for the clinical care of patients and future research are discussed.

Introduction

In recent years, there is increasing interest in the influence of illness beliefs on perception of risk.[1-7] Beliefs about illness – or illness representations – comprise multiple dimensions including illness identity (intensity of disease-attributed symptoms), timeline (duration and variability of the disease course), consequence, cause, controllability (prevention or cure) and coherence (understanding of the disease).[8-10] Illness representations have been found to underlie perception of risks of various disorders, such as breast and ovarian cancer and cardiovascular disease.[3-7,11] For example, healthy individuals were found to use established risk factors (causes) in estimating their risk of heart disease.[11] Women who reported a family history (causes) or a previous history of benign breast problems (illness identity) more often overestimated their risk of breast cancer.[3-5]

Research on the relationship between illness representations and perception of risk has primarily focused on the risk of (future) disease. One may argue that illness representations also relate to perception of prognostic risk in persons who already have a (chronic) disease, because both disease risk and prognostic risk deal with uncertain and unfavorable future health outcomes. Yet, it is also expected that several dimensions of illness representations may have a different role in perceived risk of prognosis. First, the presence of risk factors or causes were interpreted as indicators of disease risk,[3-5,11] but these may not be relevant with regard to prognostic risk. Instead, the presence of disease-attributed symptoms may be perceived as indicative of future disease progression and associated with higher perception of prognostic risk. Second, beliefs about the controllability and the duration of disease, which are dimensions that relate to prognosis, may be of greater influence. For example, patients who believe that they can control the progression of their disease, e.g. by diet or lifestyle changes, may have lower perception of prognostic risk.[12] The relationship between illness representations and perception of prognostic risk is yet unknown.

The aim of the present study was to examine the relationship between illness beliefs and perceived prognostic risk in patients recently diagnosed with multiple sclerosis (MS). MS is a chronic neurological disease which generally affects young adults between 20 and 40 years of age.[13] The disease often has disabling consequences such as wheelchair dependence and cognitive decline. The course of disease is highly variable in symptoms, poorly controllable by medication, and unpredictable.[14] In the absence of clear prognostic information, the role of illness beliefs may be particularly important in determining perception of prognostic risk of patients. If so, intervening on illness beliefs may be a promising strategy to alter apparent unrealistic perceptions of risk.

In this study, we focused on the risk of wheelchair dependence, which is a serious consequence of MS and known to all patients as a possible outcome of their disease. The lifetime risk of wheelchair dependence for MS patients is estimated to be 70-80%.[15] We have previously demonstrated that patients overestimated their 2-year and 10-year risk of wheelchair dependence and underestimated their lifetime risk.[16] They considered wheelchair dependence a serious consequence of their disease, irrespective when it would happen.[16] In the present paper, we studied the association of illness representations with perceived risk and seriousness of wheelchair dependence for these different prognoses, adjusting for differences in clinical disability status.

Method

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam) in the period of March 1999 – December 2000. Patients were diagnosed as having MS within two years before study entry, were between 18 and 55 years old, and had signed informed consent. Diagnoses were verified by senior neurologists from the academic hospitals. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the study criteria, 101 agreed to participate in the study. Mean age of the patients was 37.5 years (SD 9.5) and 70% were women. The mean time since diagnosis was only 7.8 months (SD 6.5), and the mean time since first symptoms 3.7 years (SD 4.6).

Patients underwent a neurological examination to determine their disability status. These examinations were done by physicians following a standardized research protocol. Disability status was rated on the Expanded Disability Status Scale (EDSS),[17] a scale that ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS). The inability to walk beyond five meters equals a score of 7.0. Scores from 0.0 to 2.5 indicate no to minimal disability and scores from 3.0 and higher indicate moderate to severe disability.[17] In our study population, EDSS ranged from 0.0 to 7.0. Eighteen percent of the patients experienced problems in walking as indicated by an EDSS score of 4.0 or higher. The study protocol was approved by the medical ethical committees of the participating hospitals.

Psychological instruments

Perception of the risk and seriousness of becoming wheelchair-dependent was assessed for the short- (2-year), medium- (10-year) and long-term (lifetime)

prognosis. The risk of wheelchair dependence was defined as the inability to walk beyond five meters. Patients were asked to what extent they thought they would become wheelchair-dependent for distances over five meters within these periods. Perception of risk was given by marking a 100mm visual analogue scale (VAS) which ends were anchored at 'Definitely not' (0) and 'Definitely' (100). Next, patients were asked for each period how serious they thought it would be to be wheelchair-dependent by that time. Perceived seriousness was assessed on a VAS from 'Not serious at all' (0) and 'The most serious thing I can imagine' (100). In an at-home interview, patients were asked to elucidate the VAS scores of perceived risk and seriousness.

Illness beliefs were assessed using the Illness Perception Questionnaire (IPQ).[10,18] The original IPQ consists of five scales: illness identity, cause, time-line (chronic), consequence and control (personal and treatment). The coherence and timeline (cyclical) scales were added from the revised version (IPQ-R).[18] Answers were rated on a five-point scale ranging from 'Strongly agree' to 'Strongly disagree' (scored 5 to 1), except for the illness identity scale which was rated using a four-point scale. An overview of the scales, typical questions, ranges and reliability of the scales is presented in Table 1. Internal consistency of the scales was evaluated using Coefficient α, which for this research purpose was considered adequate when higher than 0.70.[19] Several scales needed adaptations before their application in this study. First, the illness identity scale comprises intensity ratings of symptoms that patients experience and attribute to their disease. As recommended,[10,18] this scale was adapted for use in an MS population. The scale consists of 23 symptoms: twelve symptoms were taken from the IPQ list (excluding breathlessness) and eleven were added (concentration problems, coordination problems, muscular pain, numbness of limbs, loss of balance, feelings of depression, blurred vision, diplopia, bladder symptoms, bowel symptoms and spasticity). Answers were scored on 4-point scales: all of the time = 4, frequently = 3, occasionally = 2, and never = 1. These scores sum into a total score ranging from 23 to 92. Coefficient α of the new symptom scale was 0.87. Second, the cause scale originally consisting of 19 distinct causes of disease, was compressed using principal component analysis (PCA) with Varimax rotation. Five causal factors with eigenvalues exceeding 1 were found, and labeled based on their contents as psychological, external, lifestyle, chance and germ or virus (see Table 1). Finally, Coefficient α of four IPQ scales was lower than 0.70. The timeline (cyclical) scale (α = 0.32) was shortened by removing three items, resulting in a sufficient reliability (α = 0.72) with only two items left. Because these items ('My symptoms come and go in cycles' and 'I go through cycles in which my illness get

Table 1 Overview of the Illness Perception Questionnaire (IPQ) scales

Scale	Examples	Number of items	Possible range	α*
Identity	To what extent do you experience the following symptoms due to your disease? (see Methods)	23	23-92	0.87
Timeline acute/chronic	My illness will last a long time. My illness is permanent rather than temporary.	3	3-15	0.82
Timeline cyclical	I go through cycles in which my illness gets better and worse.	5	5-25	0.32†
Treatment control	There is very little that can be done to improve my illness (r). My treatment will be effective in curing my illness.	3	3-15	0.66
Personal control	There is a lot, which I can do to control my symptoms. What I do can determine whether my illness gets better or worse. Recovery from my illness is largely dependent on chance or fate (r).	3	3-15	-0.02‡
Consequences	My illness is easy to live with (r). My illness is a serious condition.	7	7-35	0.72
Coherence	The symptoms of my condition are puzzling to me (r). I have a clear picture or understanding of my condition.	5	5-25	0.82
Causal attributions				
Psychological	Personality, my behavior, family problems or worries, stress or worry, mental attitude, emotional state, overwork.	7	7-35	0.89
External	Accident or injury, poor medical care in the past, environmental pollution.	3	3-15	0.72
Lifestyle	Alcohol, diet or eating habits, altered immunity, smoking.	4	4-20	0.83
Chance	Chance or bad luck, aging and heredity.	3	3-15	0.48
Germ or virus	Germ or virus	1	1-5	-

(r) Items that are reverse scored. * Coefficient α indicates internal consistency reliability in the present study. † Coefficient α was 0.72 after item reduction (see Methods). ‡ Checked for errors in recoding.

better and worse') are most relevant in MS, we decided to use the two-item scale in further analyses. The reliability of the personal control scale and chance attributions did not improve from item reduction, and were for that reason excluded from the regression analyses together with the germ attribution scale. The treatment control scale was included in the analyses in its original form, because its reliability was considered borderline (α = 0.66).[19]

Statistical analysis

Pearson correlation coefficients were calculated to investigate the association between illness representations (IPQ scales), disability status (EDSS), perceptions of risk and seriousness. The relationship between illness representations and

perceived risk and seriousness of wheelchair dependence were studied adjusting for clinical disability status using SAS Proc Mixed Repeated Measurements. This MANOVA-like procedure was chosen because of the substantial intercorrelations of perceived risk and seriousness between the three periods (2 years, 10 years and lifetime).[16] The following strategy of analysis was adopted. Prognosis was recoded into 0, 1 and 2 representing 2-year, 10-year and lifetime risks. A full model was tested including prognosis (2-year, 10-year and lifetime risk), main effects (disability status and IPQ scales), covariates (time since diagnosis, time since first symptoms, age and sex) and first-order interaction effects of the main effects with prognosis. To simplify the model, this saturated model was reduced by eliminating non-significant covariates and interaction effects. Elimination was based on the significance of the difference in –2 log likelihood goodness of fit between the reduced and the saturated model. If the p-value was greater than 0.05 (χ^2-test), the parsimonious model was considered not significantly different from the saturated model, and used for further simplification. Regression coefficients (B) of the final model were estimated using the restricted maximum likelihood procedure (REML).

Results

Correlations between disability status and illness representations

Table 2 shows that patients with more physical limitations (EDSS) reported a higher intensity of symptoms as measured by the IPQ illness identity scale ($r = 0.53$, $p < 0.001$). The most prevalent symptom was fatigue, which was experienced 'frequently' or 'all of the time' by 61% of the patients. Other common symptoms were sensory problems (e.g. numbness of limbs; 44%), loss of strength (26%), loss of balance (25%), stiff joints (23%) and concentration problems (21%). As expected, the intensity of these symptoms was significantly higher among patients with higher physician-assessed disability status (EDSS ≥ 3.0; $p < 0.05$), except for fatigue ($p = 0.90$). Patients primarily attributed the cause of their disease to four factors: chance or bad luck (46% of the patients agreed or strongly agreed), stress or worry (45%), germ or virus (44%) and altered immunity (43%). The scales of the IPQ were interrelated (Table 2): each scale except the cyclical timeline scale, was significantly correlated to at least three other scales.

Illness beliefs and perceived risk of wheelchair dependence

Table 3 shows the relation between illness representations and perception of risk adjusting for physician-assessed disability status. Patients with more physical limitations had a higher perception of risk ($B = 3.61$, $p = 0.003$). This relationship was found for the 2-year, 10-year and lifetime prognosis, because the interaction

Table 2 Means of IPQ scales, intercorrelations and correlations with disability status

	Mean (SD)	Illness beliefs (IPQ) 1	2	3	4	5	6	7	8	9
Disability status (EDSS)		0.53***	0.04	-0.07	-0.04	0.29**	-0.17	0.09	0.22*	0.25*
Illness beliefs (IPQ)										
1. Illness identity	39.5 (8.8)		0.12	0.14	-0.09	0.48***	-0.23*	0.29**	0.20*	0.25*
2. Chronic timeline	12.7 (2.1)			0.24*	-0.43***	0.23*	0.12	0.06	-0.22*	-0.07
3. Cyclical timeline	7.0 (1.8)				0.02	0.13	-0.16	0.09	-0.15	0.08
4. Treatment control	7.1 (2.1)					-0.27**	-0.27**	0.02	0.11	0.05
5. Consequences	22.7 (4.6)						-0.12	0.19	0.07	0.19
6. Coherence	9.2 (3.9)							-0.21*	-0.20*	-0.24*
7. Psychological cause	8.6 (6.2)								0.46***	0.58***
8. External cause	2.9 (2.5)									0.60***
9. Lifestyle cause	3.7 (2.9)									

Values are Pearson correlations: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

effect of disability status and prognosis was not significant. IPQ illness identity was significantly related to perception of risk: patients who reported a higher intensity of symptoms had a higher perception of the 2-year risk of wheelchair dependence (B = 0.58, p = 0.02) and 10-year risk (B = 0.76, p = 0.009). In addition, patients who believed they had a better understanding of their disease, as indicated by higher scores of IPQ coherence, tended to have higher perception of risk (B = 0.80, p = 0.07). None of the other IPQ scales were significantly related to perception of risk.

Since IPQ illness identity was strongly correlated to clinical disability status as rated on the EDSS (r = 0.53, p = 0.0001; Table 1), we explored whether there were interaction effects between perceived symptoms and EDSS in explaining perceived risk. Therefore, we compared the effect of IPQ illness identity on risk perception between patients with high (EDSS ≥ 3.0) and low disability (EDSS < 3.0, Figure 1). The relationship between IPQ illness identity and perception of risk was stronger in the high disability group compared to the low disability group. Interaction effects between perceived symptoms and disability group were significant for each prognosis ($p < 0.05$).

Illness beliefs and perceived seriousness of wheelchair dependence

Patients with more physical limitations, as indicated by a higher EDSS score, considered wheelchair dependence to be less serious (B = -4.47, p = 0.002; Table 4). Of the illness beliefs, only coherence was a significant predictor of perceived seriousness: patients who had a more coherent understanding of their illness thought wheelchair dependence to be less serious (B = -1.10, p = 0.03).

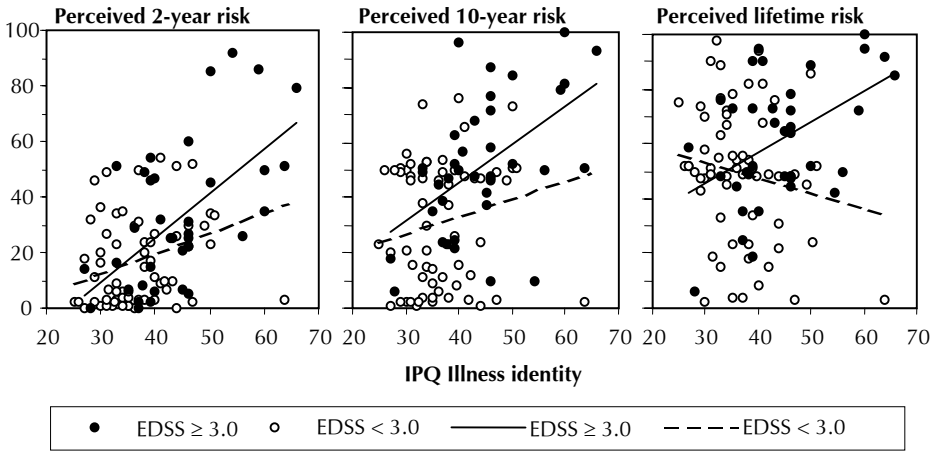

Figure 1 Relationship between IPQ illness identity and perception of risk in high and low disability groups

Dots are crude data. Lines represent linear trends of predicted values of perceived risk obtained by linear regression analyses with additional adjustment for residual confounding of EDSS within the disability groups.

Table 3 Linear model of perceived risk of wheelchair dependence on illness beliefs and disability status

		B [95% CI]	p
Disability status (EDSS)		3.61 [1.28, 5.94]	0.003
Illness beliefs:			
Illness identity[a]	2-year	0.58 [0.08, 1.09]	0.02
	10-year	0.76 [0.19, 1.33]	0.009
	lifetime	-0.02 [-0.62, 0.59]*	0.96
Chronic timeline		0.58 [-1.15, 2.31]	0.51
Cyclical timeline		-0.25 [-2.15, 1.65]	0.79
Treatment control		-1.13 [-2.87, 0.60]	0.20
Consequences		0.54 [-0.26, 1.34]	0.19
Coherence		0.80 [-0.05, 1.66]	0.07
Psychological cause		-0.23 [-0.88, 0.42]	0.49
External cause		0.11 [-1.26, 1.48]	0.88
Lifestyle cause		0.91 [-0.56, 2.39]	0.22

Non-significant interaction terms and covariates were removed from the analyses (see Methods). [a] The B coefficient of IPQ illness identity was different for each prognosis. Note that the p-values of IPQ illness identity indicate whether these interaction effects differed from zero. * The B coefficient of IPQ illness identity for the perceived lifetime risk was significantly higher than the B coefficient for the perceived 2-year risk (reference, $p < 0.05$).

Table 4 Linear model of perceived seriousness of wheelchair dependence on illness beliefs and disability status

	B [95% CI]	p
Disability status (EDSS)	-4.47 [-7.24, -1.70]	0.002
Illness beliefs:		
Illness identity	-0.05 [-0.60, 0.51]	0.87
Chronic timeline	-1.75 [-3.81, 0.30]	0.09
Cyclical timeline	-0.00 [-2.27, 2.26]	1.00
Treatment control	-1.83 [-3.89, 0.24]	0.08
Consequences	0.55 [-0.40, 1.50]	0.26
Coherence	-1.10 [-2.12, -0.09]	0.03
Psychological cause	0.16 [-0.61, 0.93]	0.68
External cause	0.56 [-1.07, 2.20]	0.50
Lifestyle cause	-0.66 [-2.42, 1.10]	0.46

Non-significant interaction terms and covariates were removed from the analyses (see Methods).

This relationship was found for the 2-year, 10-year and lifetime prognosis. None of the other illness representations played a significant role, albeit that there was a tendency that patients who had a stronger belief that their disease was chronic (B = -1.75, p = 0.09) or controllable by medication (B = -1.83, p = 0.08) considered wheelchair dependence less serious. None of the interaction effects was statistically significant.

Discussion

In our study of patients recently diagnosed with MS, we investigated whether their beliefs about the disease were associated with their perception of the risk and seriousness of wheelchair dependence. We demonstrated that perceived symptoms, as measured by the IPQ illness identity scale, significantly predicted patients' expectations about future wheelchair dependence. This relationship was found after adjustment for physician-assessed disability status and significant for the 2-year and 10-year prognosis only. Further, patients who believed they had a more coherent understanding of their disease considered the prospects of wheelchair dependence to be less serious. None of the other illness beliefs were significantly related to perceived risk and seriousness of wheelchair dependence.

Before discussing the findings of this study, two methodological issues with regard to the use of the Illness Representation Questionnaire (IPQ) need to be addressed. First, we were unable to replicate the factor structure in the causal attributions as reported in the IPQ-R paper, with the exception of the psychological

causes (see Table 1).[18] Factor analysis of causal attributions may be largely determined by the perceived co-occurrence of established causes of disease. This implies that different factor structures may be obtained in different disease populations. Clinical populations may therefore be less suitable for the identification of a general classification of related causes. Second, the personal control scale and, before modification, the cyclical timeline scale were not reliable in our population of MS patients. This may be ascribed to the uncontrollable, unpredictable and variable nature of the disease. Based on our findings, we recommend further refinement of the IPQ-R into a scale in such a way that it can be used in a broad range of diseases without additional modification. A generic illness perception scale with disease-specific modules will facilitate comparison of studies between different centers and different disease groups.

Two major findings can be deducted from this study. First, patients who reported a higher intensity of disease-attributed symptoms had higher perception of the 2- and 10-year risk of wheelchair dependence *after* adjustment for differences in disability status. Our findings and those of others suggest that patients perceive their present symptoms as being indicative of prognosis and extrapolate the presence of symptoms into expectations about future disease progression.[5,7,20] The fact that perceived symptoms were not related to perceived lifetime risk is likely explained by the unpredictability and variability of MS: also patients with lower EDSS *and* lower IPQ illness identity scores took into account that they might become wheelchair-dependent (see Figure 1). Our exploratory analyses further showed that this relationship between IPQ illness identity and risk perception was stronger in patients with more (physician-assessed) physical limitations. From a clinical point of view these sub-group analyses may be of particular relevance. High symptom perception accompanied with high perception of prognostic risk may be more realistic for patients with severe disability, whereas this may indicate maladaptive coping in those with no to minor disability. Further, low symptom perception and low perception of risk may be more realistic for patients with minimal physical limitations, but may be a sign of avoidant coping behavior in those with moderate to severe disability. Our findings suggest that perception of prognostic risk may be an intermediate factor between illness perceptions and coping.[22-24] Further, these findings indicate that clinical status is an important factor to include in future studies on illness beliefs.[21]

The second finding is that patients who believed they had a clearer understanding of their illness, as measured by the IPQ coherence scale, considered wheelchair dependence to be less serious. This relation did not differ for the short-, medium-, and long-term prognosis. This is in line with the hypothesis of Moss-

Morris et al. who suggested that illness coherence may be important in long-term adjustment.[18] An alternative explanation may be that coherence *reflects* adaptation to the disease. There was support for the latter viewpoint in our interview data. Patients who considered wheelchair dependence less serious indicated that a wheelchair would extend their mobility when they were no longer able to walk (see Chapter 10). They also mentioned that the disease could have consequences that are more serious than wheelchair dependence, or that there are still many opportunities to live a life as normal when being wheelchair-bound (see Chapter 10).

The relation between perceived symptoms and short- and medium-term perception of risk is clinically important because we have previously demonstrated that patients overestimated these short-term risks.[16] MS is an unpredictable and variable disease with a wide array of possible symptoms. For patients, it may not be easy to determine which symptoms are due to their disease and which are not. It is likely that patients may have an inaccurate perception of their symptoms, which will consequently extrapolate into inappropriate expectations about future disease progression. If so, informing patients which of their symptoms are due to MS may help them to better assess the severity of their disease status and alter eventual unrealistic expectations.

In conclusion, perceived symptoms were associated with perception of short- and medium-term prognostic risk in recently diagnosed MS patients. Contrary to our expectations, however, none of the other IPQ scales were of significant impact. As this is the first study on this topic, it is too early to conclude that illness beliefs do not play a role in perception of prognostic risk. Since illness perceptions could give insight into how patients make judgments about their risks,[1] they may provide opportunities to alter unrealistic perceptions of risk. Further research on the relationship between illness beliefs and perception of prognostic risk in MS and other chronic diseases is needed but requires refined approaches to assess beliefs.

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9

INDIVIDUAL DIFFERENCES IN PERCEPTION OF PROGNOSTIC RISK: THE ROLE OF NEUROTICISM AND PESSIMISM

Abstract

Objectives: The aim of the study was to investigate the impact of personality factors on perception of prognostic risk in multiple sclerosis (MS). We studied direct effects of neuroticism, optimism and pessimism as well as indirect effects through symptom perception. **Method:** Data on perceived prognostic risk, neuroticism (EPQ), optimism and pessimism (LOT) and symptom perception (IPQ) were obtained from 101 recently diagnosed MS patients. Perceived risk and seriousness were assessed for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Analyses were adjusted for differences in clinical disability status. **Results:** Neuroticism strengthened the impact of perceived symptoms on perception of risk (regression coefficient B = 0.20, p = 0.01) and was a predictor of perceived seriousness of wheelchair dependence (B = -1.04, p = 0.001). Patients who were more pessimistic had higher levels of symptom reporting, after adjustment for disability status (B = 0.85, p = 0.02), and considered wheelchair dependence to be more serious (B = 2.73, p = 0.003). Optimism and pessimism were not associated with perception of risk. **Conclusions:** We have demonstrated that neuroticism and pessimism affect perceived risk and seriousness of wheelchair dependence in patients with MS. These effects were either direct or indirect through modification of the impact of perceived symptoms and clinical disability.

