# Recurrences, vaccinations and long-term symptoms in GBS and CIDP

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## ABSTRACT

We determined the frequency of recurrent Guillain-Barré syndrome (GBS), whether vaccinations led to recurrences of GBS or an increase of disability in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and we assessed the prevalence of pain, fatigue and the impact on quality of life after GBS and CIDP. Additionally, we assessed the presence of common auto-immune disorders.

Four hundred and sixty-one members of the Dutch society of neuromuscular disorders received a questionnaire. Two hundred and forty-five GBS and seventy-six CIDP patients were included (response rate 70%). Nine patients had a confirmed recurrent GBS, and two patients had experienced both GBS and CIDP. Common auto-immune diseases were reported in 9% of GBS and 5% of CIDP patients. None of the 106 GBS patients who received a flu vaccination (range 1-37 times, total 775 vaccinations) reported a recurrence thereafter. Five out of twenty-four CIDP patients who received a flu-vaccination (range 1-17 times) reported an increase in symptoms. Pain or severe fatigue was reported in about 70% of patients after the diagnosis of GBS (median 10 years) or after onset of CIDP (median 6 years), and quality of life was significantly reduced.

Flu-vaccinations seem relatively safe. GBS and CIDP patients often experience pain, fatigue and a reduced quality of life for many years after the diagnosis.

## INTRODUCTION

Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are immune-mediated polyneuropathies associated with a variable clinical course and outcome. GBS patients usually reach their maximum disability within 4 weeks of onset compared to at least 2 months for CIDP patients.[1,2]

Although GBS is considered as a monophasic disorder, some patients experience a recurrence of GBS or even develop a separate episode of CIDP.[3,4] Additionally, some CIDP patients may develop GBS.[4] In this study, we aimed to obtain more information about the frequency of recurrent GBS and the occurrence of both GBS and CIDP in single patients. Additionally, we evaluated the levels of pain, fatigue and quality of life experienced by patients for an extended period after the initial phase of their disease. Pain has been documented as one of the symptoms that can precede and accompany GBS but in CIDP this has hardly been studied.[5-7]

Reports about recurrences of GBS or relapses of CIDP following vaccinations are rare, which suggests that this risk is low.[8] As we aimed to study a large number of patients that might have had multiple vaccinations over time, this information would add to the discussion whether GBS and CIDP patients could safely have vaccinations or not.

## MATERIALS AND METHODS

In June 2008, 461 members of the Dutch society of neuromuscular disorders (Vereniging Spierziekten Nederland) with GBS or CIDP were sent a combined set of questionnaires composed by the researchers. Patients were asked to return the questionnaires only if they were diagnosed with GBS, the cranial nerve variant Miller Fisher syndrome (MFS) or CIDP. Furthermore, they were asked to report the disorder they were diagnosed with. To increase the response rate, patients were sent two reminder letters. The study was approved by the Medical Ethical Committee of the Erasmus MC, Rotterdam, The Netherlands.

The questionnaires concentrated on 4 areas; preceding vaccinations (within 8 weeks before the onset of GBS or CIDP), family members with GBS or CIDP, the occurrence of common auto-immune diseases and persistent symptoms at a variable time-point after the diagnosis (the moment of completing the questionnaire). The combined set of questionnaires contained various standardised and well evaluated subquestionnaires to be filled in for the present situation at the time of completion: the numeric pain rating scale (NPRS) for pain, the fatigue severity scale (FSS) for fatigue, the hospital anxiety and depression scale (HADS) for anxiety and depression and the short form (36) health survey (SF-36, Dutch acute version 1) for quality of life.

Severe pain was defined as a score of ≥ 7 on the NPRS.[9] The FSS ranges from one (no signs of fatigue) to seven (most disabling fatigue score). Severe fatigue was defined as a mean FSS score of ≥ 5.0 (≥ 95$^{th}$ percentile in healthy controls), and corrected for depression as scored on the HADS.[10]

