Long-term follow-up of children treated with neonatal extracorporeal membrane oxygenation: neuropsychological outcome

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Long-term follow-up of children treated with neonatal extracorporeal membrane oxygenation: neuropsychological outcome

Lange termijn follow-up van kinderen behandeld met neonatale extracorporele membraan oxygenatie: neuro-psychologische uitkomst

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Today is your day,
your mountain is waiting,
so get on your way.

Dr. Seuss

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CHAPTER 1

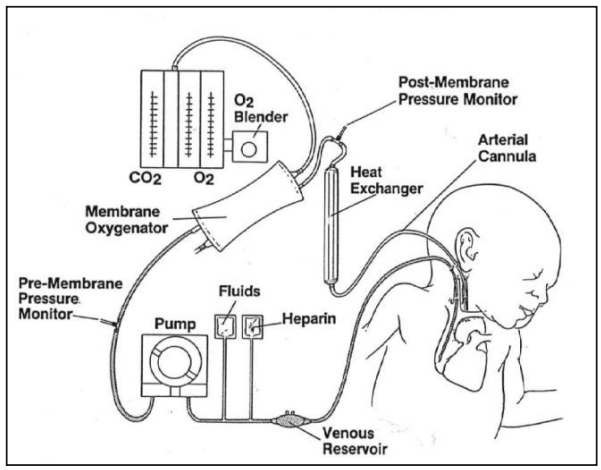
General introduction

INTRODUCTION

This thesis aims to describe the long-term neuropsychological outcome of children and adolescents treated with neonatal extracorporeal membrane oxygenation (ECMO).

ECMO is a pulmonary bypass technique providing temporary life support in potentially acute reversible (cardio)respiratory failure when conventional management fails. Bypass allows the lungs to recover without the damaging effects of ongoing mechanical ventilation with high inspired oxygen and peak pressure. It may also prevent further injury from high oxygen concentration, volutrauma and barotrauma[1]. ECMO was initially used in adults; but later was also applied in the treatment of infants and children[2,3]. In 1975, ECMO was first used to treat neonatal respiratory failure. Thus far, worldwide over 26,000 neonates with severe respiratory failure have been successfully treated with ECMO. An international registry reported an overall 75% survival rate at discharge[4]. There are two types of ECMO; venoarterial and venovenous. Venoarterial (VA) ECMO provides cardiac and pulmonary support to children with considerable circulatory instability and primary cardiac dysfunction. Primary respiratory failure is nowadays usually treated with venovenous (VV) ECMO, in all age groups. The survival rate for neonates treated with VA ECMO is estimated at 62%; that for neonates treated with VV ECMO at 85%[4].

The Erasmus Medical Center-Sophia Children's Hospital in Rotterdam and the Radboud University Nijmegen Medical Center in Nijmegen are the two established ECMO-centers in the Netherlands. Since around 1990 both centers have provided ECMO to approximately 700 neonates (before day 28 of the child's life), applying nationwide inclusion criteria. ECMO treatment in older children (pediatric ECMO) has increased over the years; the number has risen from 108 children internationally in the year 1990 to 354 in the year 2012 with a 58% survival rate[4].



Venoarterial ECMO circuit

Most of the children described in this thesis were treated with VA ECMO for primary persistent pulmonary hypertension secondary to meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH) or sepsis.

MAS occurs in only 0.2% of all births[5,6]. Hypoxic distress and gasping may cause meconium aspiration during birth and aspiration of thick meconium may occur during the respiratory effort of the first breath[7]. Consequently the airways are obstructed, which results in profound hypoxia. In addition, meconium may lead to chemical pneumonitis, parenchymal lung damage, and inactivation of surfactant[7]. ECMO treatment allows gentle ventilation and provides time for the body to absorb the meconium and for the pulmonary hypertension to resolve[8]. The survival rate of MAS has greatly improved to 94%[4]. Non-survivors treated with ECMO do not die from irreversibility of the lung disease but usually from a major intracranial complication[8].