Introduction

Communication about health risks is omnipresent in current medical practice. Still, numerous studies demonstrate that patients' understanding or perception of these risks often deviates considerably from the actual values.[e.g.[1-7]] For instance, individuals at high risk of breast cancer, prostate cancer or Huntington's disease overestimated [1-4] or underestimated [5-7] their own risk of developing the disease. This over- and underestimation of risk was associated with actual risk factors such as age and family history, but also with prior disease experience, prior health-related behavior and perceived health status.[2,5,8-10] Only a few studies have investigated the impact of personality factors on perception of risk.[5,11,12] In patients with rheumatoid arthritis, higher trait anxiety or neuroticism was associated with negative expectations about future health status.[12] This finding was in line with results from an experimental study, in which students with high neuroticism perceived their risks of negative events, such as being a victim of crime or having a financial crisis, to be higher than students with lower neuroticism scores.[11] In contrast, no significant relationship between trait anxiety and perception of risk of ovarian cancer was found among women attending a screening clinic.[5] The aforementioned experimental study also demonstrated that optimism was associated with higher perception of risk to encounter positive events and lower perception of risk to encounter (short-term) negative events.[11] There are a large number of studies on *unrealistic* optimism in perception of risk.[e.g.[13-15]] These studies are however beyond the scope of the present paper: optimism in that context denotes the finding that people, as a group, view their risk as more favorable compared to others rather than the personality characteristic.[13]

Neuroticism, optimism and pessimism can affect perception of risk through direct and indirect pathways. An association with neuroticism is suggested by the studies mentioned above. A direct relationship between optimism and perception of risk is expected because (dispositional) optimism is defined as a general tendency to hold positive expectancies about the future,[16] which may also apply to expectations about *specific* health outcomes. Another reason for a direct relationship is explained by the heuristic of availability.[17] According to this heuristic optimists will underestimate the risk of negative outcomes, because they are more focused on positive outcomes. Similarly, pessimists will overestimate risks of unfavorable prospects. In addition, personality may have an indirect impact on risk perception through its role on symptom reporting. There is consistent evidence that personality factors such as neuroticism and optimism – in opposite direction – affect symptom reporting,[18-24] which in turn may be extrapolated into expectations about future disease progression.[14]

In patients diagnosed with a chronic disease, perception of *prognostic* risk may be an important factor in the choice whether or not to start treatment, and in other major decisions about e.g. relationships, family planning, housing and work. For that reason, it is important to understand the factors that influence risk perception. In this study, we investigated to what extent neuroticism, optimism and pessimism had a direct impact on perceived risk and seriousness of wheelchair dependence or an indirect effect through symptom perception. We also investigated to what extent neuroticism, as a higher-order trait, could also explain eventual effects pessimism, because these personality factors are closely related.[16,22,25] The study was conducted in a cohort of patients who are recently diagnosed with multiple sclerosis (MS). MS is a chronic neurological disease affecting young adults between 20 and 40 years of age.[26] The course of disease is variable, unpredictable and poorly controllable by medication.[27] These disease characteristics in particular predict a role for personality factors to affect expectations about future symptom progression. We addressed patients' expectations with regard to the risk of wheelchair dependence, as this is the most widely known consequence of MS by patients. The estimated lifetime risk of wheelchair dependence is 70-80%.[28]

Methods

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC, three hospitals within the region of this academic hospital, and the VU Medical Center in the period of March 1999 – December 2000. Patients were diagnosed as having MS within two years before study entry, were between 18 and 55 years old, and had signed informed consent. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Diagnoses were verified by senior neurologists of the academic hospitals. Of the 120 patients who met the criteria, 101 agreed to participate in the study. Patients who declined participation mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine patients declined without additional comments and four never responded to our reminders. Mean age of the patients was 37.5 years (SD 9.5) and 70% were women. The mean time since diagnosis was only 7.8 months (SD 6.5), and the mean time since first symptoms 3.7 years (SD 4.6).

All patients filled out questionnaires and underwent a neurological examination. These examinations were done by physicians of the academic centers according to a standardized research protocol. Disability status was rated on the Expanded Disability Status Scale (EDSS).[29] The EDSS ranges from 0.0 (no

neurological symptoms) to 10.0 (death due to MS). In the study population, EDSS ranged from 0.0 to 7.0. Eleven percent of the patients experienced substantial problems in walking (EDSS ≥ 5.0), and another seven percent had difficulty in walking long distances (EDSS 4.0-4.5).[29] The study protocol was approved by the medical ethical committees of the participating hospitals.

Instruments

Perception of prognostic risk and seriousness were assessed for the risk of becoming wheelchair-dependent as a complication of MS. Wheelchair dependence was defined as the inability to walk beyond five meters, equaling a score of 7.0 on the EDSS.[29] We addressed patients' perception of the 2-year, 10-year and lifetime risk as an indication of their expectations about the short-, medium- and long-term prognosis. Patients were asked to what extent they thought they would become wheelchair-dependent for distances over five meters within these periods. Perception of risk was assessed by marking a 100mm visual analogue scale (VAS), which ends were anchored at 'Definitely not' (0) and 'Definitely' (100). Next, patients were asked for each period how serious they thought it would be to be wheelchair-dependent by that time. Perception of seriousness was scored on a VAS anchored at 'Not serious at all' (0) and 'The most serious thing I can imagine' (100). Detailed descriptive statistics of perceived risk and seriousness have been published elsewhere.[30]

Neuroticism is a dimension of personality consisting of negative emotions such as anxiety and anger, and cognitive and behavioral characteristics such as low self-esteem, preoccupation and insecurity.[22] Neuroticism was assessed by the 12-item neuroticism scale of the Eysenck Personality Questionnaire (EPQ).[31,32] This scale ranges from 0 to 12, with high scores indicating high neuroticism. Internal consistency reliability as assessed by Coefficient α was 0.64, which is below the 0.70 that is considered adequate for research purposes.[33] Yet, Coefficient α of the EPQ Neuroticism scale increased to 0.74 when the item with the weakest item-total correlation was removed and to 0.80 when the two 'weakest' items were excluded. The correlation coefficients between the latter scales and the original 12-item scale were 0.99 and 0.97, respectively, indicating that scale reduction only marginally improved measurement of neuroticism. This made us decide to use the original scale.

Dispositional optimism, a generalized tendency to believe in positive outcome expectancies, was assessed using the Life Orientation Test (LOT).[34,35] The LOT consists of four positively formulated items (optimism), four negatively formulated items (pessimism) and four filler items. The optimism and pessimism scales range

from 4 to 20, with higher values indicating higher levels of optimism and pessimism. The LOT has been validated for use in the Dutch population.[35] In our study, Coefficient α was 0.72 for the optimism and 0.68 for the pessimism scale.

Symptom reporting was included as the perceived intensity of symptoms that are experienced as a consequence of MS. Perceived symptoms were assessed by the illness identity scale of the Illness Perception Questionnaire (IPQ).[36] As recommended by the constructors,[36] disease-specific symptoms were added to the original list for use in this MS population, resulting in a scale of 23 symptoms. Frequency was scored on a four-point scale: all of the time (4), frequently (3), occasionally (2) and never (1). Answers summed into a total score ranging from 23 to 92. High scores on the IPQ identity scale indicate that patients report a higher intensity of symptoms due to their disease. In this study, Coefficient α of the 23-item IPQ symptom scale was 0.87.

Statistical analysis

Pearson correlation coefficients were calculated to examine the relationships between the study variables. SAS Proc mixed was used to investigate the independent relation of disability status, perceived symptoms and personality with perception of risk and seriousness of wheelchair dependence. This MANOVA-like procedure allows for simultaneous analysis of the determinants of perceived 2-year, 10-year and lifetime risk while taking into account their significant intercorrelations. The following strategy was adopted for the selection of independent variables of the final model. The analyses were started with a full model including the main effects (disability status, perceived symptoms, optimism, pessimism, neuroticism and prognosis), covariates (age, sex, time since diagnosis and time since first symptoms), all first-order interactions with prognosis and all first-order interactions between personality factors on the one hand and disability status and perceived symptoms on the other. Dummy variables were created for prognosis, which allows differentiating between the impact of the main effects on perceived 2-year, 10-year and lifetime risk or seriousness. To simplify the model, this saturated model was reduced by eliminating non-significant covariates and interaction effects. Elimination was based on the significance of the difference in –2 log likelihood goodness of fit between the reduced and the saturated model. If the p-value was greater than 0.05 (χ^2-test), the parsimonious model was considered not significantly different from the saturated model, and used for further simplification. Regression coefficients (B) of the final model were estimated using the restricted maximum likelihood procedure (REML). For the ease of interpretation of the parameters, results of the final model were presented without the main

effects of significant interaction terms. By doing this, the coefficients of the interaction effects indicate the regression coefficient of the determinant for each prognosis (2-year, 10-year and lifetime). P-values of the differences *between* the interaction effects will be presented in the text.

To determine the influence of personality factors on perceived symptoms, a multivariate regression analysis was performed. The full model included main effects (disability status, optimism, pessimism and neuroticism), covariates (age, sex, time since diagnosis and time since first symptoms) and all interaction effects between disability status and the personality factors. A backward selection strategy was used to remove non-significant ($p > 0.10$) covariates and interaction effects from the model. P-values lower than 0.05 were considered statistically significant, unless indicated otherwise. SAS 8.0 (www.sas.com) and SPSS 11.0 (www.spss.com) for Windows were used for the statistical analyses.

Results

Correlations between the study variables

Table 1 shows the correlation coefficients of the relations between personality factors, clinical disability status and perceived symptoms. As expected, patients with higher disability also reported significantly more symptoms due to their disease ($r = 0.53$, $p < 0.001$). Higher neuroticism ($r = 0.31$, $p = 0.002$) and pessimism ($r = 0.40$, $p < 0.001$) scores were associated with increased symptom reporting.

Personality factors and perceived risk

Patients who reported more symptoms due to their disease had a higher perception of the 2-year ($B = 1.00$, $p = 0.0001$) and 10-year risk ($B = 0.98$, $p = 0.001$) of wheelchair dependence, independent of clinical disability status (Table 2). This

Table 1 Means (SD) and correlations between personality characteristics, perceived symptoms and disability status

	Mean (SD)	Optimism	Pessimism	Neuroticism	Disability status
Perceived symptoms	39.5 (8.8)	-0.18	0.40***	0.31**	0.53***
Optimism	13.7 (2.5)		-0.41***	-0.35***	-0.04
Pessimism	9.0 (2.4)			0.39***	0.27**
Neuroticism	6.3 (2.5)				0.20*

Pearson correlation coefficients * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2 Linear model of perceived risk of wheelchair dependence including disability status, perceived symptoms and personality factors

		B [95% CI]	p
Disability status		3.12 [0.89, 5.35]	0.01
Perceived symptoms†	2 years	1.00 [0.51, 1.49]	0.0001
	10 years	0.98 [0.41, 1.55]	0.001
	lifetime	0.20 [-0.40, 0.80]*	0.51
Optimism		-0.14 [-1.47, 1.20]	0.84
Pessimism		0.00 [-1.49, 1.50]	1.00
Neuroticism		-1.25 [-2.58, 0.09]	0.07
Perceived symptoms * Neuroticism		0.20 [0.05, 0.34]	0.01

Linear model (SAS Proc Mixed) with B = regression coefficient and CI = confidence interval. Non-significant covariates and interaction terms were removed from the model using a backward selection strategy (see Methods). † B indicates the regression coefficient of perceived symptoms for the 2-year, 10-year and lifetime prognosis (interaction effect) with accompanying p-value. * The interaction effect of perceived symptoms with perceived lifetime risk was significantly lower than the interaction effect with perceived 2-year risk (reference, $p < 0.01$).

impact of perceived symptoms was stronger in patients with higher neuroticism scores, as indicated by the significant interaction effect (B = 0.20, p = 0.01, see Figure 1). The interaction between neuroticism and prognosis was not significant indicating that the influence of neuroticism did not differ for the 2-year, 10-year and lifetime prognosis. Optimism and pessimism did not significantly influence perception of risk, nor did they modify the effect of other variables.

Table 3 Linear model of perceived seriousness of wheelchair dependence including disability status, perceived symptoms and personality factors

	B [95% CI]	p
Disability status	-4.44 [-7.14, -1.73]	0.002
Perceived symptoms	-0.22 [-0.76, 0.31]	0.41
Optimism	-1.14 [-2.76, 0.48]	0.17
Pessimism	2.73 [0.94, 4.52]	0.003
Neuroticism	-1.04 [-2.64, 0.56]	0.20
Perceived symptoms * Neuroticism	-0.32 [-0.51, -0.13]	0.001
Disability status * Pessimism	1.40 [0.39, 2.41]	0.01

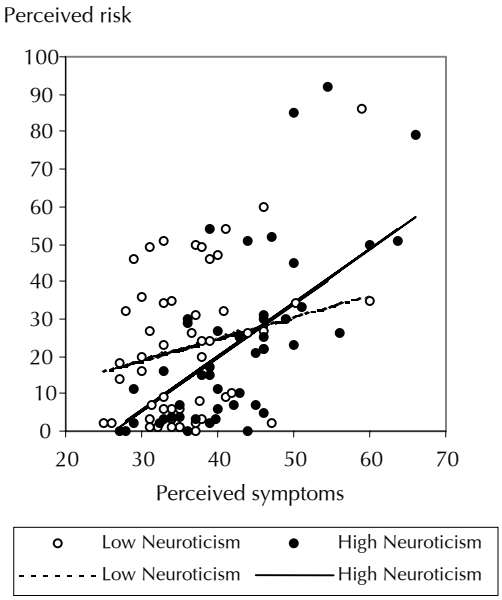
Linear model (SAS Proc Mixed) with B = regression coefficient and CI = confidence interval. Non-significant covariates and interaction terms were removed from the model using a backward selection strategy (see Methods).

Personality and perceived seriousness

Patients who were more pessimistic considered wheelchair dependence to be more serious (B = 2.73, p = 0.003; Table 3). A significant interaction effect was found between pessimism and disability status: patients who had higher disability status *and* were more pessimistic considered wheelchair dependence to be more serious (B = 1.40, p = 0.01; Figure 2). Neuroticism tended to be associated with lower perception of seriousness (B = -1.04, p = 0.20), but this association was significant only in interaction perceived symptoms (B = -0.32, p = 0.001).

Personality factors and perceived symptoms

To investigate whether personality factors may affect perception of risk through their role in symptom reporting, we conducted a linear regression analysis on the



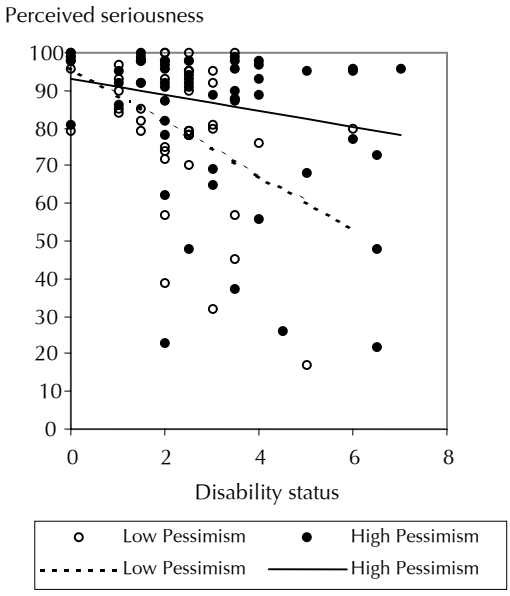


Figure 1 Perceived 2-year risk of wheelchair dependence as a function of perceived symptoms in patients with high and low neuroticism

Lines are based on predicted values obtained by regression analysis on neuroticism and perceived symptoms.

Figure 2 Perceived seriousness of wheelchair dependence within two years as a function of disability status in patients with high and low pessimism

Lines are based on predicted values obtained by regression analysis on pessimism and disability status.

Table 4 Regression model for the relation between perceived symptoms on disability status and personality characteristics

	B [95% CI]	p
Disability status	2.45 [1.50, 3.39]	< 0.001
Optimism	-0.10 [-0.76, 0.55]	0.75
Pessimism	0.85 [0.14, 1.56]	0.02
Neuroticism	0.39 [-0.27, 1.04]	0.25
R^2 = 0.36 (Adjusted R^2 = 0.33)		

Linear regression analyses (SPSS GLM). B = regression coefficient, CI = confidence interval, R^2 = Percentage of variance in perceived symptoms explained by the model. Non-significant covariates and interaction terms were removed from the model using a backward selection strategy (see Methods).

determinants of perceived symptoms. Table 4 shows that patients who were more pessimistic reported more symptoms due to their disease (B = 0.85, p = 0.02) after adjustment for clinical disability status. In contrast to the findings of the unadjusted analyses presented in Table 1, in the simultaneous analysis of all disability and personality factors, we found no evidence for a relationship between neuroticism and symptom reporting (B = 0.39, p = 0.25).

Effects of pessimism explained by neuroticism?

To determine whether neuroticism, as a higher-order trait, could also explain the significant relationships of pessimism with perceived symptoms and perceived seriousness, we repeated the analyses excluding pessimism. We found that neuroticism did not become a significant predictor of perceived symptoms (B = 0.58, p = 0.08). Also, the main effect of neuroticism on perceived seriousness was still not significant (B = -0.48, p = 0.57) and the interaction effect of perceived symptoms and neuroticism became less significant (B = -0.19, p = 0.05).

Discussion

The aim of the present study was to investigate the direct and indirect impact of personality characteristics on the perception of prognostic risk and seriousness in patients with MS. Five findings of this study will be commented upon.

First, we found that perceived symptoms had a stronger impact on risk perception in patients with higher EPQ neuroticism scores (Figure 1). The finding that neuroticism modified the impact of perceived symptoms extends previous correlational findings of Radanov *et al.* (1997). Contrary to our expectations and the results of experimental studies,[11] there was no evidence for a significant

impact of optimism and pessimism on perception of risk. Even though optimism is defined as a tendency to hold positive expectations, this does not appear to apply to *specific* prognostic outcomes. Apparently, the contribution of other determinants prevails when it comes to specific health-related prospects.

Second, we found that patients with higher disability and those scoring lower on pessimism evaluated wheelchair dependence as less serious. Moreover, patients who had more physical limitations *and* were less pessimistic considered wheelchair dependence even less serious (see Figure 2). This lower perception of seriousness in patients with higher levels of disability is likely due to successful coping with the altered prospects of having a progressive disorder.[30] A question that emerges from these findings is: why is *low pessimism* rather than *high optimism* associated with lower perception of seriousness? A possible answer may be the congruence in the valence of pessimism and unfavorable prognostic outcomes such as wheelchair dependence. Affect congruence predicts that pessimism and neuroticism will be associated with biases in judgment of negative events, and optimism with biases in positive events.[e.g. 37] Such effects have been demonstrated for neuroticism in several experimental studies,[11,37,38] and may also apply to pessimism. For example, Lipkus *et al.* (1993) found that pessimistic students and not those with low optimism had higher perception of risk of negative events.

Third, we found a significant interaction effect of neuroticism and perceived symptoms on perception of seriousness. A lower perception of seriousness among patients who reported more symptoms is not surprising given the similar impact of perceived symptoms and disability status (see above). However, the finding that this relationship was stronger among patients with higher neuroticism scores is counter-intuitive. The same significant interaction effect was found in the analysis of perception of risk. A possible explanation is that lower perception of seriousness in high-neuroticism patients reflects minimization of the threat of wheelchair dependence.[39] By reducing the perceived impact of the outcome, these patients are able to handle the prospects of their unfavorable prognosis. Minimization may be an effective coping strategy on the short term, but can lead to inadequate adaptation on the long run. This finding may have brought to light an important clinical problem, which needs to be studied further in future studies.

Fourth, we found that pessimistic patients reported significantly more symptoms due to their disease than patients who were less pessimistic. This relationship was found after adjustment for differences in clinical disability status, and could not be explained by neuroticism. This finding adds to the existing literature in that no earlier study of perceived symptoms had included optimism,

pessimism and neuroticism all together while taking into account differences in actual physical limitations. Many previous studies reported significant associations between neuroticism and symptom reporting, but these had not simultaneously considered pessimism and clinical health status.[19-21,23,24] In line with these studies, we also found a significant crude correlation between neuroticism and perceived symptoms when not adjusting for other variables (Table 1). When adjusting for pessimism the effect of neuroticism was not significant in our study. This suggests that pessimism instead of neuroticism could also have been a major predictor of symptom reporting in these aforementioned studies. Two other studies reported significant associations between total LOT scores and symptom reporting, but did not discriminate between effects of optimism and pessimism.[18,22] In the light of our findings, it is expected that these effects of bipolar optimism could have been explained by pessimism alone.

Fifth, there was partial overlap between pessimism and neuroticism ($r = 0.39$, $p < 0.001$), but significant effects of pessimism on symptom reporting and perceived seriousness could not be explained by neuroticism. Neuroticism is conventionally viewed as a higher-order trait and multifaceted construct that in part consists of the absence of optimism (i.e. pessimism).[e.g.16] Smith *et al.* (1989), however, have suggested that pessimism is merely a weaker instrument for the assessment of neuroticism. Our findings contradict the suggestion of Smith *et al.* (1989). We conclude that in our study pessimism and neuroticism are distinguishable psychological constructs, with shared and unique impact on psychological outcome variables.

Three methodological issues remain to be elucidated. First, we have investigated the impact of personality, disability status and perceived symptoms *as determinants* of perception of risk and seriousness. The data used to test this hypothesis were derived from a cross-sectional study, which cannot prove the direction of these relationships. Yet, given the relative stability of personality traits and the short duration of disease, we think it is valid to assume that personality had affected symptom perception and perception of risk, and that disability status preceded symptom reporting as well as perception of risk in the causal pathway. Also, we considered it likely that perceived current symptoms influenced perception of future disease progression. The direction of this relationship may be subject for debate. It can be argued that patients, who do not want to face their unfavorable prognosis, may underestimate or ignore the presence of their symptoms.

Second, *objective* clinical disability status was significantly associated with pessimism ($r = 0.27$) and neuroticism ($r = 0.20$). In this study, disability status was

assessed using the EDSS, a physician-assessed rating scale for the ranking of MS-related functional limitations.[29] The EDSS scores are based on the results of neurological examinations, some of which rely on patient symptom reporting and may thus be determined by personality explaining the association of the EDSS to personality in our study and that of others.[18-23] Though the scale has been criticized for this subjectivity,[40] it is still the most widely used disability scale.