SF-36 percentage scores were transformed to norm-based scores using a T-score transformation (mean = 50, SD = 10), giving the opportunity to compare the results from one domain meaningfully with those from other domains, and in particular to compare these with the distribution of scores in the general Dutch population (n = 1742).[11-13] A high SF-36 score is an indication of a better health status, and scores below 50 are interpreted as below average in the general Dutch population. Missing values that could not be traced were substituted with person-specific estimates if the respondent answered at least 50% of the items in a domain according to the half-scale rule from the SF-36 developers.[12] In the case of missing values in the other standardised questionnaires or when other major items were lacking, such as diagnosis or severity at nadir, patients were contacted to obtain missing information. Data were checked by two researchers (K.K. and M.B.E.). When patients reported having had recurrent GBS, both GBS and CIDP, or having relatives with GBS or CIDP, medical information was obtained and verified by the researchers (K.K. and P.D.). When evaluating fatigue, patients were considered mildly affected by their disease when they were able to walk unaided (GBS-disability scale score ≤ 2) at nadir.[14]

Differences in characteristics, and self-reported pain, fatigue, and quality of life were calculated using the $\chi^2$ test, Fisher exact test, Mann-Whitney *U* test or t-test. Spearman's correlation coefficient ($r_s$) was used to analyse the correlation between fatigue and GBS disability score or the time since diagnosis. A p value $< 0.05$ was considered significant. Data were analysed using SPSS version 15.0.

## RESULTS

A total of 323 questionnaires were returned: a response rate of 70%. Two patients were excluded; one with a chronic idiopathic axonal polyneuropathy and one with an unknown diagnosis. Patients completed the questionnaire after a variable time from onset of GBS (median 10 years, range 0-62) or CIDP (median 6 years, range 0-29).

Of the 321 patients, 245 were diagnosed with GBS and 76 with CIDP. Of the 245 GBS patients, four had MFS and five had an MFS/GBS overlap. One patient had Bickerstaff encephalitis. Nineteen GBS patients reported recurrent GBS, and in nine of these patients (4%) we could confirm this, but in the other 10 it remained unclear from the medical information available whether these patients had indeed had another GBS episode. Two patients had both GBS and CIDP. One of these patients has been described previously.[4]

Eight GBS patients and one CIDP patient had a relative with an immune-mediated polyneuropathy, which was verified by checking medical records. Six GBS patients had a first till fourth degree relative with GBS. One GBS patient had a grandson with CIDP and another had a cousin with multifocal motor neuropathy. One CIDP patient had a brother with CIDP.

Twenty-three GBS (9%) and eight (11%) CIDP patients reported a preceding vaccination, within 8 weeks form onset of symptoms. The most often reported vaccination was a flu vaccination (Figure 1).

None of the 106 GBS patients who received a flu vaccination (range 1-37 times, in total 775 vaccinations) in the years after they experienced GBS reported a recurrence of GBS. Of the 24 patients who received a flu vaccination (range 1-17 times) after being diagnosed with CIDP, five reported an increase in symptoms after one or more vaccinations.

Twenty-three patients with GBS (9%) and four patients with CIDP (5%) are currently diagnosed with a common auto-immune disease, most often a thyroid disorder (Figure 2).