CDH is a rare congenital anomaly of the diaphragm and both lungs, which occurs in about 1 per 2500 births[9]. The alveoli and pulmonary vessels are not well developed because the abdominal organs have herniated into the chest cavity[9]. In around 85% of patients, the diaphragmatic defect is located left[9-11]. CDH is potentially life-threatening due to severe pulmonary hypoplasia and therapy-resistant pulmonary hypertension[9]. Besides, surgical treatment in addition to ECMO may raise mortality and morbidity in this specific group of patients. Survival rates have improved over the past years to 65-90% in live-born children[12-15]. However, the overall survival rate in

CDH patients treated with ECMO is 51%[4] due to case selection as it is applied in the most critically ill.

Neonatal sepsis occurs in an estimated 1-2 patient per 1000 live births mostly due to Group B Streptococcus or Escherichia coli[16]. Sepsis results from a harmful or damaging response to infection[17]. Early onset sepsis is associated with acute respiratory distress, pneumonia, cyanosis, shock, fever, irritability, leucopenia, and rapid deterioration[17]. The overall survival rate in ECMO-treated neonates with septic shock is currently 75%[18].

Not only survival rates following neonatal ECMO differ between diagnosis subgroups, medical characteristics differ as well. For example, children with CDH need ECMO for a longer time, stay longer time on assisted ventilation, and have longer hospital stays than children with other diagnoses[19]. Long-term follow-up is recommended not only for children with CDH[19], but also for all other children who were critically ill and underwent invasive treatment modalities such as ECMO in their neonatal period. The use of ECMO treatment, particularly in CDH patients, is still debated mostly because of concerns about long-term morbidity. ECMO treatment can affect cerebral blood flow[20] and is a risk factor for cerebral injury such as intracranial hemorrhage[21]. Four randomized trials have studied the efficiency of neonatal ECMO; in two of them CDH patients were excluded. All four trials have proven that ECMO treatment provides better survival rates than conventional management[22]. The largest trial is from the United Kingdom and also evaluated long-term outcome for children treated with neonatal ECMO or with conventional management. This study found a survival advantage with ECMO treatment compared with conventional management without an associated increase in severe disability[23-25]. Moreover, ECMO treatment proved cost-effective till the age of seven[25]. However, only very few CDH patients survived in this trial. Also, none of the studies were primarily designed to evaluate ECMO in high-risk (respiratory insufficiency within the first 6 hours of life) CDH patients.

Ensuing disability or morbidity in surviving patients is a cause for concern. Because more children treated with neonatal ECMO survive, mortality is no longer the main outcome of interest. Our responsibility in providing optimal care for these children is not finished after hospital discharge. The long-term outcome of these children in

different areas of development, as well as the balance between healthcare costs and long-term outcome are important concepts when discussing the feasibility of neonatal ECMO treatment. Different studies on developmental outcome for children treated with neonatal ECMO examined different, mostly small, cohorts and also used different outcome assessments; the results are hard to compare therefore. Furthermore, most studies report outcome only till (pre)school age. We therefore need to structurally and longitudinally evaluate whether the scale of mortality and morbidity is not shifting out of balance towards higher rates of (severe) morbidity. This is why multidisciplinary long-term follow-up is strongly recommended when evaluating outcome for children treated with neonatal ECMO[26]. Follow-up teams should longitudinally assess, signal and report developmental delay and provide interventions when needed[26]. Also the impact of the ECMO treatment and the morbidity associated with this treatment on quality of life deserves attention.

Both in Rotterdam and in Nijmegen a multidisciplinary follow-up team was set up at the beginning of this millennium for children treated with (neonatal) ECMO. Each team consists at least of a paediatrician, a paediatric physiotherapist and developmental psychologists. Nijmegen has added a speech-language pathologist. The following disciplines are involved as well, either structurally or on demand: in case of children with CDH: a paediatric surgeon and a clinical geneticist; for all diagnoses: a social worker. In Rotterdam a team of dedicated Intensive Care Unit nursing staff runs a 24-hours telephone helpline. Children are regularly assessed on lung function, exercise capacity and development until the age of eight years (Nijmegen) or 18 years (Rotterdam) and, when needed, prepared for transition to adult hospital care. Long-term outcomes in different areas have already been evaluated till the age of 12 years[27-35].