And third, personality factors determine the usual way a person thinks, behaves, and reacts to everything in the environment. Therefore, we interpreted the interaction effects as that personality factors modify the influence of perceived symptoms and disability status on perception of risk and seriousness. Yet, these interaction effects can also be explained in another way: e.g. perceived symptoms and disability status may modify the impact of neuroticism and pessimism. For example, the influence of pessimism may be stronger in patients with higher disability and may not play a role when patients have no physical limitations. Although we can not exclude such alternative interpretation of the interaction effects, we considered this to be less likely.

In conclusion, we have demonstrated that personality characteristics play a significant role in perceived risk and seriousness of wheelchair dependence in patients recently diagnosed with MS. The most pronounced role for personality may be in modifying the influence of other determinants such as perceived symptoms, or prior disease experience, prior health-related behavior and perceived health status.[2,5,8-10] To our knowledge, this is the first study that simultaneously addressed several personality characteristics and investigated their interaction effects with other determinants. Therefore, our findings are awaiting replication by other studies. Further studies of unavoidable health outcomes such as prognostic and genetic risks may help to gain a better understanding of the role of personality factors on risk perception.

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10

'IT MIGHT HAPPEN OR IT MIGHT NOT': HOW PATIENTS WITH MULTIPLE SCLEROSIS EXPLAIN THEIR PERCEPTION OF PROGNOSTIC RISK

Abstract

Aim: To examine, in a qualitative study how patients with multiple sclerosis base their perception of the risk and seriousness of wheelchair dependence. **Methods:** Perceived risks, both absolute and comparative, were assessed for 2-year, 10-year and lifetime prognosis of wheelchair dependence using visual analogue scales (VAS). In the semi-structured interviews, patients (n = 85) were asked to elucidate these VAS scores. **Results:** Explaining perceived absolute risk, patients mentioned disease-related factors as well as psychological factors. Uncertainty about future disease progression was a predominant factor for all patients, even those with low and high perceptions of risk. In assessing their comparative risk, patients perceived themselves as being equally at risk compared to others, since they did not know what to use as a basis for comparison. Wheelchair dependence was perceived as serious primarily because of its possible implications such as loss of independence. When perceptions of 2-year, 10-year and the lifetime prospect of wheelchair dependence were compared, it was found that patients discriminated in their perception of absolute risk, but less in that of the comparative risk and seriousness. **Conclusions**: Comparison of quantitative and qualitative assessments indicated good construct validity for perception of the absolute risk and seriousness of wheelchair dependence, but not for the comparative prognostic risk.

Introduction

Multiple Sclerosis (MS) is a chronic neurological disease, which affects young individuals between 20 and 40 years of age. Patients with MS face enormous prognostic uncertainty as the variation in type, severity and progression of symptoms is high.[1] Although patients are generally aware that the disease may have major consequences for their lives, there is no way to provide them with an individual prognosis. This lack of prognostic information may contribute to the high levels of uncertainty that have been reported in patients with MS and which have been associated with poorer psychological well-being.[2-4] The lack of clinical prognostic information may affect patients' decisions about treatment as well as having children, changing jobs, or buying houses.[5,6] Patients are compelled to make these decisions based on uncertain expectations about their future health.

For patients with MS, wheelchair dependence is one of the most serious and recognized consequences of the disease. We have previously studied expectations of wheelchair dependence in recently diagnosed patients and found that they overestimated their 2-year and 10-year risk of wheelchair dependence but underestimated their lifetime risk of wheelchair dependence.[7] As anticipated, perceptions of risk were higher among patients with higher levels of clinically assessed disability.[7] In addition, patients who experienced more general and disease-related symptoms had higher perceptions of their short- and medium-term risks (Chapter 8). This relation between perceived symptoms and perception of risk was strongest in patients with higher neuroticism (Chapter 9). Although these studies brought some correlates of perceived risks to light, they have provided little insight into how these factors affect perception of risk.

The aim of the present interview study is to get insight into the perception of prognostic risk of patients recently diagnosed with MS. Perceived risks and seriousness were examined for the short, medium and long-term prognosis of wheelchair dependence using visual analogue scales; these perceptions were further elucidated in interviews. The study examines the following questions: 1) What do recently diagnosed persons with MS use to base their perception of absolute and comparative risk, and the seriousness of future wheelchair dependence? 2) Do patients distinguish between perceptions across the different prognoses (2-year, 10-year and lifetime) and for what reasons?

Methods

Procedures and participants

Participants were recruited through the Departments of Neurology of the Erasmus Medical Center (Rotterdam), three hospitals within the region of this academic

hospital, and the VU Medical Center (Amsterdam) from March 1999 to December 2000. Patients were eligible if they had been diagnosed with MS[9] within 2 years before entry in the study, were between 18 and 55 years old, and gave informed consent. Patients with serious co-morbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate in the study. Patients who declined to participate mentioned the emotional burden (n=3) or a lack of interest (n=3). Nine patients declined without additional comments, and four never responded to our reminders.

Patients underwent a neurological examination, filled out questionnaires, and were interviewed. The questionnaires were sent one week before the neurological examination and had to be completed before the interview, which was scheduled one week after the examination. Details of the neurological examination have been published elsewhere.[7] The study protocol was approved by the medical ethical committees of the participating hospitals.

Instruments

Perceived risk of becoming wheelchair-dependent was assessed over the short (2-year), medium (10-year) and long term (lifetime). The risk of wheelchair dependence was defined as the inability to walk beyond five meters, which equals a score of 7.0 on the Expanded Disability Status Scale (EDSS).[10] The actual risks of becoming wheelchair-dependent as a consequence of MS have been derived from epidemiological data and are estimated as 5-10% within two years, 20-25% within ten years and 70-80% over the lifetime.[11] Patients were asked to what extent they thought they would become wheelchair-dependent for distances over five meters within these periods (absolute risk). In addition, patients were asked to what extent their risk was lower or higher than the risk of other patients of similar age, similar sex and with similar disease symptoms (comparative risk). Perception of risk was assessed by 100mm visual analogue scales (VAS).[12,13] The end points of the VAS were anchored at 'Definitely not' (0) and 'Definitely' (100) for perceived absolute risk and 'much lower' (0) and 'much higher' (100) for perceived comparative risk. For the 2-year, 10-year and lifetime risk of wheelchair dependence, patients were asked how serious they thought it would be to be wheelchair-dependent by that time. Perceived seriousness was assessed on a VAS from 'Not serious at all' (0) to 'The most serious thing I can imagine' (100).

Patients were interviewed to learn more about their perceptions of risk and seriousness. The interviews were semi-structured and carried out by a psychologist [CJ] at the patient's home. For each question, patients were asked why they put their mark at that specific point of the VAS. Patients' explanations were tape-

recorded and transcribed verbatim. Sixteen interviews could not be used because patients had not completed their questionnaires at the time of the interview or because tape-recording failed, so that 85 complete interviews remained.

Data analysis

For the presentation of the distribution of perception of the absolute and comparative risk and the seriousness of future wheelchair dependence, VAS scores were recoded into 11 categories: 0-5 into 0, 6-15 into 10, 16-25 into 20, and so on. To determine whether patients discriminated between perceptions of risk and seriousness for the three time frames, difference scores were calculated. Cut-off scores were based on patients' explanations in the interviews. For example, when patients explained that they saw no difference for example between their 10-year and lifetime risk, the difference between these VAS scores was typically between -5 and +5. This margin was therefore taken to determine whether patients distinguished between perception of risk and seriousness of the 2-year and 10-year and between the 10-year and lifetime prospects of wheelchair dependence.

The qualitative analysis of the interview data involved approximately 160 pages of transcribed interviews. An interpretive reading of the interviews was conducted, which involved inferring meaning from the data.[14] The analysis consisted of two iterative activities: fragmenting and connecting.[15] In the first activity, the informative parts of each interview were extracted, categorized, and labeled with codes (open coding), using the program *Winmax.*[16] Some categories such as 'perception of seriousness' and 'comparative risk' were clearly defined by the theoretical framework, whereas others such as 'positive thinking' and 'fear of total dependence' emerged from the data. The second activity in the analysis process consisted of connecting the coded interview parts to patients' VAS scores and identifying explanations for the three different time frames. The first phase of open coding was conducted by one researcher, a sociologist [HB], and the final analysis was discussed with the second researcher [CJ], a psychologist, in order to ensure that the same interpretations were made, and to enhance inter-rater reliability.[17] Data extracts are presented to illustrate the main lines of reasoning of patients and to provide for a possible control. Reference is made to the different interviews (e.g., R1 = Respondent 1).

Results

The mean age of the participants was 37.5 years (SD 9.5), and 70% were women. The mean time since diagnosis was 7.8 months (SD 6.5), and the mean time since first symptoms 3.7 years (SD 4.6; median 2.1). EDSS scores ranged from 0.0 to 7.0

(median 2.5). Eighteen percent of the patients already experienced problems in walking, indicated by an EDSS score of 4.0 or higher.

Perception of absolute risk

Perceived 2-year risk

Figure 1 shows patients' perceptions of the absolute risk of becoming wheelchair-dependent within two years, ten years or during their lifetime. The first graph shows that the majority of patients perceived their 2-year risk of wheelchair dependence as being between 0 and 50%. The qualitative data of the interviews show that these patients did not expect to need a wheelchair within two years, although they were not sure about that:

> *'I don't think that I'll need a wheelchair and why, I don't know, but well, I don't know. Intuitively, I think I won't, just because I feel that it isn't progressing that fast, that it won't be that fast, but that isn't based on anything, really. It's a bit like you never know for sure. I mean it could happen, but I don't expect it to happen.' (R62)*

Some participants indicated in the interview that they were confident that their risk was lower than 50% because they had experienced a benign course so far or had fully recovered from earlier exacerbations. Others were hopeful because previous relapses had not involved their legs, which gave them reason to believe that a future relapse would again not affect their walking ability. Several women perceived their 2-year risk to be lower than 50% because they believed that previous relapses had been triggered by pregnancies and as they did not intend to become pregnant again they reasoned that their risk of relapses was low.

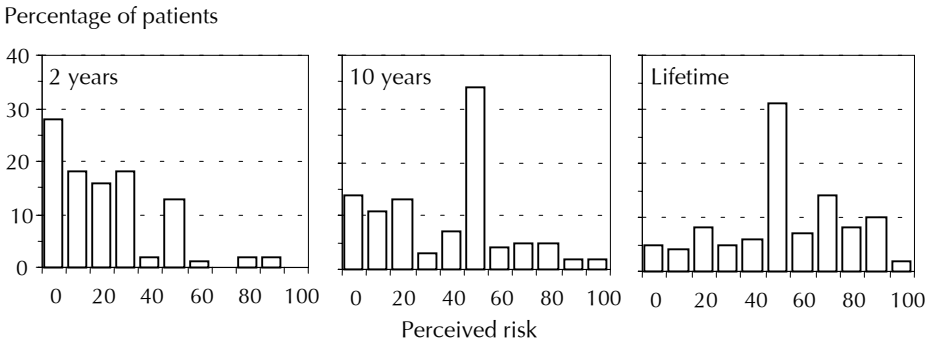

Figure 1 Perceived absolute risk of wheelchair dependence

Patients not only explained why they did not expect to become wheelchair-dependent within two years, but also why they were not sure. Above all, they mentioned the ubiquitous uncertainty of their disease. One patient, who put his mark close to 'definitely not', explained that 'with this disease you can never say something very definite; there is always a question mark.' Others had some reserves because they had a fresh memory of a recent upheaval of the disease or had recently been confronted with wheelchairs in their environment.

Some participants perceived their 2-year risk to be nil, as they could not imagine their illness progressing that fast. Several patients were convinced that they would not become wheelchair-dependent within two years, because this would be preceded by severe relapses or continuous disease progression, which they had not had so far. Others perceived their risk to be nil because they would not even consider the possibility, rejecting it out of hand:

> *'Yes, I assume that I have a mild form of the disease, probably also because I simply don't want it, It's just that I don't want to assume this, I don't want to allow the possibility that it may happen, so I don't believe it will happen, no.' (R70)*

Several participants chose to put their marks in the middle of the scale (50%). They argued that they just did not know what would happen and stressed the uncertainty with phrases like 'It might happen or it might not happen,' and 'I have no idea'. Only a few patients perceived their 2-year risk of wheelchair dependence to be higher than 50%. These patients primarily mentioned that they had already experienced severe physical limitations and expected that this progression would continue in the years to come. None of the patients marked the utmost right position of this VAS.

Perceived 10-year risk

The second graph of Figure 1 shows that a substantially larger group of patients put their cross in the middle of the VAS, perceiving their 10-year risk of wheelchair dependence as significantly higher than the 2-year risk. They gave two reasons why they chose the middle more often. The first group of patients stressed that they really did not know what to expect: it might happen or it might not. As one person explained:

> *'Yes, I don't know, that's why I marked the middle, because I simply don't know. I can't say that I will definitely be in a wheelchair, no, because I simply*

don't know that now. But, I can't say 'definitely not'. It's not even a little more 'definitely yes' or a little more 'definitely not'.' (R51)

Some patients were uncertain about life in general. One woman, who mentioned she had had a sudden onset of MS after her pregnancy, emphasized that 'anything can happen any time. You can be stabbed tomorrow and have a spinal cord injury. You don't know.'

For the second group, the 50% response was a balance, a neutral option between two sides of the scale. Some patients who anticipated that they might become wheelchair-dependent marked the middle because they still hoped that their disease would not progress that fast or did not want to believe that it would: 'I've had this wheelchair for more than half a year now, but I've hardly used it. I still hope that I'll recover'. One patient marked the middle of the line because she remembered having read that the risk of becoming wheelchair-dependent within ten years after diagnosis was 50%. Another 50% responder remembered that 80% of patients were still able to walk after ten years:

'Yes, statistics say that ten years after diagnosis 80% are still able to walk, so then I think let's keep it fifty-fifty. I don't know, it's just a guess. Let's say, it's an answer between hope and fear. So that's fifty-fifty.' (R55)

Forty-eight percent of the patients perceived their 10-year risk of wheelchair dependence as less than 50%. Two dominant explanations were put forward by patients: they were only mildly affected by the disease and did not expect to have a progressive form of MS or they hoped to prevent or postpone the need for a wheelchair by adopting a very positive attitude. One woman was optimistic because her doctor had told her it was unlikely that her disease would progress very fast. In addition, other patients explained that so far MS had not affected their legs or motor skills:

'With me it started very different and not in my limbs. It started with my eyesight, with seeing double and I didn't have strange legs or shaky knees or tingling legs, and that's why I don't think there's more than a twenty to thirty percent ten years.' (R73)

While most respondents expressed some hesitation, some patients were convinced that 'it's just not going to happen'. These patients put their mark at the extreme lower end of the scale, because they wanted to be strong and not

surrender to MS. Again, only a few patients marked the VAS between the middle and the upper end of the scale. These patients referred to the problems they had already experienced walking and expected that their condition would continue to worsen over the next years. However, they were also not sure: with a little luck, exercise and therapy they thought they might be able to postpone the use of a wheelchair for shorter distances.

Perceived lifetime risk

The last graph of Figure 1 shows that a larger group of patients did expect to become wheelchair-dependent over the long term. They acknowledged that MS is a progressive disease and that as time passes their disabilities might worsen despite exercise, medication and therapy. However, with a few exceptions, these patients did not mark the upper end of the VAS ('definitely yes'). They still hoped that they would not become wheelchair-dependent, because 'nobody can tell for sure that you'll need one'. One patient referred to having read that 80% of patients eventually needed a wheelchair, but hoped to be part of the 20% 'for whom a walking stick would be sufficient'. Several patients mentioned that through positive thinking, they might avoid the need for a wheelchair. Only two patients selected the utmost right position for their perceived lifetime risk. These patients were convinced that they would sooner or later need a wheelchair based on what they had read about the disease or heard from their neurologist.

With regard to the perceived lifetime risk of wheelchair dependence, many participants also put the cross in the middle of the scale, again explaining this with expressions such as 'It's a neutral position,' 'I just don't know,' and 'It's fifty-fifty'. Here as well, patients really did not know or chose a balance between two extremes:

> *'Yes, I put that mark in the middle because I think it might happen sometime, but I don't want to think about that possibility, I simply don't want to think about that. That's it.' (R29)*

Patients who perceived their lifetime risk as lower than 50% primarily explained that they did not want to anticipate that possibility, that they hoped it would not happen or that positive attitude would help. A few patients hope that by that time effective medication would have been developed. And finally, several patients commented that they did not mark the lower end of the scale because that would be naive, fooling or lying to oneself, and because one should be honest with oneself.

How perceptions of absolute risk in different time periods are related

Comparing perceived absolute risk of the 2-year, 10-year and lifetime prognosis of wheelchair dependence, it was found that 45% of the patients did discriminate between these time periods (Table 1). They shifted to a higher risk perception from the short to the long term. Even patients who were optimistic about the role of positive thinking on the course of MS moved from the lower end 'definitely not' for their 2-year risk perception to the middle or even higher for the long-term risk: they did not believe that they could fight major disease progression even if they did their utmost. Nineteen percent of the patients made no distinction between the 2-year and 10-year risk but perceived these as lower than the lifetime risk, and 25% made no distinction between the 10-year and lifetime risk but perceived these higher than the 2-year risk. Both groups did not expect to need a wheelchair soon but acknowledged the progressive and unpredictable nature of MS over the longer term. Eleven percent of the patients did not discriminate between the three timeframes. They either consistently marked the VAS at the lower end ('I have a positive attitude'), or at the higher end ('In view of my current health, it's quite possible that I'll need a wheelchair within two years') or in the middle of the VAS ('I don't know').

Table 1 Distinctions between 2-year, 10-year and lifetime prospects in the perception of risk and seriousness of wheelchair dependence

	Absolute risk	Comparative risk	Seriousness
All different	45	16	25
2 years = 10 years ≠ lifetime	19	8	11
2 years ≠10 years = lifetime	25	13	32
All the same	11	63	32
Total	100	100	100

Values are percentage of patients.

Perception of comparative risk: comparison with other patients

When asked to compare their risk with that of other patients, the vast majority of patients responded in the middle of the VAS (Figure 2) explaining that all patients of the same age, sex and with the same symptoms have equal chances:

> *'Umm, that's looking into the future, why should I have a lower chance than anybody else? That's such an uncertain factor and my chance is as high or as low as the next person. So, I just don't know.' (R72)*

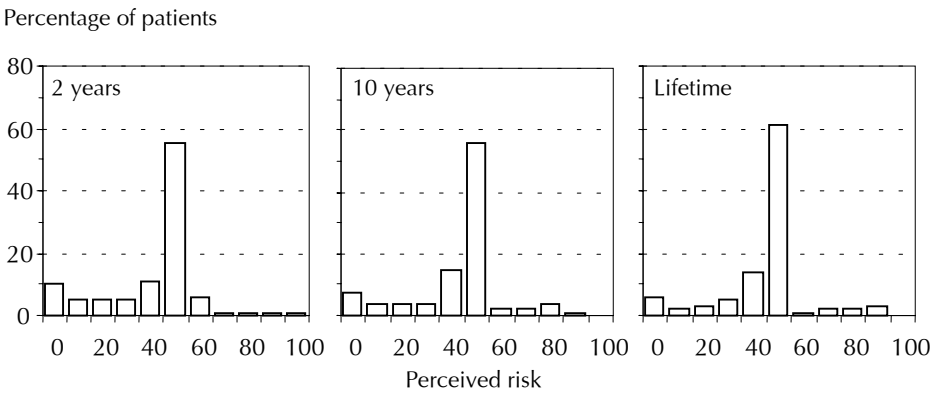

Figure 2 Perceived comparative risk of wheelchair dependence

Several patients in this group stated that they were no better than anybody else and did not want to act arrogantly. Others referred to this as just being a neutral answer.

Some patients believed they had a lower chance of needing a wheelchair because they would try to influence their illness with their willpower and would therefore have a lower risk of wheelchair dependence compared to others who did not make a comparable effort. Few patients thought their chances were higher, acknowledging they might have a malignant type of MS, which would probably have a faster disease progression in the future.

Many patients had great difficulty imagining a group of patients of similar age, similar sex and with similar symptoms ('I don't know anyone comparable') and some compared themselves with MS patients they knew or with other persons they knew who were wheelchair-dependent. Four patients would not answer these questions on perceived comparative risk at all: they were unwilling to compare themselves with hypothetical others.

How perceptions of comparative risk in different time periods are related

Sixty-three percent of the patients did not make a distinction between their perceived comparative risk for the 2-year, 10-year and lifetime prognosis of wheelchair dependence (Table 1). Of these patients, 85% evaluated their risk the same as other patients and 13% perceived themselves at lower risk. Patients who made a distinction (37%) primarily tended to perceive their 2-year risk as lower than that of others and their lifetime risk as higher, but they had no explicit explanations for these differences.

Perception of the seriousness of future wheelchair dependence

When asked whether they considered wheelchair-dependence within the short, medium or long term having serious consequences (Figure 3), three groups could be identified. The first and largest group found the image of using a wheelchair daunting. Loss of mobility, loss of independence, a shrinking social world, adaptations in the house or even having to move, and the need for help were mentioned as things they considered serious consequences. At the same time, these patients believed they might regard the wheelchair as an increase of mobility after a period of having walked with great difficulty and expected that they would therefore get used to it.

Although these patients considered wheelchair dependence having serious consequences, they could still think of more serious ones. Examples of more serious consequences included dying of MS, losing vision, speech, hearing, cognitive functions, hand and arm function, or becoming incontinent.

> *'Yes, for sure it's serious, but not as serious as if I lost my vision or if I went insane; a wheelchair isn't the most serious thing. I think if I lose my vision, that's serious, or if I go insane, that something is wrong with my brains, that I no longer remember what day it is or when I say this isn't my husband, or if I'm not able to respond.' (R52)*

One patient mentioned that wheelchair dependence would be particularly bad if people ignored and isolated you as a result of being wheelchair bound. Several other patients mentioned worse events not related to MS such as cancer, pain, stroke or a serious accident. Others found it worse if something terrible were to happen to their children, their partner or other close family members. And others

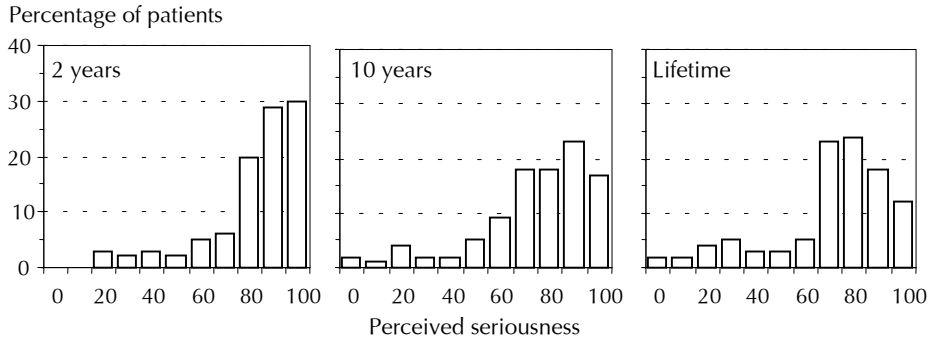

Figure 3 Perceived seriousness of wheelchair dependence

put their illness into perspective, saying that the world goes on and that a world war would be far worse.