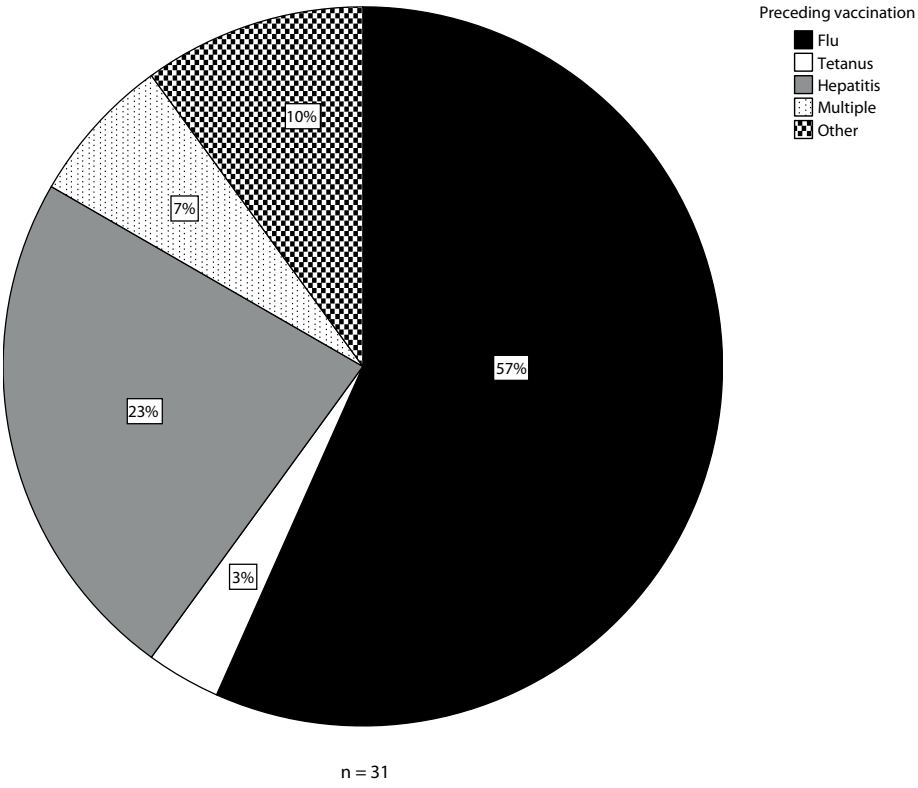


**Figure 1. Reported vaccinations prior to onset of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy**

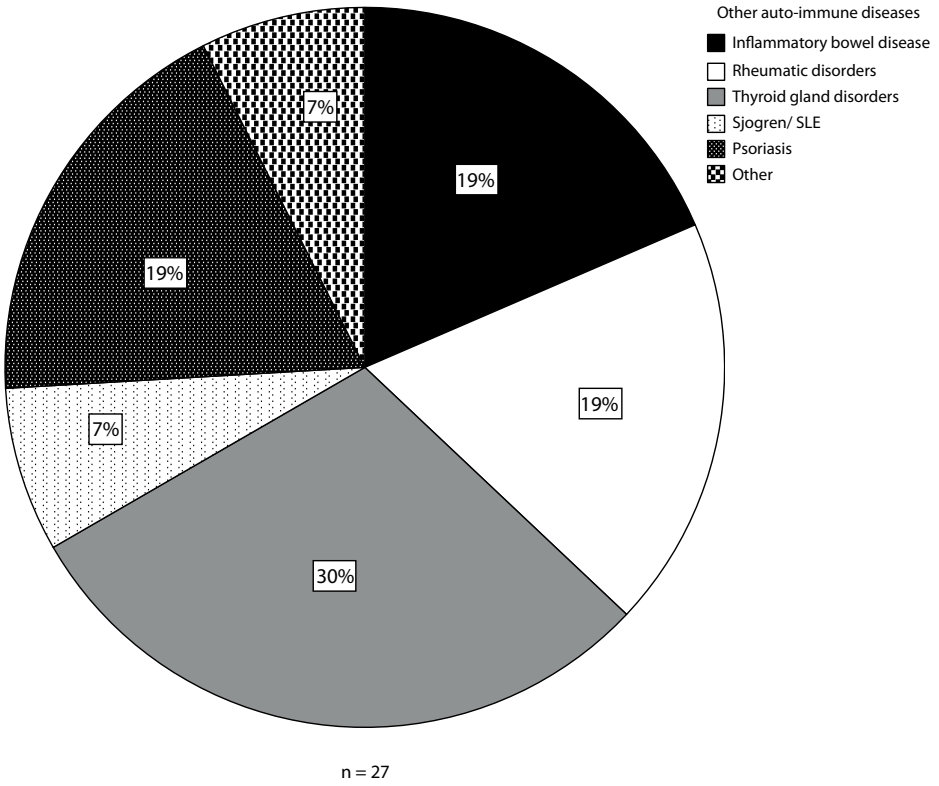


**Figure 2. Reported auto-immune diseases in patients with Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy**

Pain was reported in 71% of GBS and in 72% of CIDP patients long after the diagnosis, and severe pain in 8% of GBS and 17% of CIDP patients. Several years after the diagnosis, severe fatigue was still prominent, and 45% of GBS and 25% of CIDP patients experienced fatigue as their most disabling symptom (Table 1). Severe fatigue was more pronounced in the patients who were still severely affected as assessed with the GBS-disability scale, than in the mildly affected patients (85% vs 68%, p=0.008), and the GBS-disability score correlated weakly with the FSS score ($r_s$ = 0.5, p < 0.01). Fatigue was not significantly related to the time since start of the GBS symptoms ($r_s$ = 0.04, p = 0.5).