It was found that children treated with neonatal ECMO have normal lung volumes and stable expiratory flows in the below average range in their first year of life[29]. At the age of five years they seem to have a normal cognitive development and experience visual motor integration and behaviour problems in the normal range[28,30]. However, they are at risk for problems in the motor domain[28,30] and impaired exercise capacity that deteriorates over time till at least 12 years of age, irrespective of the underlying diagnosis[34]. Residual lung function significantly decreases between five and 12 years, specifically for children with CDH[32]. Overall, children with CDH are

likely to have the worst outcome[27,30,32,33,35]. A poor health-related quality of life (HRQOL) was found in CDH patients (treated with and without ECMO) at 1-4 years and 5-15 years of age[31].

The purpose of this three-part thesis is to describe neuropsychological outcome and HRQOL, in more detail, of a nationwide cohort of children treated with neonatal ECMO till the age of 18 years.

The first part deals with neurodevelopmental outcome assessed by cognitive outcome and motor function. Each chapter deals with a different element of neurodevelopmental outcome. Cognitive outcome is analysed as mental outcome at preschool age and intelligence at school age. Furthermore, in older children, we analyse specific cognitive skills such as concentration span and behaviour problems, particularly attention problems. At 18 years of age, we examine executive functioning skills. These skills are needed for behavioral and cognitive regulation such as inhibition, working memory, cognitive flexibility, goal selection, planning, and organization.

In **chapter 2** we describe the predictive value of mental development and motor development at two years of age for intelligence and motor function at the age of five years.
In **chapter 3** we analyse the incidence of sensorineural hearing loss at five years of age and describe the influence of this hearing loss on verbal and non-verbal mental outcome at two years of age and on intelligence and language at five years of age.
In **chapter 4** we evaluate neurodevelopmental, educational and behavioural outcome at eight years of age.
In **chapter 5** we compare intelligence and motor function outcome at the age of eight years for CDH patients treated with or without neonatal ECMO.
In **chapter 6** we evaluate executive functioning skills at 18 years of age.

In the second part we analyse the impact of ECMO treatment, and the associated morbidity, on psychological outcome assessed by health status (HS) and HRQOL. HS is defined as the ability to function normally in everyday live while HRQOL is defined as the impact of HS on quality of life[36]. These two concepts are gaining

importance, but definitions may differ between studies. Therefore, we also compare two questionnaires both claiming to assess HRQOL.

In **chapter 7** we evaluate HS at five years of age.
In **chapter 8** we compare two HRQOL questionnaires administered at the ages of eight and 12 years.

The final part of this thesis (**chapter 9 and 10)** provides an discussion and overview of all the findings reported in this thesis. Furthermore it goes into possible limitations of the studies and discusses clinical implications of the findings and suggestions for future studies.

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PART 1

Neurodevelopmental functioning

CHAPTER 2

Predicting mental and motor outcome for five-year-old children treated with neonatal ECMO: a nationwide multicenter study

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Submitted

ABSTRACT

Objective

To increase the efficiency of follow-up and identify predictive factors for delayed outcome we developed prediction models for mental and motor outcome at five years for children treated with neonatal ECMO.

Study design

Multicenter, nationwide follow-up study of neonates who received ECMO support from 1996-2005 at one of the two designated ECMO centers in the Netherlands. Mental and motor development was assessed at two years of age (Bayley Developmental Scales); intelligence and motor function at five years.

Results

With the use of probability scores (derived from multiple logistic regression) a receiver operating characteristics curve was calculated and the cut-off probability score with the most effective sensitivity and specificity (e.g. lowest number of children missed) was derived. Delayed mental outcome (n=155) was predicted with a diagnosis other than meconium aspiration syndrome, non-Dutch ethnicity, low SES of the parents, and a mental outcome <85 at two years. Using this prediction model (91% sensitivity; 47% specificity), the efficiency improved with 41%; however, we would have missed two children. Delayed motor outcome at five years of age was predicted with: low SES of the parents and a motor score <85 at two years. Using this prediction model (77% sensitivity; 57% specificity), the efficiency improved with 48%; however, we would have missed 10 children.