The second group considered wheelchair dependence the worst thing that could happen to them because their visible disability would encourage other people to treat them as disabled persons and pity them or because they would lose all their independence. Finally, the third group consisted of a small group of patients who were glad that they were still alive and saw the wheelchair as a minor inconvenience.

How perceptions of seriousness in different time periods are related

One-third of the patients did not discriminate in the seriousness of the 2-year, 10-year and lifetime prognosis of wheelchair dependence: the need of a wheelchair within two years was perceived as equally serious as needing a wheelchair within ten years or after an even longer period. Another third of the participants distinguished between the short-term risk of wheelchair dependence on the one hand, and the 10-year and lifetime prospect on the other. They reasoned that there would not be enough time to get used to the idea and there would be less time left for things they wanted to do, for instance enjoying the relationship with the partner, raising children, working or traveling. Patients also considered wheelchair dependence within two years as being more serious, because this would indicate a rapidly progressing form of MS:

> *'Yes, I think that's serious, because then it's only two years, I still would have liked to do this and this, but than it goes very, very fast. That would be frightening, yes. Because, when the disease progresses very slowly, than you get worse step by step, that may be easier to accept. And if I need a wheelchair in two years, what will happen in four years? Ten years, that's still a long way off, then I can still do a lot of things in the years to come.' (R68)*

Discussion

In this study, perceptions of prognostic risk of patients with MS were investigated with a focus on the risk of wheelchair dependence. The predominant finding is the omnipresence of disease uncertainty, which is in line with previous studies on uncertainty in MS.[2-4] Uncertainty not only explained the 50% scores of patients, but lower and higher perceptions of risk were also explained as being based on the uncertainty about what would happen. Although wheelchair dependence was defined as being unable to walk more than five meters, and though the patients

were all assessed within a short period after diagnosis, patients did not feel confident ruling out the short-term possibility of wheelchair dependence.

To explain their perceptions of risk, patients mentioned disease-related factors such as presence and type of symptoms, the course of MS, recent disease progression and medication. But psychological factors such as hope and fear were also considered important, in particular for medium- and long-term risk perception. These qualitative data demonstrate that the VAS measurements directed the expectations about future wheelchair dependence. Because our patients were not hindered by knowledge of actual risks, which are generally not communicated to MS patients, expectations were clearly from an individual perspective, rather than based on knowledge of population risks. This can be seen in the elucidations of patients who used the 50% response. As has also frequently been found in other studies,[e.g.][18] these patients did not necessarily believe that the 'actual' population risk is 50%. We argue that this does not threaten the validity of perception of absolute risk assessment, since perception addresses individual beliefs rather than knowledge of epidemiological risks.

In the interview study, we found ample evidence that patients used heuristic reasoning to perform their risk analysis.[19] First, the fact that several patients could not imagine themselves being wheelchair-dependent and perceived their risks to be low, literally follows the heuristic of availability. In addition, the reason why vivid memory of recent relapses and the familiarity with wheelchair-dependent patients were mentioned by patients to explain why their risk would be higher, is explained by the same heuristic. Second, patients mentioned factors that would indicate a higher risk, such as previous symptoms affecting walking ability, severe relapses or continuous disease progression, and, as they had not experienced these symptoms, concluded that they were at lower risk. This reasoning is according to the heuristic of representativeness.[19] And finally, according to the heuristic of anchoring and adjustment, patients who responded with 50% may have refrained from further adjustment or evaluation whether their risk would be more or less likely,[19] perhaps because thinking about the possibility was too threatening. This heuristic may also explain the 50% responses, since patients who primarily stressed that they did not know what to expect, did not usually add reasons why it would not be more or less likely.

Our study demonstrated that patients had difficulty comparing themselves with hypothetical others. A few patients would not answer these questions, whereas others compared themselves with patients they knew or with the average MS patient. One explanation, also put forward by the participants themselves, is that they did not know whom to compare with. Earlier studies on unrealistic optimism,

where subjects on average perceive their risks to be lower than those of others, have shown that this lower perception of comparative risk is associated with the attribution of preventive actions to oneself and not to others.[20] In MS, opportunities to control the disease by medication or lifestyle changes are limited, and this may be the reason why patients feel their risk to be equal to that of others. Further, most patients did not discriminate between the three time periods. We therefore conclude that the usefulness of comparative risk perception is questionable for unpredictable and poorly controllable (prognostic) risks. Thus, comparison of quantitative and qualitative assessments indicated good construct validity for perception of the absolute risk and seriousness of wheelchair dependence, but not for the comparative prognostic risk.

In coping with the uncertainty of their illness, MS-patients tended to focus on controlling their state of mind and their optimism, lacking other means of control.[5,21] Seeing oneself in the distant future and giving meaning and direction to a life with MS, seems an almost impossible task for patients and decreases their well-being.[8] Therefore, it is deemed clinically important to help them deal with uncertainty. For many MS patients, in particular those who have been diagnosed recently and those with minimal neurological symptoms, short-term risks of serious consequences of MS are low or unlikely but far from completely uncertain. Our study implies that when communicating with patients, it is important for health professionals to first verify what consequences are of major concern to the patient and then to discuss the prognosis of these outcomes under the condition of modest uncertainty (we don't know for sure) rather than complete uncertainty (we don't know at all). Patients may even benefit from this uncertain information as it may give them some idea about their prognosis in the near future and help them to maintain a grip on life.

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11

LONGITUDINAL STUDY OF PERCEPTION OF PROGNOSTIC RISK IN RECENTLY DIAGNOSED PATIENTS WITH MULTIPLE SCLEROSIS AND THEIR PARTNERS

Abstract

Background: In a two-year follow-up study, expectations of prognosis with regard to the risk and seriousness of wheelchair dependence were investigated in patients with multiple sclerosis (MS) and their partners. In patients, the determinants of perceived risk and seriousness, as well as the predictors of change were studied. **Method:** Perception of the risk and seriousness were assessed for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Data were obtained in 101 patients with MS and 78 partners at baseline, six-month, one- and two-year follow-up. Clinical disability, perceived symptoms and illness beliefs were assessed at each visit, whereas personality (pessimism and neuroticism) was measured at baseline only. **Results:** Both in patients and partners, perceptions of the 2-year and 10-year risk of wheelchair dependence significantly increased during the 2-year follow-up. Perceived lifetime risk and perceived seriousness did not change over time. Patients who reported more symptoms had higher perception of their 2-year (regression coefficient $B = 0.78$, $p < 0.0001$) and 10-year risk ($B = 0.87$, $p < 0.0001$) after adjustment for disability status. The relation between perceived symptoms and risk perception was stronger among patients with high neuroticism ($p = 0.0004$) and this effect significantly increased during follow-up ($p = 0.001$). Only changes in perceived symptoms were associated with changed in perception of risk ($B = 0.786$, $p_{interaction} = 0.0007$). **Conclusions:** Perception of the short- and

medium-term risk of wheelchair dependence increased in the first years after diagnosis in patients and their partners. This increase was associated with increased symptom perception. Our findings suggest that educating patients about MS-related symptoms and their significance for future disease progression can lower perception of risk.

Introduction

Although multiple sclerosis (MS) is a chronic disabling disorder, the majority of patients do not experience major complications in the early phase of disease. Yet, patients are usually informed at diagnosis about the possibility of future disease complications. For patients it may be difficult to comprehend prognostic risks of outcomes such as wheelchair dependence. As a consequence, their expectations may considerably deviate from 'actual' risks. In this study, patients recently diagnosed with multiple sclerosis (MS) and their partners overestimated their short- and medium-term risks of wheelchair dependence (Chapter 6). As expected, higher perceptions of risk were significantly associated with more physical limitations of the patient (Chapter 6). But in addition, patients who reported more symptoms due to their disease had higher perception of risk – after adjustment for differences in clinical disability status (Chapter 8). Since patients' perceptions of the risk and seriousness of major complications are important determinants in major life decisions and emotional well-being, it is important to know how perceptions develop during the first years after diagnosis.

For several reasons, expectations about future wheelchair dependence of patients and partners may change in the first years after diagnosis. In the first place, expectations may change because patients will or will not develop (new) symptoms. Most patients experience variable phases of remission, whereas in others the disease will gradually worsen from onset.[1] We and others have shown that patients use their present disease status to predict future disease progression (Chapter 8).[2-4]. A second reason why expectations may change is coping. Particularly in this early period after diagnosis, patients and partners have to find ways to live with the uncertain prospects of the disease. Also, they may seek information about MS and get better informed about the future complications. Early symptom development and coping may have different effects on perceived risk and seriousness of wheelchair dependence. On the one hand, patients may learn that the risks of major complications are not as high as they thought, or may be encouraged by recovery from early symptoms and the absence of new ones. In these situations, expectations may become more optimistic. On the other hand, expectations may become more pessimistic when patients experience further

disease progression. Both ways predict that patients' clinical status – objective or perceived – is an important determinant of perception of prognostic risk.

In a two-year follow-up study, we investigated perception of prognostic risk in patients recently diagnosed with MS and their partners. We intended to answer the following questions: (1) Do perceptions of prognostic risk of patients and their partners change in the first two years following their diagnosis? (2) Do factors that were associated to the patients' perceived risk and seriousness at baseline (disability status, perceived symptoms, personality and illness beliefs) also play a role in perceptions of risk at follow-up? (3) Are changes in these determinants associated with changes in perception of risk and seriousness at follow-up?

Methods

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the VU Medical Center (Amsterdam) in the period of March 1999 – December 2000. Patients were eligible if they were diagnosed with definite or probable MS[5] within two years before entry in this study, were between 18 and 55 years old, and had given informed consent. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate in the study. Ninety out of 101 patients had a partner, of whom 78 (87%) participated in the study. This prospective study consisted of a baseline and three follow-up assessments (at six months, one year and two years). Of the 101 patients who entered the study, 98 (97%) completed the half-year and 97 (96%) the one-year follow-up. The data-collection is still ongoing, but 81 patients were already invited for the fourth exam, of whom 72 (89 %) participated. Seventy-eight partners started the study, of whom 72 (92%) completed the one-year follow-up. Fifty-five partners (out of 66, 83%) already participated in the two-year follow-up assessment. Baseline characteristics of patients and partners are presented in Table 1.

Patients completed questionnaires at all assessments and were scheduled for a neurological examination at baseline, one-year and two-year follow-up and a psychological interview at baseline. At these visits, also partners filled out questionnaires. Questionnaires for patients and partners were sent by mail one week prior to the neurological examinations and had to be handed in at the time of the psychological interview (baseline) or the neurological examinations (follow-up) or returned by mail. At baseline, partners were given their questionnaires at the time of the patient's interview and were asked to complete these in another room.

Table 1 Baseline characteristics of patients and partners

Time since diagnosis (months):	0-6	7-12	13-24	Total
Patients	n = 58	n = 18	n = 25	n = 101
Age (years)	37.7 (9.0)	40.8 (11.3)	36.6 (9.1)	37.5 (9.5)
Sex (women)	66%	72%	80%	70%
Time since diagnosis (months)	3.1 (1.5)	9.3 (1.7)	17.6 (3.6)	7.8 (6.5)
Time since first symptoms (years)	3.2 (3.7)	4.8 (7.4)	4.2 (4.0)	3.7 (4.6)
Diagnosis (definite MS)	90%	94%	88%	90%
EDSS (median, IQR)	2.5 [2.0, 3.5]	1.5 [1.0, 2.5]	2.5 [2.0, 4.0]	2.5 [1.5, 3.5]
Partners	n = 45	n = 12	n = 21	n = 78
Age (years)	39.0 (8.4)	42.5 (10.2)	38.2 (8.4)	39.3 (8.7)
Sex (women)	44%	25%	24%	36%

Values are means (SD) or percentages, unless otherwise indicated. EDSS = Expanded Disability Status Scale, IQR = inter-quartile range.

At one- and two-year follow-up, patients and partners were mailed their questionnaires simultaneously, with an explicit request to complete the questionnaires on their own. The study protocol was approved by the medical ethical committees of the participating hospitals.

Measurements

Perceptions of prognostic risk. Perception of risk and seriousness was targeted at the risk of becoming wheelchair-dependent as a consequence of MS. Wheelchair dependence was defined as the inability to walk beyond five meters. This definition equals a score of 7.0 on the Expanded Disability Status Scale (EDSS).[6] Perception of risk and seriousness were assessed for the short- (2 years), medium- (10 years) and long-term (lifetime) prospects of wheelchair dependence. Perception of risk was measured using a 100mm visual analogue scale (VAS) from 'Definitely not' (0%) and 'Definitely' (100%). Further, patients were asked for each time period how serious they think it is to be wheelchair-dependent by that time. Perceived seriousness was assessed on a VAS from 'Not serious at all' (0) and 'The most serious thing I can imagine' (100). Partners completed the same questions, addressing the patient's risk of wheelchair dependence and the seriousness of their partner becoming wheelchair-dependent.

Perceived symptoms. Perceived symptoms were assessed using illness identity scale of the Illness Perception Questionnaire (IPQ).[7] The identity scale includes intensity ratings of symptoms that are experienced by patients and attributed to their disease. As recommended,[7,8] this scale was adapted for use in a MS

population. The adapted scale consisted of 23 symptoms: twelve symptoms were taken from the IPQ list (excluding breathlessness) and eleven were added (concentration problems, coordination problems, muscular pain, numbness of limbs, loss of balance, feelings of depression, blurred vision, diplopia, bladder symptoms, bowel symptoms and spasticity). Answers were scored on a four-point scale: all of the time = 4, frequently = 3, occasionally = 2, and never = 1. These scores sum into a total score ranging from 23 to 92. The scale had good internal consistency reliability (Coefficient $\alpha = 0.87$).

Illness beliefs. The Illness Perception Questionnaire (IPQ) and its revised version (IPQ-R) were also used to assess patients' beliefs about the controllability of MS by treatment (treatment control, 3 items), the duration of their disease (chronic timeline, 3 items) and their understanding about the disease (perceived coherence, 5 items).[7,8]. Answers were rated on a five-point scale ranging from 'Strongly agree' to 'Strongly disagree' (scored 5 to 1).

Personality. Neuroticism was included as the dimension of personality consisting of negative emotions such as anxiety and anger, and cognitive and behavioral characteristics such as low self-esteem, preoccupation and insecurity.[9] Neuroticism was assessed by the 12-item neuroticism scale of the Eysenck Personality Questionnaire (EPQ).[10,11] The scale ranges from 0 to 12, with high scores indicating high neuroticism. Pessimism was assessed using the Life Orientation Test (LOT).[12,13] The LOT pessimism scale consists of four negatively formulated items (pessimism) with a possible range of 4 to 20. High scores on the pessimism scale indicate greater pessimism.

Clinical data. Neurological examinations were conducted by physicians following a standardized research protocol. Functional limitations were rated on the EDSS,[6] which ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS). Date of first symptoms was assessed during the neurological examination. Date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the medical records and verified by a senior neurologist.

Statistical analyses

We used the SAS Proc Mixed Repeated measurement procedure for the analyses of longitudinal data. This procedure takes into account that the same individual contributes information at different time points and allows the inclusion of subjects with incomplete follow-up. Available data and the matrix of covariance are used to predict missing data.[14] This likelihood-based procedure generates more accurate estimates of the parameters than analyses of available data or of data from patients who completed all measurements only.

We first examined the course of perceived risk and seriousness of wheelchair dependence in patients and partners by comparison of estimated means using SAS Proc Mixed with time (0, ½, 1 and 2 years) and time since diagnosis at inclusion (0-3, 4-6, 7-12 and 13-24 months) as independent categorical variables. Analyses were conducted for patients and partners and for the perceived risk and seriousness of 2-year, 10-year and lifetime wheelchair dependence separately.

Second, we analyzed the determinants of perception of risk and seriousness at follow-up. Since possible determinants were only assessed in patients, these analyses are limited to patients. Based on results of the baseline analyses (Chapter 6, 8 and 9), the role of disability status, perceived symptoms, personality and illness beliefs as well as their significant interaction effects (perceived symptoms * neuroticism and disability status * pessimism) were studied. Whether the impact of determinants changed over time was investigated by the interaction of the main effects with time (0, ½, 1 and 2 years, recoded into 0, 1, 2 and 4). Whether the influence of determinants differed for short-, medium- and long-term prognosis was investigated by the interaction of the main effects with prognosis (2 years, 10 years and lifetime, recoded into 0, 1 and 2). Analyses were adjusted for time since diagnosis, time since first symptoms, age and sex. Using SAS Proc Mixed, the following strategy was used. A full model was tested including aforementioned main and interaction effects. The saturated model was simplified by eliminating non-significant covariates and interaction effects. Elimination was based on the significance of the difference in –2 log likelihood goodness of fit between the reduced and the saturated model. If the p-value was higher than 0.05 (χ^2-test), the parsimonious model was considered not significantly different from the saturated model, and used for further simplification. Regression coefficients (B) of the final model were estimated using the restricted maximum likelihood procedure (REML).

Third, to determine whether changes in disability status and perceived symptoms were associated with changes in perception of risk and seriousness of wheelchair dependence, the analyses were repeated using difference scores for perception of risk and seriousness and differences in scores of determinants mentioned above. These difference scores were obtained by extracting baseline values from scores at one- and two-year follow-up. Baseline values of neuroticism and pessimism were taken to assess their influence in the change of perception of risk and seriousness. As above, we investigated whether changes differed for short-, medium- and long-term prognosis by including interaction effects of the main effects with prognosis (2 years, 10 years and lifetime). The same strategy for model simplification was used. P-values < 0.05 were considered statistically significant.

Results

Disability status and perceived symptoms during 2-year follow-up

Median EDSS scores did not change during the 2-year follow-up (median = 2.5 at each visit). Also, the means of perceived symptoms did not change significantly: the mean score of perceived symptoms was 39.5 (SD 9.3) at baseline, 39.6 (SD 9.2) and 40.1 (SD 9.7) at follow-up (B for linear trend = 0.20, p = 0.17).

Perception of risk and seriousness during 2-year follow-up

Figure 1 shows estimated means of perceived risk of patients and partners. Means are presented for four groups defined by time since diagnosis at inclusion in the study (0-3, 4-6, 7-12 and 13-24 months). Because patients were diagnosed up to 2 years prior to study entry, the present data cover the first four years after diagnosis. In both patients and partners, perception of the 2-year and 10-year risk

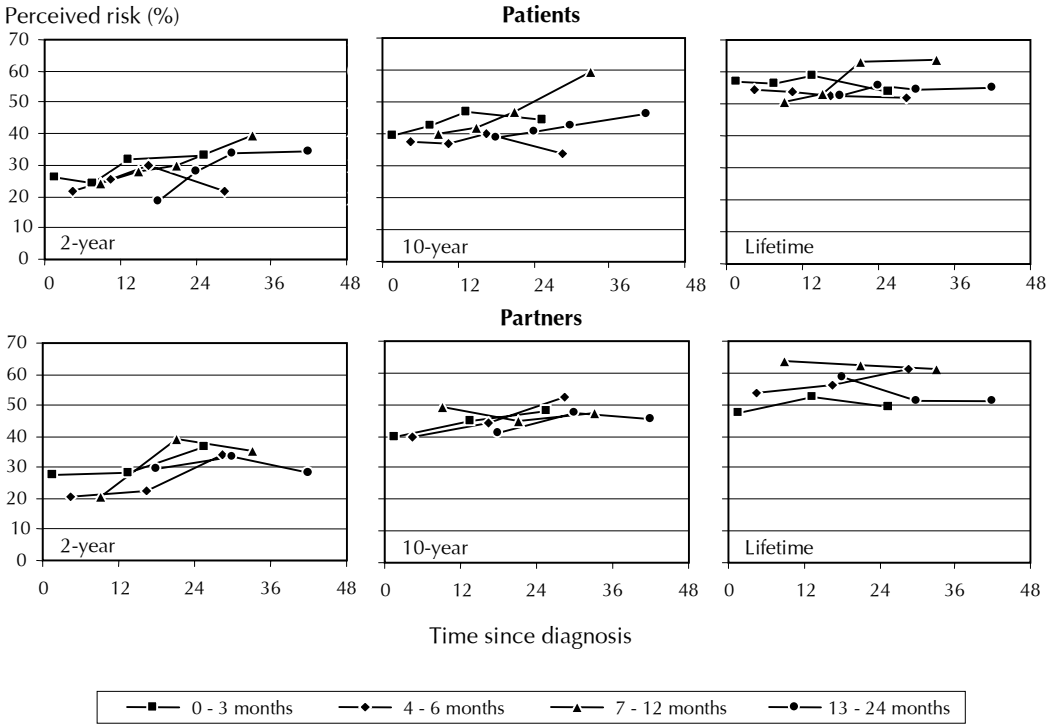

Figure 1 Estimated means of perceived risk of wheelchair dependence of patients and partners during follow-up

Groups are defined by time since diagnosis at baseline (see Methods).

increased significantly during the 2-year follow-up ($p < 0.05$), but the mean perception of the lifetime risk did not change over time. Patients and partners considered wheelchair dependence a serious consequence of MS, and this evaluation of seriousness did not change at follow-up ($p > 0.05$; Figure 2).