CIDP patients scored significantly lower than the GBS patients on three items of physical functioning (Table 1). GBS and CIDP patients scored significantly lower in all physical health items of the SF-36 as well as in two items of mental health (vitality and social functioning) when compared with the normal Dutch population (Figure 3).[13]

**Table 1. Long-term symptoms in Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)**

| | Patients | | |
|---|---|---|---|
| | GBS (n = 245) | CIDP (n = 76) | p value |
| Time since diagnosis, y | 10 (0-62) | 6 (0-29) | 0.001 |
| Age when participating in this study, y | 59 (7-94) | 59 (9-85) | NS |
| Disability (GBS-disability score) | | | |
| Median (range) | 2 (0-4) | 2 (0-4) | NS |
| Pain (NPRS) | | | |
| Median (range) | 2.2 (0-10) | 2.3 (0-8) | NS |
| Severe pain[#] | 8% | 17% | 0.028 |
| Depression (HADS) | | | |
| Depressed | 6% | 9% | NS |
| Fatigue (FSS) | | | |
| Median (range) | 5.8 (1-7) | 5.9 (1-7) | NS |
| Severe fatigue* | 69% | 74% | NS |
| Quality of Life (SF-36) | | | |
| Physical functioning | 36.2 (13.7) | 32.6 (13.2) | 0.046 |
| Role-physical | 41.7 (11.8) | 38.6 (11.2) | 0.042 |
| Bodily pain | 46.5 (10.7) | 45.3 (12.0) | NS |
| General health | 44.6 (11.5) | 39.1 (11.7) | <0.001 |
| Vitality | 43.6 (10.6) | 41.2 (10.2) | NS |
| Social functioning | 45.8 (9.0) | 46.2 (9.2) | NS |
| Role-emotional | 50.0 (10.0) | 50.0 (10.8) | NS |
| Mental health | 50.0 (9.3) | 50.1 (9.8) | NS |

NS = not significant ($p > 0.05$)
Continuous or categorical variables presented as median (range) and compared using Mann-Whitney *U* test.
Numeric variables presented as percentage and compared using $\chi^2$- test or Fisher exact test.
Continuous variables regarding the SF-36 are presented as norm-based mean scores (SD) using a T-score transformation (mean = 50, SD 10) according to the general Dutch population and compared using t-test.
NPRS = numeric pain rating scale
HADS = hospital anxiety and depression scale
FSS = fatique severity scale
SF-36 = Short Form (36) health survey
[#] NPRS ≥ 7.
* FSS ≥ 5.0 corrected for depression.

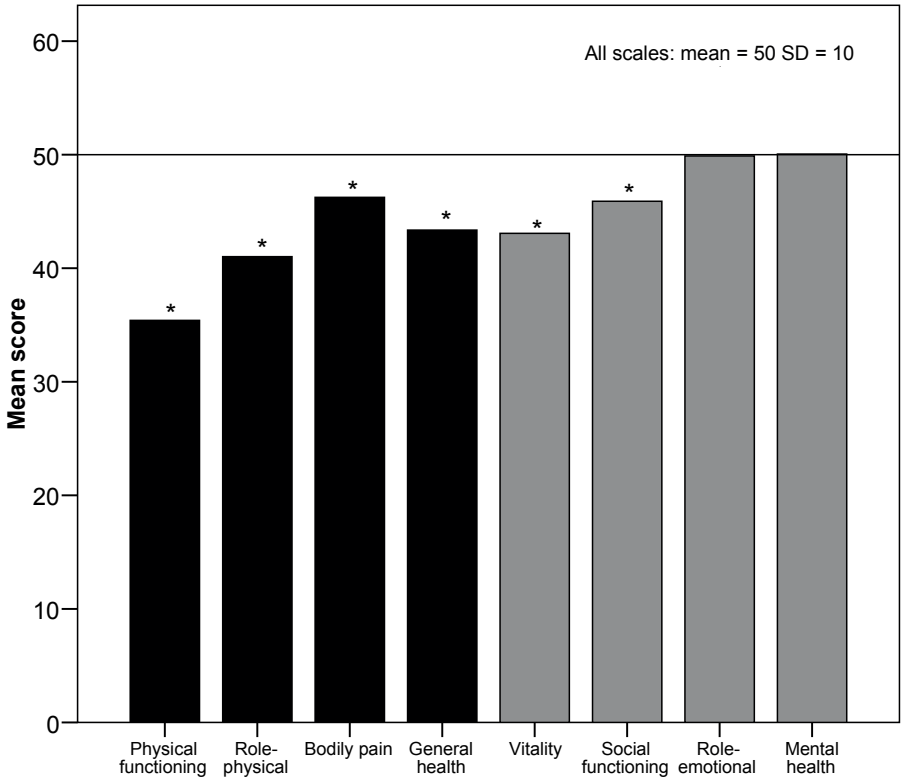


**Figure 3. SF-36 health survey in Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy patients (norm-based scoring)**
* = $p < 0.001$.