Conclusions

These prediction models can improve the efficiency of the follow-up at preschool age. The children who are not invited for an assessment at five years of age should be assessed with (online) questionnaires.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) can stabilize and support critically ill newborns suffering from acute, but potentially reversible (cardio)respiratory failure. It is most frequently applied in children with persistent pulmonary hypertension due to meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), or sepsis[1,2]. Because these children are at increased risk for adverse neurodevelopmental outcome, they are usually monitored in follow-up programs throughout childhood and adulthood[3].

Follow-up studies have shown – mostly cross-sectionally – that neonatal ECMO survivor's overall mental and motor outcome within the first years of life falls within the normal range[4-8]; with normal outcome in 73-75% of them[1,7,8]. Overall average intelligence at preschool age has been reported[9-12]; with normal cognitive outcome in 65-87% of the children[3,9,10]. Furthermore, normal motor outcome was found in 67-87% of children treated with neonatal ECMO. However, their overall motor outcome seems to be below average and motor problems are more frequent than in the normal population[9-11].

These results suggest that many children treated with neonatal ECMO survive without overall deficits. On the other hand, close monitoring is indicated for those at risk of developmental delay. A follow-up program should therefore provide for assessment of vulnerable children at crucial time points. Two studies (one in preterm-born children and one – from our own institution – in children with major anatomical non-cardiac congenital anomalies) have reported risk factors that predict developmental outcome from two to five years of age[13,14].

The present study is based on previously published prediction-studies and aimed to develop models to predict both mental and motor function outcome in neonatal ECMO survivors at 5 years of age.

PATIENTS AND METHODS

Population

A follow-up study was conducted in children who at neonatal age had received ECMO support between January 1996 and December 2005 in either of the two designated ECMO centers in the Netherlands: the Erasmus MC-Sophia Children's Hospital in Rotterdam and the Radboud University Nijmegen Medical Centre in

Nijmegen. ECMO support was given in case of reversible severe respiratory failure and an estimated mortality risk of higher than 80% using the criteria reported by Stolar and colleagues[15]. Treatment protocols were similar in both centers and included cerebral ultrasound (CUS) once prior to and daily during ECMO-treatment. Entry criteria and exclusion criteria were previously described[10,11,16] and did not change during the study period. The study was part of a structured prospective post-ECMO follow-up program initiated in 2001 in which lung function, growth and developmental parameters are regularly assessed until 18 years of age[10,11]. The assessment protocol is the standard of care in the Netherlands. The Medical Ethical Review Board Erasmus MC stated that “Medical Research in Human Subjects Act (in Dutch: "WMO”) does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed”. Therefore IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes.

Design

In this multicenter, longitudinal study, parents completed a questionnaire on socio-economic status (SES; based on maternal education)[17] and ethnicity (e.g. one of the parents being non-Dutch). The children’s development was tested by a developmental psychologist and a paediatric physical therapist. The following clinical data were retrieved from the medical records and the computerized patient data management system: underlying diagnosis (classified as: meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), other diagnoses); ECMO type (venoarterial (VA)/venovenous (VV)/VV conversion to VA); gestational age; birth weight; time on ECMO in hours; duration of ventilation in days; presence of chronic lung disease (CLD) defined according to Jobe and Bancalari[18]; and abnormal CUS during ECMO.

Assessments

At 2 years (corrected age for prematurity):

The Dutch translation of the Bayley Developmental Scales (BOS 2-30) was administered. This standardized instrument assesses the mental and motor development of 2 to 30-month-old children[19]. From December 2003, the new version

of the BOS 2-30 was used: the Bailey Scales of Infant Development – Second Edition – Dutch version (BSID-II-NL)[20]. The BOS 2-30 and the BSID-II-NL are substantially related to each other[20]. Both tests provide a mental developmental index (MDI) and a motor developmental index (PDI) score with a mean (SD) score of 100 (15)[19,20]. The BSID-II-NL was administered to 54 children for mental outcome and 108 children for motor outcome.