Determinants of perceived risk and seriousness

We investigated the determinants of perceived 2-year, 10-year and lifetime risk in a simultaneous analyses of the cross-sectional data over time. Table 2 first shows that perception of risk was significantly different for the three prognoses (mean 2-year risk = 22.9%, 10 years 38.9% and lifetime 54.5%). Also after adjustment for other determinants the increase in perception of risk was significant for the 2-year ($B = 2.15$, $p = 0.0004$) and 10-year prognosis ($B = 1.55$, $p = 0.02$). Further, perception of risk was significantly higher among patients with higher disability

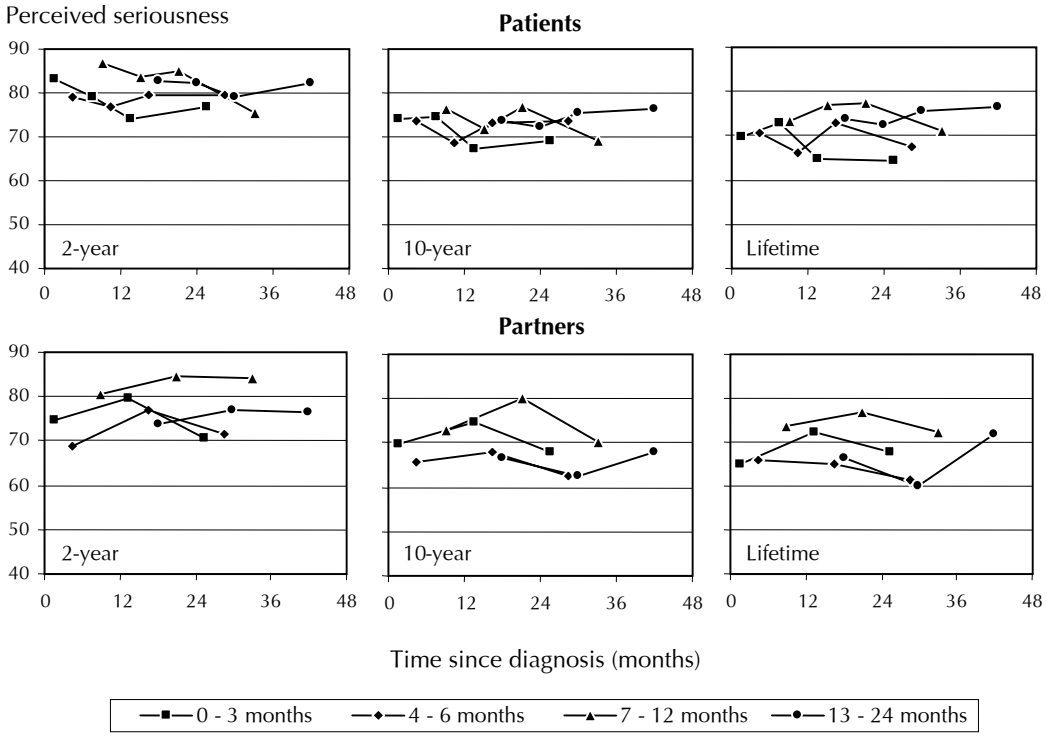

Figure 2 Estimated means of perceived seriousness of wheelchair dependence of patients and partners during follow-up

Groups are defined by time since diagnosis at baseline (see Methods).

status, as measured by the EDSS (B = 3.39, p < 0.0001). The impact of EDSS did not change over time and did not differ between the three prognoses, because these interaction effects were not statistically significant. After adjustment for EDSS, it was found that patients who reported more symptoms of their disease had higher perception of the 2-year (B = 0.78, p < 0.0001) and 10-year risk (B = 0.87, p < 0.0001). The association between perceived symptoms and perception of risk increased during the 2-year follow-up, as indicated by the significant interaction term (B = 0.20, p = 0.001). Patients who thought they had a better understanding of their disease had higher perception of risk at baseline, but this effect of perceived coherence was less pronounced at follow-up. Finally, neuroticism modified the effect of perceived symptoms: the relation between symptom reporting and perceived risk of wheelchair dependence was significantly stronger in those scoring high on neuroticism (B = 0.20, p = 0.0004).

Using a similar strategy, the determinants of perceived seriousness were investigated (Table 3). The table first shows that perceived seriousness of the 2-year prognosis (mean = 81.3%) was significantly higher than the seriousness of

Table 2 Determinants of perceived risk of wheelchair dependence: cross-sectional analysis of follow-up data

		B [95% CI]	p
Prognosis	2 years	22.91 [19.59, 26.23]	
	10 years	38.94 [34.92, 42.96] ***	
	Lifetime	54.50 [50.08, 58.93] ***	
Prognosis · time	2 years	2.15 [0.99, 3.32]	0.0004
	10 years	1.55 [0.30, 2.80]	0.02
	Lifetime	0.01 [-1.31, 1.33] **	0.99
Disability status		3.39 [1.77, 5.00]	< 0.0001
Perceived symptoms · prognosis:	2 years	0.78 [0.41, 1.15]	< 0.0001
	10 years	0.87 [0.48, 1.26]	< 0.0001
	Lifetime	0.27 [-0.15, 0.69] *	0.20
Perceived symptoms · time		0.20 [0.08, 0.31]	0.001
Perceived coherence		0.70 [0.04, 1.37]	0.04
Perceived coherence · time		-0.38 [-0.65, -0.11]	0.006
Neuroticism		-0.67 [-1.76, 0.42]	0.22
Neuroticism · perceived symptoms		0.20 [0.09, 0.31]	0.0004

SAS Proc Mixed Repeated Measurements. B = regression coefficient, CI = confidence interval. Non-significant covariates and interaction effects were removed from the model using a backward selection strategy (see Methods). * p for interaction < 0.05, ** p < 0.01, *** p < 0.001 indicate significance of differences between interaction effects (2-year period = reference).

Table 3 Determinants of perceived seriousness of wheelchair dependence: cross-sectional analysis of follow-up data

		B [95% CI]	p
Prognosis	2 years	81.29 [77.84, 84.74]	
	10 years	74.83 [71.09, 78.57] ***	
	Lifetime	73.31 [69.59, 77.03] ***	
Disability status		-3.44 [-5.55, -1.34]	0.0002
Disability status · time		0.82 [0.14, 1.51]	0.02
Perceived symptoms · prognosis:	2 years	-0.04 [-0.38, 0.30]	0.81
	10 years	0.16 [-0.19, 0.51] *	0.37
	Lifetime	0.39 [0.01, 0.76] ***	0.04
Pessimism		1.88 [0.32, 3.44]	0.02
Pessimism · disability status		-0.32 [-1.02, 0.39]	0.38
Neuroticism		-0.80 [-2.23, 0.64]	0.27
Neuroticism · perceived symptoms		-0.05 [-0.18, 0.08]	0.44
Treatment control		-1.26 [-2.54, 0.01]	0.05
Chronic timeline		-1.47 [-2.70, -0.25]	0.02
Perceived coherence		-0.71 [-1.46, 0.04]	0.08

SAS Proc Mixed Repeated Measurements: B = regression coefficient, CI = confidence interval. Non-significant covariates and interaction effects were removed from the model using a backward selection strategy (see Methods). * p for interaction < 0.05, ** p < 0.01, *** p < 0.001 indicate significance of differences between interaction effects (2-year period = reference).

wheelchair dependence for the 10-year (74.8%) and lifetime prognosis (73.3%). Patients with higher EDSS scores thought wheelchair dependence to be less serious (B = -3.44, p = 0.0002). This association was less pronounced at follow-up as indicated by a significant interaction effect in the opposite direction (B = +0.82, p = 0.02). Perceived symptoms were significantly related to perceived seriousness of the lifetime prognosis of wheelchair dependence (B = 0.39, p=0.04). Patients who were more pessimistic considered wheelchair dependence to be more serious (B = 1.88, p = 0.02). The interaction effects of perceived symptoms and EDSS with personality were not significant in this cross-sectional analysis of the follow-up data. Both patients who had a stronger belief that MS is controllable by medication (B = -1.26, p = 0.05) and those who had a stronger belief that the disease is chronic (B = -1.47, p = 0.02) perceived wheelchair dependence to be less serious. Neither perception of risk nor perception of seriousness was significantly related to time since diagnosis, time since first symptoms, age and sex.

Table 4 Predictors of change in perceived risk and seriousness of patients

		Δ Perceived risk		Δ Perceived seriousness	
		B [95% CI]	p	B [95% CI]	p
Prognosis	2 years	8.58 [4.44, 12.72]	< 0.0001	-5.19 [-9.40, -0.99]	0.02
	10 years	5.69 [1.48, 9.89]	0.008	-2.81 [-7.31, 1.68]	0.22
	Lifetime	1.68 [-2.84, 6.17] **	0.47	-1.03 [-6.00, 3.94] *	0.68
Δ disability status		-0.29 [-2.72, 2.14]	0.82	0.27 [-2.41, 2.95]	0.84
Δ Perceived symptoms		0.76 [0.32, 1.19]	0.0007	0.17 [-0.29, 0.62]	0.47
Pessimism		-		0.33 [-1.46, 2.12]	0.71
Pessimism * Δ disability status		-		-1.46 [-2.55, -0.36]	0.01
Neuroticism		1.35 [0.07, 2.63]	0.04	-0.17 [-1.84, 1.51]	0.84
Neuroticism * Δ perceived symptoms		0.16 [-0.01, 0.34]	0.07	-0.00 [-0.20, 0.19]	0.96
Δ Treatment control		-		-1.06 [-2.62, 0.51]	0.18
Δ Chronic timeline		-		-1.44 [-2.97, 0.10]	0.07
Δ Perceived coherence		-0.13 [-1.04, 0.78]	0.78	-0.22 [-1.25, 0.81]	0.67

SAS Proc Mixed Repeated Measurements. B = regression coefficient, CI = confidence interval. Non-significant covariates and interaction effects were removed from the model using a backward selection strategy (see Methods). * p for interaction < 0.05, ** p < 0.01, *** p < 0.001 indicate significance of differences between interaction effects (2-year prognosis = reference).

Determinants of change in perceived risk and seriousness

Finally, we investigated whether changes in determinants were associated with changes in perception of risk and seriousness. Table 4 first shows that changes in perception of the 2-year and 10-year risk (mean increase 8.58 and 5.69, respectively) were significantly higher than the change in perceived lifetime risk (mean increase 1.68). Further, changes in perceived symptoms were accompanied by significant changes in perception of risk (B = 0.76, p = 0.0007). As indicated by the borderline significant interaction term (B = 0.16, p = 0.07), this effect was stronger in patients with higher neuroticism. Changes in EDSS were not significantly related to changes in perceived risk. Since perceived symptoms may be in the 'causal' pathway between EDSS and perceived risk, the analyses were repeated without perceived symptoms in the model. However, in this model EDSS was still not significantly related to perceived risk (B = 0.76, p = 0.57). The second column shows that the decrease in perceived seriousness of the 2-year prognosis of wheelchair dependence was significant after adjustment for the other variables in the model (B = -5.19, p = 0.02). Of all determinants, only the interaction effect between pessimism and disability status was significant (B = -1.46, p = 0.01).

Discussion

This paper aimed to investigate perception of risk and seriousness of wheelchair dependence in the first years after the diagnosis of MS. Several findings can be deducted from this study. First, perception of the 2-year and 10-year risk of wheelchair dependence significantly increased during the 2-year follow-up, both in patients and in partners. Perceived lifetime risk and perception of seriousness did not change over time. The lack of association of perceived lifetime risk with putative determinants such as clinical status and perceived symptoms in our study contradicts with similar studies on risks of cardiovascular disease and cancer. These studies reported that perceived lifetime risks were associated with self-reported risk factors or did find that patients discriminated between different lifetime risks.[4,15] The absence of associations may be explained by the unpredictable nature of the disease; a benign early course of disease does not guarantee a favorable lifetime prognosis, and minor changes in early symptoms may not need to have significant consequences to patients for the perceived lifetime risk.

Second, disability status, as measured by the EDSS, was significantly associated with perception of risk and seriousness at baseline (Chapter 6) and in the cross-sectional analyses of the follow-up data (Table 2): patients with higher disability have higher perception of risk and lower perception of seriousness. However, disability status was not associated with perceived risk and seriousness in the analyses of changes over time (Table 4). This lack of association may be explained by the fact that, overall, EDSS did not change during our 2-year follow-up, either because there was no progression in disability status, or that progression was too minor to change EDSS scores.[16] It is also likely that changes in disability status are actually not accompanied by changes in perception of risk, because other factors are more important.

Third, perceived symptoms were significantly related to perceived risk in all analyses. Even though patients' subjective evaluations of symptoms on average as a group did not change over time, individual changes in perceived symptoms were associated with changes in risk perception. From an epidemiological perspective, this is strong evidence for a causal relation. This finding is compatible with the view that patients extrapolate their present symptoms into expectations of future wheelchair dependence. Yet, the opposite reasoning – that perception of risk influences symptom reporting – cannot be ruled out. Patients who do not want to face their higher risks of wheelchair dependence – and who will likely indicate that this risk is low – may underestimate or even deny the presence of symptoms.[17] This is a plausible explanation, but will likely be found in only a

subgroup of patients. For the majority, we argue that it is more likely that the perceived presence and intensity of symptoms determines their expectations of future disease progression (see also Chapter 10).

The wide variety of symptoms that can occur in MS makes it difficult for patients to know the difference between common symptoms and MS-related symptoms. This may be particularly a problem in the early phase of the disease in which symptoms are generally mild. Attributing common health problems to MS may lead to the impression to the patient that one is more ill than one actually is, and may consequently result in pessimistic expectations about wheelchair dependence and other consequences that are not clinically justified.[18] In our study, it was consistently found that patients who reported more symptoms due to their disease had higher perception of risk. It is important to note that this symptom questionnaire included both common non-MS-related health problems and MS symptoms. Further, this relationship between perceived symptoms and perception of risk was found in all analyses, after adjustment for clinical disability status. These findings combined suggest that patients may have inaccurate perception of their present symptoms, and most likely overestimate their present health status by attributing common non-MS-related symptoms to their disease. Given the implications for patients' expectations about future disease progression, it will be important to investigate the accuracy of symptom perception in further detail.

In conclusion, patients' evaluations of their symptoms are consistently associated with perception of the short- and medium-term risk of wheelchair dependence. These findings imply that for their consultations with patients, neurologists and other health professionals may improve the understanding of disease of patients considerable by discussing the symptom perception of patients in order to help them distinguish MS symptoms from symptoms of other common diseases. This may eventually result in more appropriate expectations about future disease progression.

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12

THE ASSOCIATION BETWEEN PERCEPTION OF PROGNOSTIC RISK AND ANXIETY, DEPRESSION AND DISTRESS IN RECENTLY DIAGNOSED MULTIPLE SCLEROSIS: A 2-YEAR FOLLOW-UP STUDY

Abstract

Background: In a 2-year follow-up study of recently diagnosed patients with MS and their partners, we investigated the association between perception of risk and seriousness of wheelchair dependence and feelings of anxiety, depression and distress. **Methods:** Perceived risk and seriousness were assessed for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Anxiety, depression and disease-related distress were measured at baseline, 6-month, 1-year and 2-year follow-up. **Results:** Mean levels of disease-related distress decreased both in patients and their partners during the 2-year follow-up, but levels of anxiety and depression remained unchanged. In patients, higher perception of the 2-year and 10-year risk of wheel-chair dependency was significantly related to poorer psychological well-being, whereas higher perception of seriousness was consistently related to higher distress and anxiety. An increase in perception of the 2-year risk of wheelchair dependence was associated with a significant increase in levels of anxiety, depression and distress. **Conclusion:** Patients' perception of the short- and medium-term risk of wheelchair dependence was consistently related to psychological well-being. Our findings raise the question whether the psychological well-being of patients with MS may be improved by adjusting their perception of risk of wheelchair dependence.

Introduction

Expectations about future disease or complications of disease are important determinants of psychological well-being.[1-4] In our cohort of patients recently diagnosed with multiple sclerosis (MS), higher perception of the short-term risk of wheelchair dependence was associated with increased levels of anxiety, depression and disease-related distress. Of note is that MS patients shortly after diagnosis particularly overestimated their short- and medium term risks of wheelchair dependence (Chapter 6) and that their levels of anxiety were significantly higher than in controls from the general population (Chapter 4).

In the previous chapter, it was demonstrated that patients' perception of their short-term risk of wheelchair dependence increased during follow-up. Given the association between perceived short-term risk and psychological well-being (Chapter 7), this raises the question whether levels of anxiety, depression and disease-related distress also increased during follow-up. Several psychological reactions are possible. First, following the associations observed at baseline, one expects that, due to the increase in perception of the short-term risk, patients also have higher levels of anxiety, depression and distress at follow-up. Second, the strong correlations between perceived risk and well-being found at baseline may have been a finding that is typical for the early period after diagnosis, because that period is generally characterized by both uncertainty and high levels of stress. Such a confounding effect may not be present at follow-up. Third, when patients manage to cope with the uncertain prospects of their disease, one may argue that they may face their high risks of future wheelchair dependence without emotional disturbances. In the last two situations, the increased perception of the short-term risk will not be accompanied by a decrease in emotional well-being.

In this paper, we investigated the association between perception of prognostic risk and psychological outcomes in a longitudinal study to confirm and extend our previous cross-sectional findings. First, the course of anxiety, depression and MS-related distress in patients and their partners is examined. Second, in patients the relation between perception of risk and seriousness and these psychological outcomes is investigated cross-sectionally during follow-up. And third, we investigated whether changes in perceived risk and seriousness were accompanied by changes in psychological outcomes.

Methods

Participants and procedures

Patients were recruited through the Departments of Neurology of the Erasmus MC (Rotterdam), three hospitals within the region of this academic hospital, and the

VU Medical Center (Amsterdam) in the period of March 1999 – December 2000. Patients were eligible if they were diagnosed with definite or probable MS[5] within two years before entry in this study, were between 18 and 55 years old, and had given informed consent. Patients with serious comorbidity or with insufficient understanding of the Dutch language were excluded. Of the 120 patients who met the criteria, 101 agreed to participate in the study. This prospective study consisted of four time points: baseline, 6-month, 1-year and 2-year follow-up. At present, the data collection for the 2-year follow-up is still ongoing. Of the 101 patients who entered the study, 98 completed the half-year follow-up, 97 the one-year and, to date, 72 (out of 81 patients invited) have finished the 2-year follow-up. Ninety out of 101 patients had a partner, of whom 78 (87%) did participate. Of the 78 partners who started the study, 72 completed the one-year and, up until now, 55 (out of 66 partners invited) have finished the two-year follow-up. Baseline characteristics of patients and partners are presented in Chapter 11 (Page 145).

Patients completed questionnaires at all assessments and were scheduled for neurological examination at baseline, 1-year and 2-year follow-up. At these visits, also partners filled out questionnaires. Questionnaires for patients and partners were sent by mail one week prior to the neurological examinations and had to be handed in at the time of the psychological interview (baseline), at the neurological examinations (follow-up) or returned by mail. At baseline, partners were given their questionnaires at the time of the patient's interview, which was scheduled one week after the neurological examination, and were asked to complete these in another room. At one- and two-year follow-up patients and partners were mailed their questionnaires simultaneously, with an explicit request to complete the questionnaires on their own. The study protocol was approved by the medical ethical committees of the participating hospitals.

Measurements

Perceptions of prognostic risk. Perception of risk and seriousness were assessed for the risk of becoming wheelchair-dependent as a consequence of the disease. Wheelchair dependence was defined as the inability to walk beyond five meters. This definition equals a score of 7.0 on the Expanded Disability Status Scale (EDSS).[6] Perception of risk and seriousness were assessed for the short- (2-year), medium- (10-year) and long-term (lifetime) prospects of wheelchair dependence. Perception of risk was measured using a 100mm visual analogue scale (VAS) from 'Definitely not' (0%) and 'Definitely' (100%). Patients were asked for each prognostic period how serious they think it is to be wheelchair-dependent by that time. Perceived seriousness was measured using a VAS anchored at 'Not serious at

all' (0) and 'The most serious thing I can imagine' (100). Partners completed the same questions, addressing the patient's risk of wheelchair dependence and the seriousness of their partner becoming wheelchair-dependent.

Psychological outcomes. Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS).[7] The anxiety and depression scales range from 0-21 with high scores indicating higher levels of anxiety and depression. Internal consistency reliability at baseline in our study was high:[8] Coefficient α was 0.83 for the anxiety and 0.81 for the depression scale. Scale scores of 8 and higher indicate a high risk of anxiety and depressive disorder. Disease-related distress was assessed using the Impact of Event Scale (IES).[9] This questionnaire addresses the psychological distress of having MS by focusing on the intensity of thoughts and feelings that relate to the disease. The questionnaire comprises two scales addressing the intrusion (range 0 - 35) and avoidance (0 - 40) of MS-related thoughts and feelings. Intrusion refers to the degree of being overwhelmed by thoughts and feelings about MS. Items include 'Any reminder brought back feelings about it' and 'I had dreams about it'. Avoidance refers to tendency to keep off these thoughts and feelings and is measured by items such as 'I tried not to think about it' and 'I stayed away from any reminders of it'. In our study, Coefficient α at baseline was 0.82 for the intrusion scale and 0.75 for the avoidance scale. Intrusion and avoidance are always positively correlated.[10] Although this seems paradoxical, avoidance can be thought of as a way of coping with high levels of intrusive thoughts: if disease-related thoughts and feelings are too disturbing, patients may restore emotional equilibrium by avoidance.

Clinical data. Present disability was assessed by physicians from the academic hospitals following a standardized research protocol. Functional limitations were rated on the EDSS,[6] which ranges from 0.0 (no neurological symptoms) to 10.0 (death due to MS). Date of first symptoms was assessed during the neurological examination. Date of diagnosis and diagnostic certainty (probable or definite MS) were obtained from the medical records and verified by senior neurologists.

Statistical analyses

We used the SAS Proc Mixed Repeated measurement procedure for the analyses of longitudinal data. This procedure takes into account that the same individual contributes data to the analysis at different time points and allows the inclusion of subjects with incomplete follow-up. This likelihood-based procedure generates more accurate estimates of the parameters than analysis of available data or of patients who completed all assessments only by using the available data to predict the missing data of subjects who are censored.[11]

We first examined the course of anxiety, depression and MS-related distress in patients and partners by comparison of estimated means using SAS Proc Mixed with time (0, ½, 1 and 2 years) and time since diagnosis (0-3, 4-6, 7-12 and 13-24 months) as independent categorical variables. Analyses were conducted for patients and partners separately. To test for a linear and quadratic trend, the analyses were repeated using time since diagnosis as a continuous variable.

Second, in patients the association between their perception of risk and seriousness and psychological outcomes was analyzed in the follow-up data. Using SAS Proc Mixed, the following strategy was used for each period of prognosis (2 years, 10 years and lifetime) and each psychological outcome (anxiety, depression, intrusion and avoidance). A full model was tested including perceived risk and seriousness of wheelchair dependence, disability status (EDSS), a linear and quadratic time effect, all first-order interaction effects and the covariates (time since diagnosis, time since first symptoms, age and sex). To simplify the model, this saturated model was reduced by eliminating non-significant interaction effects and covariates. Elimination was based on the significance of the difference in –2 log likelihood goodness of fit between the reduced and the saturated model. If the p-value was greater than 0.05 (χ^2-test), the parsimonious model was considered not significantly different from the saturated model, and was used for further simplification. Regression coefficients (B) for the final model were estimated using the restricted maximum likelihood procedure.

Third, to determine whether changes in perception of risk and seriousness were associated with changes in anxiety, depression and MS-related distress, the analyses were repeated using difference scores. Difference scores were obtained by subtracting baseline values from scores at 1-year and 2-year follow-up. The full model included change in perception of risk, perception of seriousness and disability status, and their interaction effects between these main effects and time. For this purpose, time was recoded into 0 and 1 representing the first and second year of follow-up. The model was reduced using the aforementioned procedure. P-values lower than 0.05 were considered statistically significant. Analyses were performed in SAS 8.0 (www.sas.com) and SPSS 11.0 (www.spss.com).