## DISCUSSION

The frequency of recurrent GBS (4%) in the current study is comparable with the 2-6% that has been described previously.[3,15] We found two patients who had had both GBS and CIDP. Although the combination of having both GBS and CIDP could be by chance, these patients support the hypothesis that GBS and CIDP may constitute a clinical continuum or that there are common host factors which influence susceptibility to these disorders.[4] We identified nine patients (eight GBS and one CIDP) having a relative with an immune-mediated polyneuropathy, which may suggest, but does not prove, a genetic susceptibility factor; some of these patients have been described previously.[16] The GBS and CIDP patients included in our study had a slightly higher prevalence of common auto-immune diseases than the 5% previously reported in the general population.[17]

Our study indicates that the risk of developing another GBS episode after a flu vaccination is small. This confirms a recent study that found no evidence of an increased

risk of GBS after seasonal influenza vaccination.[18] Another study has also suggested a low risk following vaccination, where only 4% (11/311) of GBS patients and 8% (5/65) of CIDP patients experienced a recurrence of symptoms following a vaccination.[19]

The occurrence of pain long after the diagnosis of GBS in our study was similar to the 69% that has been described before in 50 GBS patients long after the diagnosis (median 10 years).[20] Severe fatigue was also a major complaint even long after the diagnosis of GBS or CIDP. Fatigue is reported to occur more often in patients with an immune-mediated neuropathy than in healthy controls (median 6.1 vs. median 2.9, $p < 0.0001$).[10] In a group of 113 patients with an immune-mediated neuropathy, severe fatigue appeared to be present in 80% of patients several years (median 5.1 years) after the diagnosis.[10] Some of these patients were probably also included in our study, but our study contained three times more GBS as well as CIDP patients and the median time from disease onset was longer. We did not find a correlation between the time since diagnosis and the presence of fatigue. In contrast to what has been reported previously, our study suggests that severe fatigue was more pronounced in patients who were more severely affected by the disease at the time of completing the questionnaire. Both GBS and CIDP patients scored significantly lower on the SF-36 than the general Dutch population, except for two items regarding mental health, which has been described before.[20,21] When we compared GBS patients with those having CIDP, CIDP patients scored significantly lower on three items regarding physical health. This has not been reported before but can be explained by the chronic and often still active course of disease in CIDP.

Our study was a survey of members of a patient organisation, which may have given rise to several methodological limitations. As only members from a patient organisation were included, selection bias could have occurred. Patients who are or remain a member of a patient organisation are probably more likely to be severely affected. Patients were asked to return the questionnaire if they were diagnosed with GBS or CIDP. As we could not verify the diagnosis in all patients, some patients with another diagnosis might have been included. The retrospective nature of part of the questionnaires could have introduced recall bias. It is difficult to draw firm conclusions from a questionnaire in which patients report their recurrences after vaccinations themselves. It seems that patients are more likely to respond to a questionnaire when they did experience a recurrence.

Furthermore, the fact that not all patients responded to our questionnaire might have introduced some bias, although some members might have not replied due to the fact that they had been diagnosed with another disease or were healthy relatives of a patient. Strong points of our study are the large number of GBS and CIDP patients and the extended length of time between diagnosis and questionnaire completion.

The occurrence of recurrent GBS, GBS and CIDP in single patients or in families, and the slightly higher rate of common auto-immune diseases in GBS and CIDP patients may indicate a certain, possibly genetic, susceptibility factor. The common seasonal flu

vaccinations seem relatively safe in patients who have had GBS or still have active CIDP. Several years after the diagnosis of GBS (median 10 years) or CIDP (median 6 years) a significant number of patients still have residual symptoms, such as pain and severe fatigue, as well as a reduced quality of life, which clearly warrants recognition and support when possible.

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# Chapter 3