Results

Course of anxiety, depression and distress

Figure 1 shows the course of anxiety and depression in the 2-year follow-up of patients and their partners. Means are presented for four groups defined by time since diagnosis (0-3, 4-6, 7-12 and 13-24 months). Because patients were diagnosed up to 2 years prior to entry in the study, the present data cover the first

four years after diagnosis. Neither in patients nor in partners, a significant change in anxiety or depression was found (p for trends > 0.05, see Figure 1). Of the patients who had clinically relevant levels of anxiety (scores ≥ 8.0) at baseline, 63% (20/32) also showed these high scores at 1-year and 55% (12/22) at 2-year follow-up. Also in partners, these percentages remained high at 1-year (57%; 16/28) and 2-year follow-up (62%; 13/22). Of the patients who had clinically relevant levels of depression (scores ≥ 8.0) at baseline, 80% (8/10) also had high depression scores at 1-year and 38% (3/8) at 2-year follow-up. In partners, these percentages were 60% (6/10) and 38% (3/8). Intrusion of MS-related thoughts and feelings (Figure 2) significantly decreased in this 2-year follow-up in patients ($p < 0.0005$) and in partners ($p = 0.02$). Patients also showed significantly lower scores of avoidance at follow-up ($p < 0.0001$).

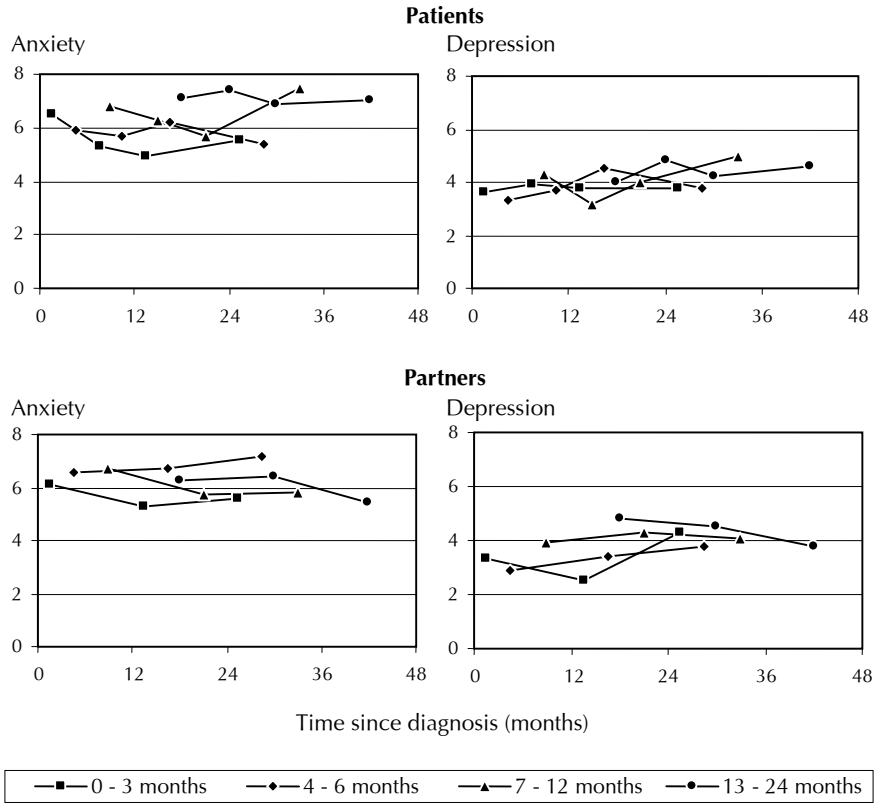

Figure 1 Anxiety and depression of patients and partners during 2-year follow-up

Groups are defined by time since diagnosis at baseline (see Methods).

Perceived risk and seriousness and psychological well-being

Table 1 shows the cross-sectional relation between perception of risk and seriousness of wheelchair dependence and the psychological outcomes assessed at different points of follow-up. Perception of risk and seriousness of the 2-year and 10-year prognosis were significantly and consistently related to intrusion, avoidance, anxiety and depression. In contrast, perceived risk of the lifetime prognosis was only related to intrusion of MS-related thoughts and feelings. Perceived seriousness was significantly related to all outcomes, except depression. Disability status was a significant predictor of psychological outcomes in all analyses ($p < 0.03$). The effect of EDSS on psychological outcomes remained statistically significant in all analysis, but was stronger in the analyses of perceived risk and seriousness of lifetime prognosis compared to short-term prognosis.

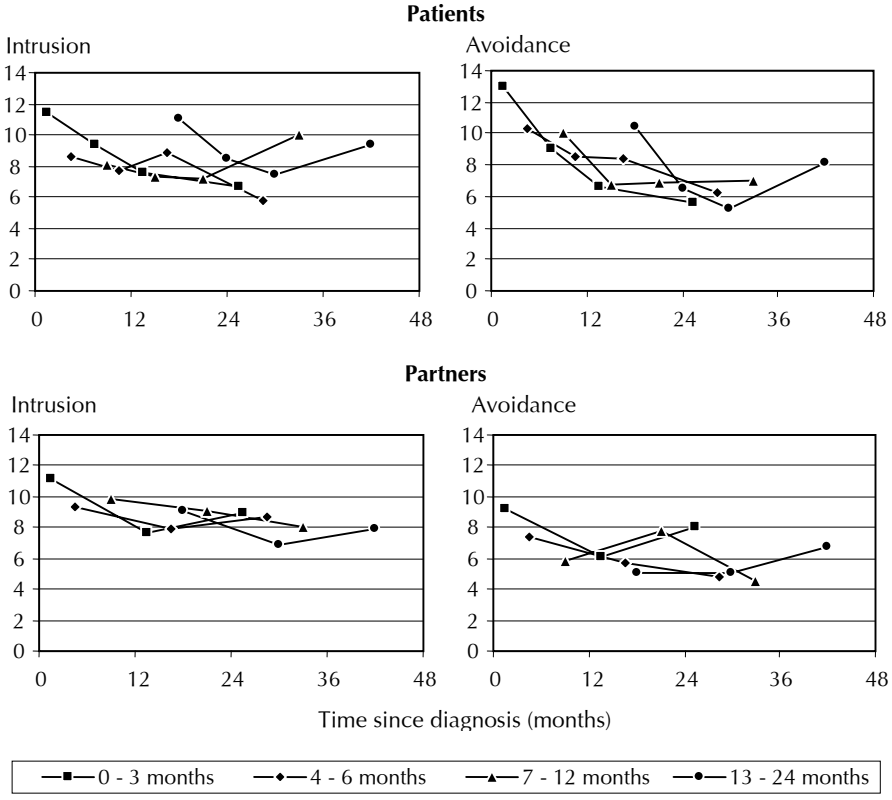

Figure 2 Disease-related distress of patients and partners during 2-year follow-up

Groups are defined by time since diagnosis at baseline (see Methods).

Table 1 Association between perception of risk and seriousness of wheelchair dependence and psychological outcomes in patients (cross-sectional analysis)

	Intrusion	Avoidance	Anxiety	Depression
Short-term prognosis				
Perceived 2-year risk	0.86	0.72	0.46	0.30
	[0.48, 1.24] ***	[0.27, 1.17] ***	[0.26, 0.66] ***	[0.14, 0.47] ***
Perceived 2-year seriousness	0.54	0.89	0.45	0.15
	[0.15, 0.92] **	[0.43, 1.34] ***	[0.24, 0.66] ***	[-0.02, 0.32]
Medium-term prognosis				
Perceived 10-year risk	0.78	0.49	0.21	0.26
	[0.42, 1.13] ***	[0.06, 0.90] *	[0.02, 0.40] *	[0.11, 0.41] ***
Perceived 10-year seriousness	0.62	0.91	0.38	0.07
	[0.27 0.97] ***	[0.49, 1.32] ***	[0.19, 0.58] ***	[-0.08, 0.23]
Long-term prognosis				
Perceived lifetime risk	0.46	-0.03	0.04	0.08
	[0.11, 0.81] **	[-0.44, 0.37]	[-0.15, 0.23]	[-0.08, 0.23]
Perceived lifetime seriousness	0.48	0.83	0.33	0.04
	[0.15, 0.80] **	[0.45, 1.21] ***	[0.15, 0.51] ***	[-0.10, 0.19]

B (95% CI) is presented per 10 points increase in perception of risk and seriousness. Analyses are adjusted for disability status, age, sex, time since diagnosis, time since first symptoms. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Predictors of change in psychological well-being

Finally, we examined in a longitudinal analysis whether changes in perception of risk and seriousness were associated with changes in the psychological outcomes. Table 2 demonstrates that increases in perception of the 2-year risk of wheelchair dependence were accompanied by significant increases in intrusion, avoidance, anxiety and depression. Also, an increase in perceived 10-year risk was accompanied by significant increases in intrusion and depression. With regard to the seriousness of wheelchair dependence, a change in perceived seriousness of the 2-year, 10-year and lifetime prognosis was significantly associated with avoidance and anxiety at follow-up. Changes in EDSS were not significantly associated with changes in the psychological outcomes (all $p > 0.05$).

Discussion

The early period after diagnosis is a stressful period for MS patients and their partners. We have previously reported that patients and their partners had high levels of disease-related distress and higher levels of anxiety than people from the general population (Chapter 4). In the present paper, it was demonstrated that both in patients and partners levels of disease-related distress, measured by the intrusion

Table 2 Predictors of change in psychological outcomes: the role of perceived risk and seriousness of wheelchair dependence in patients

	Δ Intrusion	Δ Avoidance	Δ Anxiety	Δ Depression
Short-term prognosis				
Δ Perceived 2-year risk	0.80	0.55	0.41	0.21
	[0.31, 1.29] **	[0.00, 1.11]*	[0.17, 0.66] ***	[0.01, 0.41]*
Δ Perceived 2-year seriousness	0.30	0.74	0.49	0.09
	[-0.21, 0.82]	[0.14, 1.34] *	[0.23, 0.74] ***	[-0.12, 0.30]
Medium-term prognosis				
Δ Perceived 10-year risk	0.52	0.29	0.22	0.30
	[0.04, 1.00] *	[-0.23, 0.81]	[-0.01, 0.45]	[0.12, 0.47] **
Δ Perceived 10-year seriousness	0.32	0.73	0.37	-0.06
	[-0.22, 0.85]	[0.14, 1.32] *	[0.11, 0.62] **	[-0.26, 0.14]
Long-term prognosis				
Δ Perceived lifetime risk	0.31	-0.24	0.14	0.10
	[-0.15, 0.77]	[-0.74, 0.27]	[-0.09, 0.37]	[-0.08, 0.28]
Δ Perceived lifetime seriousness	0.19	0.67	0.29	-0.07
	[-0.25, 0.62]	[0.19, 1.15] **	[0.07, 0.50] **	[-0.24, 0.10]

B (95% CI) is presented per 10 points increase in perception of risk and seriousness. Analyses are adjusted for disability status, age, sex, time since diagnosis, time since first symptoms. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

and avoidance of MS-related thoughts and feelings, decreased significantly during the 2-year follow-up of this study. As an illustration, these changes are comparable to that found in a one-year follow-up of individuals who were informed about their genetic predisposition of Huntingtons's Disease.[12] These results indicate that the high levels of disease-specific distress at baseline may have reflected early stages of patients' coping processes. Despite the substantial decrease in distress, levels of anxiety did not significantly decrease. Also at follow-up, patients and partners were more anxious than controls from the general population.[13] Of the patients and partners with clinical relevant levels of anxiety (scores ≥ 8.0) at baseline, 55% and 62% still had these high levels at 2-year follow-up. These findings are in line with those of others who have demonstrated high levels of anxiety in later phases of MS.[14-17] We add that the psychological burden also persisted in the first years after diagnosis in at least a subgroup of patients and partners. Screening for symptoms of anxiety using the 7-items HADS Anxiety scale may be a short and effective strategy to identify patients who need psychological support.

Depression is a frequent symptom of MS.[17-19] Nevertheless, we previously demonstrated that levels of depression were not increased compared to general population controls (Chapter 4). The present results showed no significant increase

in depression during the 2-year follow-up of this study. Symptoms of depression were more frequent among patients with higher disability. Moreover, higher anxiety scores at the first time points were not associated with higher depression at the final visit. These findings combined suggest that depression is a feature of later stages of the disease, rather than the result of enduring stress.[20]

The main topic of this paper concerned the analyses of the relationship between perception of prognostic risk and emotional well-being in the follow-up data. The present findings confirmed the association between perceived 2-year risk and anxiety, depression and disease-related distress. In addition, perceived 10-year risk was significantly related to all indicators of psychological well-being during follow-up. Compared to the baseline analyses (Chapter 7), the regression coefficients of the perceived 2-year risk were lower at follow-up than at baseline, whereas those of the perceived 10-year risk were higher. One may argue that this is a result of successful coping: patients may be better informed about their disease and may be more confident that their disease will not severely progress within two years. As a result, these short-term expectations may have become less stressful.

One of the most important findings of this longitudinal analysis was that a change in the perception of the 2-year risk of wheelchair dependence was significantly associated with change in anxiety, depression, intrusion and avoidance. The association could not be explained by changes in disability status as measured by the EDSS. These associations suggest a causal relationship between perceived short-term risks and psychological well-being. However, the direction of this relationship may be subject to debate. It can be argued that a somber mood leads to more pessimistic expectations of future wheelchair dependence. In that case, however, one would also expect these influences on perceived 10-year and lifetime risk, but this was not supported by the findings of this study. Therefore, we argue that our data support the view that perception of the short-term risk of wheelchair dependence determines psychological well-being. This short-term risk may be particularly important because it implies a major disruption in the life of patients. When patients believe that this threat is more likely to occur, they may as a consequence feel more anxious and distressed.

The association between perceived seriousness and psychological outcomes in this follow-up study confirmed our previous findings in the baseline analyses: perceived seriousness was consistently related to intrusion, avoidance and anxiety, but not to depression. The fact that perceived seriousness was not consistently associated with anxiety in the baseline analyses was likely due to a lack of statistical power. Our longitudinal analysis of the change in perception of seriousness showed a significant association to change in avoidance and anxiety

consistently in all analyses. Like perception of the short-term risk, also seriousness reflects the perceived threat of wheelchair dependence, and for that reason may be related to anxiety and distress.

In conclusion, also the longitudinal studies demonstrated a significant relationship of perceived risk and seriousness with psychological well-being that could not be explained by changes in disability status. Taken in mind that patients overestimated their short- and medium-term risks (Chapter 6), these findings underscore the importance of further research on the communication of uncertain information to patients aiming to reassure patients about their short-term prognosis.

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13

GENERAL DISCUSSION

The aim of this study was to investigate expectations of prognosis in patients recently diagnosed with MS. Disease- and person-related determinants of perception of risk and seriousness of wheelchair dependence, as well as the relationship between risk perception, psychological well-being and QoL were investigated. In this chapter, the findings of the study are summarized and discussed. First, methodological issues with regard to the design of the study and the instruments used are reviewed. Then, the main findings of the study are discussed from a psychological and clinical perspective. And finally, topics for future research are addressed.

Methodological issues

Data collection: postal distribution of questionnaires

The first methodological issue to be discussed concerns the data collection within couples. To ensure the independent assessment of observations within couples, it is crucial that spouses fill out their questionnaires separately. In our study, procedures for completion of the questionnaires differed at baseline and follow-up. At baseline, patients filled out their questionnaires before the interview, whereas partners completed theirs while the patient was interviewed. At follow-up, all questionnaires were sent and returned by mail. Patients and partners had then more opportunity to confer their answers, which may have biased the follow-up assessments. It can be postulated that such bias would be revealed by higher correlations between patient and partner scores at follow-up. Table 1 demonstrates that correlations of the key variables were not consistently higher at follow-up, suggesting that the postal distribution of questionnaires has not biased the findings.

Table 1 Pearson correlation coefficients between patient and partner scores of major study variables at baseline and follow-up measurements

Measurement		Baseline	1-year follow-up	2-year follow-up
Anxiety		0.31	0.36	0.27
Depression		0.36	0.24	0.30
Intrusion		0.10	0.17	0.17
Avoidance		0.27	0.36	0.14
Perceived risk:	2-year	0.45	0.50	0.53
	10-year	0.48	0.46	0.57
	Lifetime	0.45	0.55	0.31
Perceived seriousness:	2-year	0.27	0.34	0.48
	10-year	0.31	0.23	0.38
	Lifetime	0.24	0.39	0.36

Selection of the study population

Our study aimed to include patients who were diagnosed with definite or probable MS within two years prior to study entry and were between 18 and 55 years old. Patients with serious comorbidity or insufficient understanding of the Dutch language were excluded. For the generalization of our findings, it is important to evaluate whether the participants were a representative sample of this patient population, and if not, whether the findings were biased by patient selection.

Second opinion

Since patients were recruited primarily through academic hospitals, an unknown number may have visited these centers for a second opinion. These patients either came on their own initiative or were referred by their treating neurologist. The potential overrepresentation of patients referred for a second opinion may have influenced several of the findings. First, it can be anticipated that these patients were the least satisfied with the diagnostic procedures at their local hospital. Hence, the percentage of patients who were dissatisfied with the timing of diagnosis (Chapter 3) may be lower in an unselected patient population not derived from an academic center. Yet, the conclusion that patients prefer an early diagnosis will remain unchanged, because this was primarily based on the group that was satisfied and had a short duration of the diagnostic workup. Second, the high level of anxiety and distress (Chapter 4) may be overestimated. Anxiety and distress may have been the reason to seek for confirmation in a second opinion, or the result from the uncertainty of being sent for one. This may imply that in an

unselected population levels of anxiety and distress may be lower. The relationship between perception of risk and anxiety and distress will only be overestimated when in the latter patients low levels of anxiety and distress are associated with high perception of risk.

Emotional burden in non-responders

Of the 120 patients who were invited to participate in the study, 19 refused. The reasons for non-participation were known in six patients (Chapter 2), of whom three mentioned the high emotional burden of the disease and three others showed lack of interest. The emotional burden of being confronted with the disease is expected an important reason for non-participation in more patients, implying that the prevalence and mean levels of anxiety, depression, distress and QoL may be underestimated in our study. Again, the relationship between perception of risk and psychological outcomes will only be overestimated when in these patients high levels of anxiety and distress were associated with low perception of risk.

Definite and probable MS

To investigate the influence of diagnostic certainty on perception of risk and psychological well-being, the PROMS study included patients with definite and probable MS.[1] Yet, only ten patients with probable MS were included, which number was not large enough to provide statistical power for comparisons with patients with definite MS. Although no clear conclusions can be drawn, the differences between patients with probable and definite MS tended to be small. This may be explained by the fact that the majority of patients with probable MS anticipated that their diagnosis would finally be definite: seven out of ten patients perceived their risk of developing definite MS as 80% or higher at each time point of the study. However, due to the low number of patients with probable MS, the findings of this study are primarily generalizable to patients with definite MS.

Validity and reliability of instruments

The majority of instruments used in this study were validated and known to be reliable. The validity of two instruments is discussed in more detail: the assessment of perceived risk and seriousness by visual analogue scales (VAS) and clinical disability by means of the Expanded Disability Status Scale (EDSS).

Perceived risk and seriousness

Perception of risk and seriousness of wheelchair dependence were measured on a blank VAS (see Appendix A). The VAS is a widely-used instrument for the

quantification of subjective phenomena including attitudes, pain, discomfort and perception of risk.[2,3] In this study, comparisons between perceived risk and seriousness assessed by VAS scores and patients' explanations in the interview (Chapter 10) indicated good face validity. For example, when patients explained that they thought they would definitely not become wheelchair-dependent they marked the line between 0-5mm, and patients who said that 'it might happen of not' had scores between 45-55mm. Our interview findings confirmed that 50%-responders primarily stressed their uncertainty about the future, rather than explained that the numerical risk was actually 50% (see also Chapter 6).[4] Although, for these patients as well as all others, there is a difference between this individual perspective (I don't know, low or high) and population perspective (the risk is 50%, 20% or 80%), this may not necessarily reduce the validity of the findings on perception of risk. In this light, it is important to realize that also the actual population risk is the mean of all individual risks, namely a 20% risk means that the risk is 100% in 20 out of 100 patients and 0% in 80 patients. Although individual perception of risk cannot be compared to this mean actual risk, it is valid to compare the latter with the mean perception of risk.

EDSS as a measure of disability status

Despite its widespread use as an instrument to rate disability in MS, the EDSS has many documented imperfections.[5,6] The instrument has poor responsiveness, large inter-rater variability and is primarily focusing on mobility at the higher end of the scale.[5,6] It can be argued that in a relatively homogenous population the EDSS is inadequate for the measurement of small differences in disability status. This may have implications for our study of patients' perception of their symptoms. The variation in *perceived* symptoms, given a certain level of objective limitations as assessed by the EDSS, may still reflect residual variation in *actual* functional limitations. If true, this could mean that the relationship between perceived symptoms and perception of risk, adjusted for EDSS (Chapter 8 and 9), is due to residual confounding of actual physical limitations. However, the significant adjusted association between perceived symptoms and personality (Chapter 9) indicates that perceived symptoms, at least in part, are subjective and less likely explained by residual confounding alone.

Main findings

Psychological well-being and quality of life in the early phase

At baseline, on average eight months after diagnosis (Chapter 4), patients and partners were substantially bothered by the intrusion of MS-related thoughts and

feelings. In our study, 70% of the patients were satisfied with the timing of their diagnosis and 24% had preferred to be diagnosed earlier (Chapter 3). The probability of satisfaction with the timing of diagnosis significantly decreased with a longer duration of the diagnostic workup at the neurological clinics. This period may be crucial, because a referral to a medical specialist indicates that symptoms were serious enough to warrant further examination (Chapter 3). Patients commented that the burden of uncertainty was a major reason for preferring an earlier diagnosis. This burden of uncertainty before the diagnosis is in line with previous MS studies on the impact of diagnostic information.[7-9] In two studies, levels of anxiety and distress tended to be lower after the diagnosis although this decrease was not as profoundly as anticipated.[7,8] The third study reported an increase of these negative feelings after diagnosis, next to an increase in positive feelings such as courage for fighting the disease and clarity about their situation.[9]

Intrusive thoughts and feelings decreased during the 2-year follow-up (Chapter 11). Patients also demonstrated high levels of avoidance at baseline, but not at follow-up. In comparison, the mean levels of distress in this study were higher than that found in patients and partners awaiting presymptomatic test results for Huntington's disease or hereditary breast and ovarian cancer.[10] It has been argued that these high levels of distress may reflect coping processes and adaptive reactions in apparent stressful situations such as the early phase after diagnosis (see previous paragraph).[11,12] The finding that distress was lower at follow-up supports this coping hypothesis.

Patients as well as partners also reported significantly more symptoms of anxiety than individuals from the general population (Chapter 4). These high levels of anxiety remained unchanged during the 2-year follow-up, despite the substantial decrease in disease-related distress (Chapter 11). In fact, 50% of the patients and 60% of the partners who had clinically high levels of anxiety at baseline still had these high levels at the two-year follow-up. In contrast to studies in later phases of MS,[13-15] mean scores of depression were not higher in these recently-diagnosed patients compared to general population controls.

Quality of life (QoL) – Previous studies have demonstrated that patients with MS report poorer health-related QoL than individuals from the general population (see Introduction). The present study shows that patients, including those with no to minimal functional limitations, also reported poorer QoL in the early period after diagnosis (Chapter 4). The poorer QoL among patients with few functional limitations may be explained by increased feelings of anxiety or depression. Anxiety and depression may lower QoL or may lead to reporting poorer QoL (Chapter 5).[16] An alternative explanation may be a lack of response shift,[17,18]

which predicts that patients may still have compared their health status with the expectation of 'perfect' health. This phenomenon may explain the poorer QoL even in the absence of moderate to severe physical limitations (Chapter 5).

In summary, patients and partners experienced a high emotional burden in this early period after diagnosis. Although disease-related distress decreased during the 2-year follow-up, there was no significant reduction in the feelings of anxiety: at least 12% of the patients and 16% of the partners had clinically high levels of anxiety during the 2-year period of follow-up. This may have clinical implications as discussed in the section Clinical implications (Page 182).

Perception of risk and seriousness of wheelchair dependence

Perception of risk

The key question in this thesis was: what do patients recently diagnosed with MS expect of future disease progression? And how do these expectations change in the first years after diagnosis? Based on comparison of mean perception of risk and estimated risks, patients overestimated their 2-year and 10-year risks of wheelchair dependence, and underestimated their lifetime risk (Chapter 6). In the two-year follow-up, perception of the 2-year and 10-year risk slightly but significantly increased, whereas perceived lifetime risk remained unchanged (Chapter 11). Several findings are of interest in light of our understanding of perception of prognostic risk.

First, a significant number of patients perceived their risks to be about 50%. These patients predominantly explained in the interviews that they did not know what to expect: it might happen or it might not, confirming findings of others that 50%-answers indicated complete uncertainty of the future.[19] Patients may have used this response, because 'this allows them to give a number without feeling that they have committed themselves to a specific answer'.[20] Indeed, the 50%-response is equally defensible whatever actually happens.[21] Patients may also have given a 50%-response, because they did not want to think about whether their risk would be higher or lower. Using the heuristic of anchoring and adjustment, Tversky and Kahneman predict that in such situations patients stick to scale anchors, e.g. the ends or the middle of the scale as the 50%-responders did.[22]

Second, as expected, perceived risks were higher for the longer time periods. But despite the longer time interval between the 10-year and lifetime prognosis, the mean difference between perceived 10-year and lifetime risk approximated the mean difference between the perceived 2- and 10-year risk. That is, respondents did not discriminate between ten years and lifetime.

Third, many studies on risk perception reported that individuals overestimated[23-26] or underestimated[27] their risks of e.g. cancer. In our study, conclusions of over- and underestimation varied with the time perspective: patients overestimated short- and medium-term risks and underestimated lifetime risks. These findings emphasize the importance of careful selection and definition of outcomes in studies of risk perception (see page 188).

Why did patients overestimate their short- and medium-term risks and underestimate their lifetime risk of wheelchair dependence? One may speculate that patients may overestimate their risks to prevent future disappointment or to anticipate coping with future disease progression. Alternatively, patients may underestimate their risks not because they believe it is low, but to prevent excessive or unnecessary worry, also referred to as defensive optimism.[28] Our findings of the interview study are compatible with this view (Chapter 10). And finally, patients may deny that they are at increased risk. In our study, it is difficult to distinguish between these psychological motivations because patients were often not aware of their numerical risks and did not know whether they were under- or overestimating. Notwithstanding, patients were knowledgeable of the lifetime possibility of wheelchair dependence and of the unpredictability of their disease. In that light, the considerable underestimation of the lifetime risk in a subgroup of patients - several patients perceived the *lifetime* risk even lower than 5% (Chapter 6) - may be an indication of defensive optimism or denial.

Perception of seriousness

Patients considered wheelchair dependence to be a very serious consequence of their disease (Chapter 6). This opinion did not change during the 2-year follow-up. Although patients considered short-term wheelchair dependence to be more serious than long-term wheelchair dependence, the differences between periods were only small. This lack of variation may be a result of the seriousness of wheelchair dependence itself: a wheelchair would always disrupt life, no matter at what point in time. In the interviews, patients did mention that short-term wheelchair dependence would be particularly serious, because this would severely disrupt their life and future plans and moreover, that the disease in that case has an extremely progressive course (Chapter 10).

Associations between perceived risk and psychological well-being

Perceived risk

The most important finding of our studies of correlates with risk perception is that perception of the short-term risk of wheelchair dependence was most consistently

Table 2 Summary of results on psychological correlates of perceived risk

		Time period								
		2 years			10 years			Lifetime		
	↔	Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Anxiety	↑	***	***	***	--	*	+	--	--	--
Depression	↑	**	***	*	--	***	**	--	--	--
Intrusion	↑	**	***	**	***	***	*	**	**	--
Avoidance	↑	*	***	*	--	*	--	--	--	--

↔ = Direction of the relationship, ↑ = Positive; Baseline = Cross-sectional associations at baseline (Chapter 7), All = Cross-sectional associations at all assessments (Chapter 12) Δ = Associations between changes in perception of risk and changes in psychological well-being (Chapter 12); *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, + $p < 0.10$, -- $p > 0.10$.

and convincingly related to psychological well-being (Table 2). Moreover, changes in perception of the short-term risk were strongly associated with changes in psychological well-being. These results remained significant after adjustment for clinical disability status, indicating that the relationship between risk perception and emotional well-being is unlikely confounded by disability status (see comments on page 174). This particular association of short-term risk perception and psychological well-being is in line with the explanations of patients in the interviews that short-term disability may have a more disruptive and threatening impact on family life, work, and leisure activities than disability occurring in the remote future (see page 177).

The question remains whether risk perception influences psychological well-being or vice versa. This cannot be inferred directly from our study. In Chapter 7, we put forward that if psychological well-being had influenced perception of risk this effect was expected for each time perspective (2 years, 10 years and lifetime). Such consistent relationships were found with regard to the intrusion of MS-related thoughts and feelings, but not for anxiety, depression and avoidance. Thus, it was concluded that intrusive thoughts most likely had influenced perception of risk, while the latter most likely determined levels of anxiety, depression and avoidance. Even though most[27,29,30] – but not all[31] – previous studies have considered risk perception as a determinant of psychological well-being, the main direction of this relationship needs to be further explored.

Perceived seriousness

We found that perceived seriousness was consistently related to anxiety and disease-related distress (Table 3), whereas only patients who considered short-term

Table 3 Summary of results on psychological correlates of perceived seriousness

		Time period								
		2 years			10 years			Lifetime		
	↔	Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Anxiety	↑	*	***	***	+	***	**	+	***	**
Depression	↑	*	+	--	--	--	--	+	--	--
Intrusion	↑	*	**	--	**	***	--	***	**	--
Avoidance	↑	***	***	*	***	***	*	***	***	**

↔ = Direction of the relationship, ↑ = Positive; Baseline = Cross-sectional associations at baseline (Chapter 7), All = Cross-sectional associations in all assessments (Chapter 12) Δ = Associations between changes in perception of seriousness and changes in psychological well-being (Chapter 12); *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, + $p < 0.10$, -- $p > 0.10$.

wheelchair dependence as more serious had higher levels of depression. A lower perception of perceived seriousness was associated with lower levels of anxiety and avoidance of MS-related thoughts and feelings. Previous studies that investigated the potential impact of MS on important life goals and financial security have demonstrated that patients who perceived the disease as more threatening reported more symptoms of depression, higher global distress and poorer subjective health status.[32,33] Our findings on perceived seriousness are in line with those of previous studies.[32,33]

Determinants of perceived risk and seriousness

To understand how patients came to their expectations of prognosis, we investigated what factors influenced their perception of the risk and seriousness of wheelchair dependence. Disease-related characteristics, illness beliefs and personality factors were examined in a cross-sectional (Chapter 6, 8, 9) and longitudinal design (Chapter 11). In addition, perceptions were elucidated in the interviews (Chapter 10).

Determinants of perceived risk

Not surprisingly, patients who had more physical limitations as a result of their disease symptoms, rated on the EDSS, had higher perceptions of risk (Table 4). This relationship was found for the short-, medium- and long-term prognosis of wheelchair dependence, albeit that the correlation between disability status and perceived risk was stronger for the short term. This is likely explained by the unpredictability of the disease: also patients with no to minimal disability in this early phase may develop a progressive course on the long term. Of note is that a

Table 4 Summary of results on determinants of perceived risk

		Time period								
		2 years			10 years			Lifetime		
	↔	Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Disability status	↑	***	***	--	***	***	--	***	***	--
Perceived symptoms	↑	***	***	***	***	***	***	--	--	***
Neuroticism	↓↑	+	--	*	+	--	*	+	--	*
Perceived symptoms * neuroticism	↑	**	***	+	**	***	+	**	***	+
Coherence	↑	+	*	--	+	*	--	+	*	--

↔ = Direction of the relationship, ↑ = Positive, ↓ = Inverse; Baseline = Cross-sectional associations at baseline (Chapter 6, 8, 9), All = Cross-sectional associations at all assessments (Chapter 11), Δ = Associations between change in determinants and changes in perception of risk (Chapter 11); *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, + $p < 0.10$, -- $p > 0.10$.

change in EDSS was not significantly associated to changes in perception of risk, which, as discussed, may reflect the lack of sensitivity of the EDSS (see page 174).

Of all illness beliefs studied only illness identity, or perceived symptoms, was consistently related to perception of risk after adjustment for disability status (Chapter 8). That is, in patients with similar functional limitations those who perceived more physical limitations had higher perception of risk. This relationship of perceived symptoms was primarily found with regard to the short- and medium-term risk of wheelchair dependence. Although the association with perceived symptoms may be due to residual confounding of disability status (page 174), several psychological explanations may also be considered (Chapter 10). First, patients may extrapolate present or past experiences, e.g. the presence of risk factors or symptoms, into predictions about future disease status.[34-36] Second, patients who reported more physical limitations may consider themselves to be more similar to patients who will likely become wheelchair-dependent. These explanations refer to the heuristic of representativeness, which would predict a higher perception of risk among patients who reported more symptoms.[22] And third, the (perceived) presence of symptoms, MS-related or not, may elicit higher perceptions of risk by a reminder process in which vulnerability beliefs are aroused by somatic cues.[37] In other words, patients will be more aware of their higher risk of wheelchair dependence because they are repeatedly reminded of it by the presence of their physical limitations. Tversky and Kahneman explained such reminding process by the heuristic of cognitive availability.[22]

Of the three personality factors studied – optimism, pessimism and neuroticism – only neuroticism was a significant determinant of perceived risk.

That is, perceived symptoms appeared to have a stronger relationship with perception of risk in high-neuroticism patients. It is thought that persons scoring high on this personality dimension are more likely to be self-focused and therefore more likely to detect changes in physical status.[38] Above that, this attention for physical symptoms is loaded with anxiety and uncertainty, through which these patients may interpret minor symptoms as having major consequences more than do patients scoring low on neuroticism.[38-40] For this reason, perceived symptoms may be stronger related to perception of risk in high-neuroticism patients.

Contrary to our expectations, there was no consistent association between risk perception and time since diagnosis, time since first symptoms and illness beliefs other than perceived symptoms. Time since diagnosis was probably not associated because this period was relatively short for all participants. Time since first symptoms was not directly, but indirectly related to risk perception: patients with longer time since first symptoms tended to have higher disability (Chapter 4). Further, of the eight illness beliefs studied, only perceived symptoms was associated with perception of risk (Chapter 8). A problem with the interpretation of these findings is that these illness beliefs may have been too general to relate to the perceived risk of a specific disease complication. For example, a patient may believe that the disease is a chronic condition (high IPQ Chronic timeline), which cannot be treated effectively by medication (low IPQ Treatment control), without expecting to become wheelchair-dependent.

Determinants of perceived seriousness

Similar to the analyses performed on perceived risk, we investigated the determinants of perceived seriousness. The findings are summarized in Table 5. Paradoxically, patients with a relatively good physical condition considered the prospect of wheelchair dependence as more serious than did patients with higher disability (Chapter 6). An explanation for this finding may be that patients with few neurological symptoms have more to lose than patients with advanced functional limitations. Alternatively one can argue that patients with higher disability may recognize that a wheelchair finally extends rather than reduces mobility, even though compared to their present physical condition, this may still be a major step backwards.

Patients who were less pessimistic considered wheelchair dependence as less serious. The fact that wheelchair dependence is a negative event may possibly explain why pessimism rather than optimism was associated with perceived seriousness (see also Chapter 9). The findings for the other determinants were equivocal. The baseline analysis suggested that pessimism strengthened the

Table 5 Summary of results on determinants of perceived seriousness

		Time period								
		2 years			10 years			Lifetime		
	↔	Baseline	All	Δ	Baseline	All	Δ	Baseline	All	Δ
Disability status	↓	***	**	--	***	**	--	***	**	--
Pessimism	↑	***	*	--	***	*	--	***	*	--
Disability status * pessimism	↑↓	**	--	**	**	--	**	**	--	**
Perceived symptoms	↓↑	--	--	--	--	--	--	--	*	--
Neuroticism	↓	--	--	--	--	--	--	--	--	--
Perceived symptoms * neuroticism	↓	***	--	--	***	--	--	***	--	--
Chronic timeline	↓	+	*	+	+	*	+	+	*	+
Treatment control	↓	+	+	--	+	+	--	+	+	--
Coherence	↓	*	+	--	*	+	--	*	+	--

↔ = Direction of the relationship, ↑ = Positive, ↓ = Inverse; Baseline = Cross-sectional associations at baseline (Chapter 6, 8, 9), All = cross-sectional associations at all assessments (Chapter 11), Δ = Associations between change in determinants and perception of seriousness (Chapter 11); *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, + $p < 0.10$, -- $p > 0.10$.

association between disability status and perceived seriousness, but the longitudinal analyses showed the opposite. Also, illness beliefs (chronic timeline, treatment control and coherence) were not consistently associated with perception of seriousness.

Most variables considered were not significantly or consistently associated with perception of seriousness. As discussed earlier, variation in perception of seriousness was limited which may have affected the statistical power of our study. Based on the findings from the interview study (Chapter 10), it may be argued that psychosocial factors such as family life (having young children or care for family members) job activities (being breadwinner or having career perspectives), leisure activities, housing and social life may have a stronger impact. These factors determine whether and to what extend the lives of patients are threatened by the prospects of wheelchair dependence.

Clinical implications

Preference for an early diagnosis

Our study demonstrates that the probability of patients being satisfied with the timing of diagnosis decreases with a longer duration of the diagnostic workup at the neurological clinics. Yet, this probability did not substantially decrease within

twelve months after the first visit to the neurologist. On the one hand, these findings indicate that there is no need to delay diagnostic procedures to prevent psychological harm in patients, as was advocated in neurological practice.[41,42] On the other hand, our data also show that there is no need to rashly conduct investigations.

Patients clarified that a long duration of the diagnostic workup was stressful because they had symptoms and did not know what caused them. This suggests that patients may benefit when neurologists explain the symptoms and probable diagnoses that are considered. The latter seems counter-intuitive as discussing the possibility of disabling diseases may increase anxiety and worry for diagnoses that will not be confirmed later on. However, a previous study in cancer revealed that patients had lower levels of anxiety after disclosure of the diagnosis when they were prepared for a possible diagnosis of cancer.[43] Another reason is that in light of rapid developments at the Internet it may be better to discuss the possibilities with the patients. Consider a patient with a first presentation of optic neuritis who has a 50% risk of developing MS within 20 years.[44] It is still common practice to tell these patients that they have a temporary inflammation of the optic nerve.[42] However, when patients search at the Internet for more information they will easily learn about the possibility of MS: an Internet search at www.google.nl using the Dutch keyword 'oogzenuwontsteking', i.e., inflammation of the optic nerve, yielded no less than six out of ten results at page one that referred to specific MS sites (see Appendix B). So, withholding this information may increase anxiety, as patients are not able to discuss this with their neurologist. Needless to say there also is a high risk that patients will (mis)diagnose themselves.

High levels of anxiety and distress in patients and partners.

Where the initially high levels of disease-related distress in patients and partners significantly decreased over time, such a decrease was not found for anxiety: at least 12% of the patients and 16% of the partners had clinically high levels of anxiety (HADS ≥ 8.0 at all assessments during this study). Monitoring symptoms of anxiety during the first years after diagnosis using the 7-item HADS Anxiety scale can be a short and effective strategy to identify patients who may need psychological support in order to deal with the psychological burden of disease. Such screening can be readily incorporated in the regular visits with for example the MS nurse.

Equally important is the finding that feelings of anxiety did decrease below that cut-off score in most patients and partners. These participants managed to deal with the emotional burden of the disease within a reasonable period of time. As

most patients will continuously face disappointments and losses in the future, it is important that they get the feeling of being able to deal with this on their own. It can be argued that professional psychological support in such early phase may be unnecessary or even unwanted as this interferes with natural coping processes of the patients. This merits a restraint approach in the offer of psychological support to all patients in the very early phase after diagnosis.

Overestimation of short-and medium-term risks

The significant relationship of the 'pessimistic' short-term expectations with anxiety, depression and disease-related distress demonstrates that patients were bothered more by short-term than by long-term prognosis. This finding predicts that reassurance about the low risk of wheelchair dependence at the short term may take away major worries. Based on their clinical experience, treating neurologists can inform individual patients about the probability of specific prognostic outcomes. Even though actual numerical risks may not be available, neurologists can inform recently diagnosed patients based on the clinical features that e.g. their 2-year risk of wheelchair dependence risk is rather low or unlikely. Although such approach is not yet evaluated by appropriate controlled studies in MS, it has been demonstrated that perception of risk can be altered by individualized information,[45-49] particularly when risks are poorly controllable by preventive behavior.[50] It is obvious that such individualized information is optimized when it focuses on major concerns about the disease of patients and partners. Although for many patients the possibility of wheelchair dependence was most serious, our interview data show that some patients considered other outcomes more threatening. It is therefore recommended to verify this prior to discussion of prognosis.

Symptom reporting

In the present study, patients' perceptions of their symptoms were significantly related to perceived short- and medium-term risks of wheelchair dependence. This relationship may in part be explained by the lack of responsiveness of the EDSS (see page 174). Yet, the overestimation of the presence of symptoms can also imply that patients considered themselves to be more ill than they actually were and consequently overestimated their risks of future complications. For the clinical care of patients it is important to realize that patients may not evidently know what symptoms are a result of their illness. As MS is a highly variable disease, it may be very difficult for patients to determine which symptoms are due to their disease and which are common problems not related to MS but e.g. due to the flu, stress or

infections. Patients may gain in understanding about their illness and prognosis when they are informed about the relevance of symptoms and their relation to the course of MS by their neurologist or MS nurse. This may lower their perception of prognostic risk and hence improve psychological well-being.

In summary, in the early period after diagnosis general information about prognosis and specific information concerning perception of symptoms may lead to more optimistic expectations about short-term disease progression and decrease disease-related distress. Patients who will remain anxious for a prolonged time may benefit from professional psychological support.

Suggestions for future research

Clinical studies

In the previous section, it was recommended that neurologists should inform patients about their short-term prognosis and explain the significance of their symptoms. Although it may be expected that this may be beneficial to patients, we need to investigate how such information is best addressed in the context of prognostic risks.

The first topic for further research addresses the communication of uncertain information of prognosis. Since changes in perception of the short-term risk of wheelchair dependence were significantly associated with changes in anxiety and distress (Chapter 12), the first question to be addressed is whether reassuring about short-term prognosis may improve psychological well-being. Several recent studies have demonstrated that perception of risk can be altered by individualized information.[45-49] A possible strategy to be followed may be that neurologists ask patients and partners about their major concerns with regard to the future course of disease and discuss short- and long-term expectations for these complications or consequences. In this discussion, it will be important – where possible – to distinguish uncertain expectations ('we don't know for sure') rather than absolute uncertainty about prognosis ('we don't know at all'). It will be a challenge to investigate possibilities to communicate such uncertain information in a clinical trial. These studies may not only be limited to patients with MS, but also to other chronic diseases.

Another point of further research in MS addresses the fact that the patients' overestimation of the presence of their symptoms may underlie their pessimistic expectations of short-term disease progression (Chapter 8). Given the variability of symptoms in MS, it is important to find out whether patients are able to accurately evaluate the presence of MS symptoms and to monitor their disease activity. A first

step to follow is to investigate patients' beliefs about their illness in a qualitative study. Such study has the best chance to bring to light the common misunderstandings, which can consequently be used as a starting point for further quantitative research and for strategies on how to inform patients. In a randomized controlled study, the effect of such intervention on expectations can be evaluated. If proven successful, such information procedures may be included in the regular care of patients, e.g., the follow-up visits with the MS nurse.

Studies of perception of prognostic risk

Perception of prognostic risk is an unexplored area in clinical research. To our knowledge, this is the first study that addressed the determinants of perceived prognostic risk and its associations with psychological well-being. Where findings on the associations may be similar to those found in genetic risks, the determinants of prognostic risks may be considerably different. This study demonstrated that presence of symptoms determined perceived risk of wheelchair dependence, and that the relationship of perceived symptoms was different for the three time perspectives (2 years, 10 years and lifetime) and for patients with high and low neuroticism. These findings are summarized in a model (Figure 1).

The qualitative analysis of the interview data confirmed the role of present symptoms, but added many other factors such as disease history, the future availability of treatment and psychological factors such as hope and mental attitude. How patients think about future disease progression can be schematically

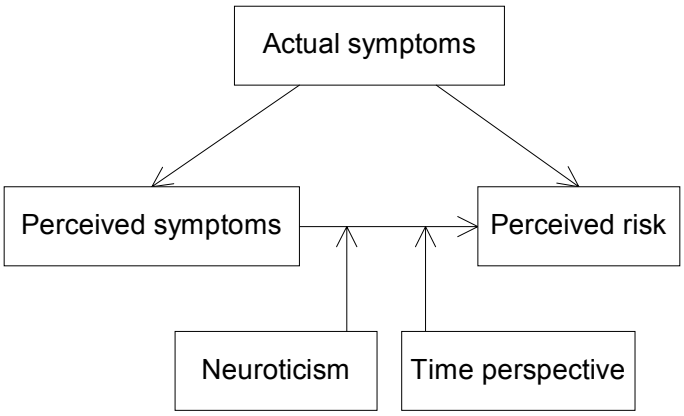

Figure 1 Schematic model of perceived risk of wheelchair dependence based on our correlational studies (directions assumed)

represented in a mental model. Mental models summarize the major lines of reasoning employed by patients, and have been previously employed in risk perception of breast cancer and in the design of risk communication strategies.[51-54] Such qualitative approach can bring to light how patients think about their risks more efficiently than correlational studies. The explanations that patients employed

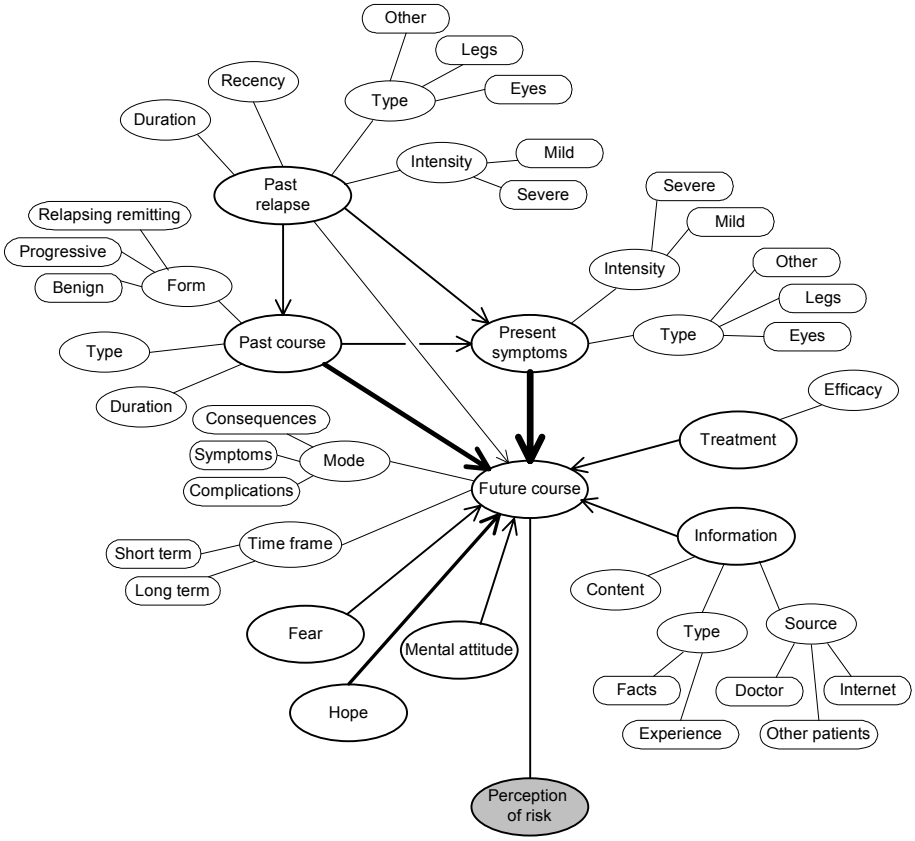

Figure 2 Towards a mental model of patients' expectations of future disease progression based on data from the interview study

Bold ellipses are key constructs, normal ellipses are attributes of these constructs and rounded squares are values of the attributes. The thickness of the arrow or line represents the frequency of use of the explanation. Perception of risk is presented as an operationalization of expectations of future disease course. For example, patients perceived their short-term (time frame) risk of wheelchair dependence as low because their past courseof disease had been benign (form) or that their symptoms (past relapse) had only included their eyes (type) and not their legs (type).

with regard to their expectations about future disease progression in our study are outlined in a preliminary model in Figure 2. In this figure, perception of risk is presented as an isolated construct, as in our view it is an operationalization of patients' expectations. This model is preliminary and based on interviews with recently diagnosed patients on their risk of wheelchair dependence only. Although the model remains to be confirmed, it may be helpful as a starting point in our understanding of patients' expectations. Future studies should be broadened by investigating the risk of wheelchair dependence in later phases of disease, but also by investigating other risks in MS and other risks in other chronic diseases as it can be assumed that patients generally extrapolate past disease course into future expectations. On the other hand, hope and fear may be more important in diseases with uncontrollable prognosis as MS, whereas behavioral influences such as diet and exercise may prevail with regard to preventable complications in for example cardiovascular diseases. Also, differences may be expected between predictable and unpredictable diseases, risk of short- and long-term complications. Unraveling the major lines of reasoning will help understanding perceived risks of patients over a potentially wide range of diseases. These studies may serve as a starting point for new quantitative studies including follow-up studies and clinical trials.

Recommendations for risk perception research

Perception of risk is an alternative way to study expectations with regard to specific (health) outcomes. This part of the discussion provides several considerations to determine whether perception of risk is a suitable operationalization of expectations in a particular clinical study.

Perception of risk can be the strategy of choice when the aim is to compare expectations between or within patients to investigate and/or to determine what factors influence expectations, or to investigate the relationship between expectations and psychological well-being. Several factors determine whether risk perception is an adequate operationalization for patients' expectations. First, a necessary condition is that there is one or a limited number of specific health outcome that are of major concern to the patient population. An outcome that is not of major concern will not affect health decisions or psychological well-being of patients. As for many people MS is associated with a wheelchair, it was anticipated in our study that this could be a major concern for recently diagnosed patients, but this may be less obvious in later phases of the disease as suggested by the decrease in seriousness of wheelchair dependence in patients with more disability. Also in the context of genetic testing, the outcome of interest may vary, as persons at the same time are at risk of being a mutation carrier, at risk of developing the disease

and at risk of dying of the disease. Second, the outcome should be relevant in the context of the research question. In MS, there are many prognostic risks that are considered as serious, but not all of them would affect psychological well-being or decision making in the early phase of disease. Relevance does also concern the time perspective. In our study, we found significant associations between perceived risk and psychological well-being only for the short-term, but not for the long-term risk of wheelchair dependence. Third, for the validity of the assessment it is important that the outcome can be described in an unambiguous way, so that all participants will have the same interpretation. For this reason, in this thesis wheelchair dependence was specified for short distances, namely 5 meters and over. Unambiguous description may be less straightforward for cognitive decline, sensory problems or psychological consequences. Finally, patients should be aware of the outcome being a consequence of the disease. In our study, wheelchair dependence was a consequence of disease that all patients knew, but it would have been unethical to ask for their perceived risk of sexual dysfunction, cognitive decline or death due to MS, as patients may not be aware of these complications or outcomes of MS.

Final remarks

This study demonstrated that patients overestimated their short- and medium-term risks of wheelchair dependence and that these perceptions were significantly related to subjective symptom reporting, higher levels of anxiety and distress. Moreover, the longitudinal data confirmed that changes in these short- and medium-term risk perception were convincingly related with changes in psychological well-being. As this is the first study on perception of prognostic risk, not only in MS but also in other chronic diseases, it is evident that replication of our findings is needed. Notwithstanding, the findings highlight the importance of addressing short-term prognosis in the clinical consultation with patients. Further intervention studies of the confirmation of uncertain information about prognosis and information on symptoms may provide opportunities to adjust patients' expectations about their future disease progression. This may help patients to cope with the prognostic uncertainty of MS and ultimately improve the health-related quality of life of patients.

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SUMMARY

The present study describes expectations of prognosis of recently diagnosed MS patients and their partners with a focus on the risk of wheelchair dependence. The three main questions in this thesis were: (1) How do recently diagnosed patients and their partners perceive the risk of wheelchair dependence? (2) How do perceptions of risk relate to psychological well-being? (3) What are the determinants of perception of prognostic risk? Before answering these key questions, the psychological burden of disease and the quality of life (QoL) of patients and partners in the early phase of MS are examined.

The thesis starts with a description of the disease and a summary of previous studies on psychological aspects of MS (**Chapter 1**). Discussed are findings on diagnostic and prognostic uncertainty, poorer health-related quality of life (QoL), higher levels of depression and anxiety, and the high psychological burden for partners. These psychological aspects have not been investigated in the early phases of disease. Also, to date, expectations of future disease progression – or perceptions of prognostic risk – of patients and partners have not been studied in MS or other chronic diseases. **Chapter 2** describes the design of the study, procedures of data collection, selection of participants, the instruments used and their psychometric properties. The prospective follow-up study consists of psychological and neurological assessments at four measurements within two years and of interviews at baseline. Hundred-and-one patients and 78 partners were included.

As an indication of the burden of uncertainty prior to the diagnosis, patients' satisfaction with the timing of diagnosis was investigated (**Chapter 3**). We found that the probability of patients being satisfied with the timing of diagnosis was highest in patients diagnosed with MS within the first year after the first visit with the neurologist. Patients explained that they preferred an early diagnosis because the burden of diagnostic uncertainty was considerable.

Chapter 4 shows that at baseline, on average eight months after diagnosis, both patients and partners had high levels of anxiety and distress. In addition, patients but not partners reported poorer health-related QoL compared to controls. As expected, poorer psychological well-being and QoL were primarily found in patients with higher disability. In **Chapter 5**, we show that disability status was significantly related only to three out of four SF-36 physical health scales, after adjustment for anxiety and depression. The relation between EDSS and these SF-36

scales was consistently higher in patients with more symptoms of anxiety or depression, suggesting that anxiety and depression strengthened the association of EDSS and these SF-36 physical health scales. The finding that EDSS was not significantly related to the SF-36 mental health scales and the general health scale when adjusting for anxiety and depression, is compatible with the hypothesis that anxiety and depression are intermediate factors in the association of EDSS with these SF-36 scales.

Chapter 6 addresses the question how recently diagnosed patients and their partners perceived the risk of wheelchair dependence. In comparison with actual risks obtained from epidemiological studies, patients and partners overestimated their 2-year and 10-year risks of wheelchair dependence, but underestimated their lifetime risks. A large number of patients were uncertain about their 2-year risk, even those with no or only minimal disability (EDSS < 3.0). One-third of the patients perceived the 10-year and lifetime risk to be 50%, which, as they explained in the interviews, reflected their uncertainty: they did not know what to expect. Patients with more functional limitations had higher perceptions of risk, but perceived wheelchair dependence as being less serious.

In **Chapter 7**, the relationship between perceived risk and seriousness and anxiety, depression (HADS) and disease-related distress (IES) was examined. We found that patients with higher perception of the risk and seriousness of wheelchair dependence had significantly higher levels of distress, after adjustment for clinical disability status. Relations were found for the 2-year, 10-year and lifetime prognosis of wheelchair dependence. Only perception of the 2-year risk and seriousness of wheelchair dependence was significantly associated with higher levels of anxiety and depression.

In Chapter 8, 9 and 10 the determinants of perception of risk were studied. **Chapter 8** focuses on the role of illness beliefs such as beliefs about the controllability, duration, and symptoms of the disease. Patients who reported a higher intensity of disease-attributed symptoms had higher perceptions of the 2-year and 10-year risk of wheelchair dependence, after adjustment for clinical disability status. None of the other illness beliefs were significantly related to perceived risk or seriousness of wheelchair dependence. In **Chapter 9**, we present the finding that neuroticism strengthens the relationship of perceived symptoms with perception of the risk and seriousness of wheelchair dependence. Patients who were more pessimistic reported more symptoms after adjustment for disability status and considered wheelchair dependence to be more serious. Optimism and pessimism were not associated with perception of risk. Our findings suggest that personality factors directly (neuroticism) and indirectly (pessimism) affect

perception of risk and seriousness of wheelchair dependence. Findings of the qualitative study of perception of prognostic risk are reported in **Chapter 10**. In line with the quantitative analyses presented in Chapter 8, patients mentioned disease-related factors such as presence of symptoms and recent disease progression to explain their perception of risk. In addition, psychological factors such as hope, fear and positive thinking were identified as determinants. Uncertainty about future disease progression was found to be omnipresent in the explanations of perceived risks. With regard to the perceived seriousness of wheelchair dependence, three groups could be distinguished: a group considering a wheelchair the worst thing that can happen, a group thinking it is serious but worse things can happen and a group considering it just a small inconvenience.

In **Chapter 11**, the course of perception of risk and seriousness and the longitudinal findings on the determinants are described. In patients and partners, perceptions of the 2-year and 10-year risk of wheelchair dependence significantly increased during the 2-year follow-up. Perceived lifetime risk and perceived seriousness did not change over time. Relationships of disability status and perceived symptoms with perception of risk were confirmed in the cross-sectional analyses of the follow-up data. Changes in perceived symptoms were associated with changes in perception of risk, confirming that perceived symptoms play an important role in perception of prognostic risk in recently diagnosed MS patients.

In **Chapter 12**, the relationship between perception of risk and psychological well-being was investigated in a follow-up study. Mean levels of disease-related distress decreased significantly both in patients and their partners, but the high levels of anxiety remained unchanged. In patients, higher perception of the 2-year and 10-year risk of wheel-chair dependency was again significantly related to poorer psychological well-being, whereas higher perception of seriousness was consistently related to higher distress and anxiety. Most importantly, an increase in perception of the 2-year and 10-year risk of wheelchair dependence was associated a significant increase in levels of anxiety, depression and distress.

In conclusion, we have demonstrated that the early period after diagnosis of MS puts a substantial emotional burden on patients and their partners. Patients and partners overestimated the short- and medium-term risks of wheelchair dependence, but underestimated the lifetime risk. Moreover, higher perceptions of the short- and medium risks were found among patients with higher symptom perception, and were associated with poorer psychological well-being. These findings are interpreted from a psychological and clinical perspective (**Chapter 13**). Further, in this chapter, suggestions for future research are discussed.

SAMENVATTING

Dit proefschrift richt zich op patiënten bij wie recent de ziekte multipele sclerose (MS) is vastgesteld en hun partners. De drie belangrijkste onderzoeksvragen waren: (1) In hoeverre verwachten patiënten en partners dat de patiënt rolstoel-afhankelijk zal worden als gevolg van MS? (2) Zijn percepties over dit risico gerelateerd aan het psychologisch welbevinden? (3) Wat zijn de determinanten van de perceptie van dit risico? Voorafgaand aan deze vraagstellingen zijn het psychologisch welbevinden en de kwaliteit van leven van patiënten en partners in deze vroege fase van de ziekte in kaart gebracht.

Hoofstuk 1 geeft een beschrijving van de ziekte en een samenvatting van het onderzoek naar psychosociale aspecten van MS dat tot op heden is verricht. De onzekerheid over de diagnose en prognose, de lage kwaliteit van leven, de gevoelens van depressie en angst en de psychologische belasting voor partners worden besproken. Psychologische aspecten blijken nauwelijks onderzocht voor de vroege fase van MS. Ook zijn verwachtingen over de toekomstige gezondheid, ofwel percepties van prognostisch risico's, van patiënten met MS en hun partners, maar ook van patiënten met andere chronische ziekten, niet eerder onderzocht.

Hoofdstuk 2 beschrijft de opzet van het onderzoek, de selectie van deelnemers en de gegevensverzameling. De keuze van de meetinstrumenten wordt toegelicht en hun eigenschappen worden geëvalueerd. In dit onderzoek werden patiënten na de diagnose in 2 jaar vier keer benaderd voor neurologisch onderzoek en psychologische vragenlijsten. Ook partners werden op drie momenten gevraagd om vragenlijsten in te vullen. Aan het begin van het onderzoek werden bovendien alle patiënten (n = 101) en partners (n = 78) geïnterviewd.

Als indicatie voor de onzekerheid van patiënten voorafgaand aan de diagnose, hebben wij onderzocht of patiënten tevreden waren met het moment waarop de diagnose werd gesteld. **Hoofdstuk 3** laat zien dat de kans dat een patiënt tevreden is over het moment dat de ziekte is vastgesteld duidelijk afneemt naarmate de periode van diagnostisch onderzoek langer is. De belangrijkste reden waarom patiënten graag eerder een diagnose hadden willen horen was dat daarmee een einde werd gemaakt aan de enorme onzekerheid over de oorzaak van hun klachten. Onze bevindingen suggereren dat patiënten de voorkeur geven aan een snelle diagnose.

Hoofdstuk 4 laat zien dat zowel patiënten als partners angstiger waren dan personen uit de Nederlandse bevolking, maar niet depressiever. Ook scoorden zij

hoog op de vragenlijst van psychologische spanning. Patiënten rapporteerden bovendien een lagere kwaliteit van leven dan personen uit de algemene bevolking. Vooral patiënten met meer lichamelijke beperkingen, als vastgesteld door een neuroloog, rapporteerden meer symptomen van angst, depressie en spanning en hadden een lagere kwaliteit van leven. Lichamelijke beperkingen waren significant gerelateerd aan drie van de vier schalen die kwaliteit van de lichamelijke gezondheidstoestand meten (**Hoofdstuk 5**). Deze relatie was consistent sterker in patiënten met meer symptomen van angst en depressie. Deze bevinding suggereert dat angst en depressie de relatie tussen 'objectieve' lichamelijke beperkingen en de ervaren kwaliteit modificeren. Lichamelijke beperkingen waren niet gerelateerd aan schalen die de kwaliteit van de mentale en algemene gezondheidstoestand meten als rekening werd gehouden met de mate van angst en depressie. Ons onderzoek suggereert dat lichamelijke beperkingen leiden tot angst en depressie, welke vervolgens de mentale en algemene gezondheidstoestand beïnvloeden.

In **hoofdstuk 6** beschrijven we de perceptie van het risico en de ernst van rolstoelafhankelijkheid. Vergeleken met epidemiologische schattingen van de risico's, overschatten patiënten en partners het risico om binnen 2 of 10 jaar rolstoelafhankelijk te worden en onderschatten zij het risico dat dit ooit zal gebeuren. Een groot aantal patiënten, waaronder patiënten met minimale lichamelijke beperkingen, geven aan dat zij niet verwachten binnen 2 jaar rolstoelafhankelijk te worden, maar waren daarover toch erg onzeker. Zoals verwacht hadden patiënten bij wie door de neuroloog meer functionele beperkingen werden vastgesteld een hogere perceptie van het risico. Tegelijkertijd vonden zij, vergeleken met patiënten met weinig lichamelijke beperkingen, het minder erg wanneer dit zou gebeuren. Patiënten met een hogere perceptie van het risico of de ernst van rolstoelafhankelijkheid waren angstiger en ervaarden meer psychologische spanning, zelfs wanneer rekening werd gehouden met de lichamelijke beperkingen van de patiënt (**Hoofdstuk 7**). Deze relatie was het sterkst voor het risico om binnen 2 jaar van een rolstoelafhankelijk te worden.

In de hoofdstukken 8, 9 and 10 werd onderzocht welke factoren geassocieerd zijn met de perceptie van het risico en de ernst van rolstoelafhankelijkheid. **Hoofdstuk 8** bestudeert de relatie met ideeën van patiënten over hun ziekte, bijvoorbeeld over de behandelbaarheid en de aanwezigheid van symptomen. Patiënten die meer MS gerelateerde symptomen ervaarden hadden een hogere perceptie van het 2- en 10-jaar risico, rekening houdend met verschillen in lichamelijke beperkingen als door de neuroloog vastgesteld. Geen van de andere ideeën over MS waren gerelateerd aan de perceptie van het risico of de ernst van rolstoelafhankelijkheid. In **Hoofdstuk 9** werd de relatie tussen persoonlijkheid en

percepties van de patiënt nagegaan. Wij vonden dat patiënten die hoger scoorden op pessimisme meer symptomen rapporteerden en dat neuroticisme de relatie tussen de ervaren symptomen van de patiënten en de perceptie van het risico en de ernst van rolstoelafhankelijkheid versterkte. Optimisme en pessimisme zelf waren niet direct gerelateerd aan de perceptie van risico. Vergelijkbaar met de bevindingen uit hoofdstuk 8, noemden patiënten in de interviews ziekte-gerelateerde factoren, zoals de aanwezigheid van symptomen en recente ziekteprogressie, als reden voor hun percepties (**Hoofdstuk 10**). Ook psychologische factoren zoals hoop, angst, positief denken, maar bovenal gevoelens van onzekerheid werden veelvuldig genoemd in de interviews waarin patienten hun percepties toelichtten.

In de hoofdstukken 11 and 12 werden de vraagstellingen opnieuw onderzocht, maar nu met de gegevens van de vervolgonderzoeken. Zowel bij patiënten als partners was de perceptie van het 2- en 10-jaar risico hoger in de vervolgmetingen (**Hoofstuk 11**). De perceptie van het levenslange risico en de ernst van rolstoelafhankelijkheid veranderde niet gedurende de looptijd van het onderzoek. Een verandering in symptoomperceptie was duidelijk gerelateerd aan veranderingen in risicoperceptie, hetgeen bevestigt dat voor patiënten de ervaren symptomen een belangrijke rol spelen in de verwachtingen over hun toekomstige gezondheid.

De psychologische spanning daalde significant gedurende de looptijd van het onderzoek (**Hoofdstuk 12**), maar een kleine groep patiënten en partners rapporteeerde een hoge mate van angst gedurende de hele periode. Onze bevindingen lieten zien dat een verandering in de perceptie van het 2- of 10-jaar risico van rolstoelafhankelijkheid significant geassocieerd was met een verandering in het niveau van angst, depressie en spanning.

Concluderend blijkt uit dit proefschrift dat de diagnose MS een emotionele druk legt op patiënten en hun partners. Patiënten en partners overschatten het risico op rolstoelafhankelijkheid voor de korte en middellange termijn maar onderschatten zij het risico voor hun gehele leven. De perceptie van het korte en middellange risico was het hoogst onder mensen die een groot aantal symptomen van de ziekten ervaarden en was daarnaast sterk gerelateerd aan het psychologisch welbevinden. De bevindingen worden geïnterpreteerd vanuit een psychologisch en klinisch perspectief in **Hoofdstuk 13**. In dit hoofdstuk worden eveneens aanbevelingen voor verder onderzoek gedaan.

CURRICULUM VITAE

Cecile Janssens was born on June 15, 1968 in Oisterwijk. She graduated from secondary school at the Maurick College in Vught in 1986 and obtained a bachelor's degree in economics at the Hogeschool 's Hertogenbosch (HEAO) in 1989. She continued her education in economics at the Erasmus University, but switched her interest to psychology. She obtained her master's degree in clinical and health psychology at the Utrecht University in 1996. As part of her training, she conducted a research traineeship at SRI International, Menlo Park (USA) on cognitive function in elderly twins (supervisors dr Dorit Carmelli and dr Gary Swan). From 1996 to 1997, she worked at the Netherlands Institute for Primary Health Care (NIVEL) where she conducted a state of the art study on psychosocial aspects of prenatal screening and diagnosis (supervisor: prof dr Jozien Bensing). In 1998, she started the studies on perception of prognostic risk in multiple sclerosis described in this thesis at the department of Neurology (former head: prof dr Frans van der Meché) and the department of Medical Psychology and Psychotherapy (head: prof dr Jan Passchier). For this project, she visited prof dr Baruch Fischhoff at Carnegie Mellon University, department of Social and Decision Sciences in Pittsburgh (USA; September to December 2000). In 2001, she obtained a master's degree in epidemiology at the Netherlands Institute of Health Sciences (nihes). Since October 2002, she has been appointed as a postdoc at the Center for Clinical Decision Sciences (head: prof dr Dik Habbema), department of Public Health, Erasmus MC, working on methodological issues in the evaluation of sequential diagnostic tests.