At 5 years:

The short version of the Revised Amsterdam Intelligence Test (RAKIT) was administered to assess intelligence, as described previously[10] with a mean (SD) score of 100 (15). The RAKIT has been referred to in international publications[10,11,21].

Motor function was evaluated with the Movement Assessment Battery for Children (MABC)[22]. The MABC consists of eight items: three manual dexterity items, two ball skill items and three balance items. A total impairment score is calculated from these items and percentile scores can be obtained using age-related normative data tables. A percentile score ≤P5 is regarded to reflect a definite motor problem; P6 - P15 borderline performance; and >P15 normal motor development[22]. A Dutch standardization study has shown that the original norm scores and cut-off points can also be applied to Dutch children[23]. Good validity and reliability have been demonstrated[22,23].

Data analysis

We categorized MDI, PDI and intelligent quotients (IQs) below 85 (<-1SD) as ‘delayed outcome’; scores ≥85 as ‘normal outcome’. For motor function at five years percentile scores ≤ P15 were categorized as ‘delayed outcome’; >P15 as ‘normal outcome’.

Differences in medical and socio-demographic background variables between participants and non-participants as well as between the two centers (Rotterdam and Nijmegen) were evaluated using Mann-Whitney tests.

Mean MDI, PDI and IQ scores were compared with normative data using one-sample t-tests. Percentages of MABC outcome (normal/borderline/problem) were compared to normative proportions using chi-square tests. Proportions of normal outcome on the tests used at two years (BOS 2-30/ BSID-II) were calculated with Fisher exact

tests. Proportions of children with normal outcome at two and five years were compared between two and five years of age were compared using Binomial Tests. Spearman rank correlation served to calculate correlations between MDI scores at the age of 2 years and IQ scores at the age of 5 years as well as between PDI scores at the age of 2 years and MABC percentile scores at the age of 5 years.

To predict outcome (IQ or MABC; normal/delayed) at five years of age, the predictive value of medical variables (diagnosis (MAS/CDH/other); birth weight; time on ECMO; presence of CLD (yes/no); CUS during ECMO (yes/no)), background variables (gender (male/female); ethnicity (Dutch/non-Dutch); SES (high/moderate/low)), and outcome at two years (MDI or PDI; normal/delayed) was calculated with univariate and multivariate logistic regression analyses.

The backwards procedure was used in the multivariate logistic regression analyses and variables were removed from the model till the individual variables were significant with a p-value of <0.03.

Assumptions of the logistic regression model were checked with the Hosmer-Lemeshow goodness-of-fit test.

We computed the balance between sensitivity and specificity using receiver operating characteristics (ROC) curves based on the predicted probabilities of the logistic multivariate regression analyses and the dichotomized outcome at five years for mental (IQ; normal/delayed) and motor development (MABC; normal/delayed). The area under the curve (AUC) served to estimate diagnostic accuracy[24]. All analyses were performed with SPSS version 20.0 (IBM, Chicago, IL, USA). All p-values are two-sided and a value of <0.05 is considered as statistically significant.

RESULTS

A total of 343 children were treated with neonatal ECMO between January 1996 and December 2005 (Figure 1). Eighty-eight children (26%) died during their first hospitalization. Of the 255 children surviving, 177 children (69%) joined the follow-up program both at two and at five years: for 147 (83%) children both mental and motor development was assessed; for 11 children (6%) only mental outcome was assessed; and for 19 children (11%) only motor outcome was assessed. Two medical variables differed significantly between participants and non-participants; i.e.

median (range) duration of ventilation (14 (1-68) and 19 (6-130), respectively; p<0.001); and presence of CLD (76% and 54%, respectively; p=0.001).

The medical and sociodemographic variables of participants are shown in Table 1). Three variables differed significantly between both centers (Rotterdam n=86 (49%) and Nijmegen n=91 (51%)); i.e. median (range) time on ECMO (121 hours (24-369) and 158 hours (81-367) respectively; p<0.001); duration of ventilation (median (range) 11 days (1-68) and 16 days (7-45) respectively; p<0.001); and having Dutch ethnicity (71% and 89%, respectively; p=0.003).

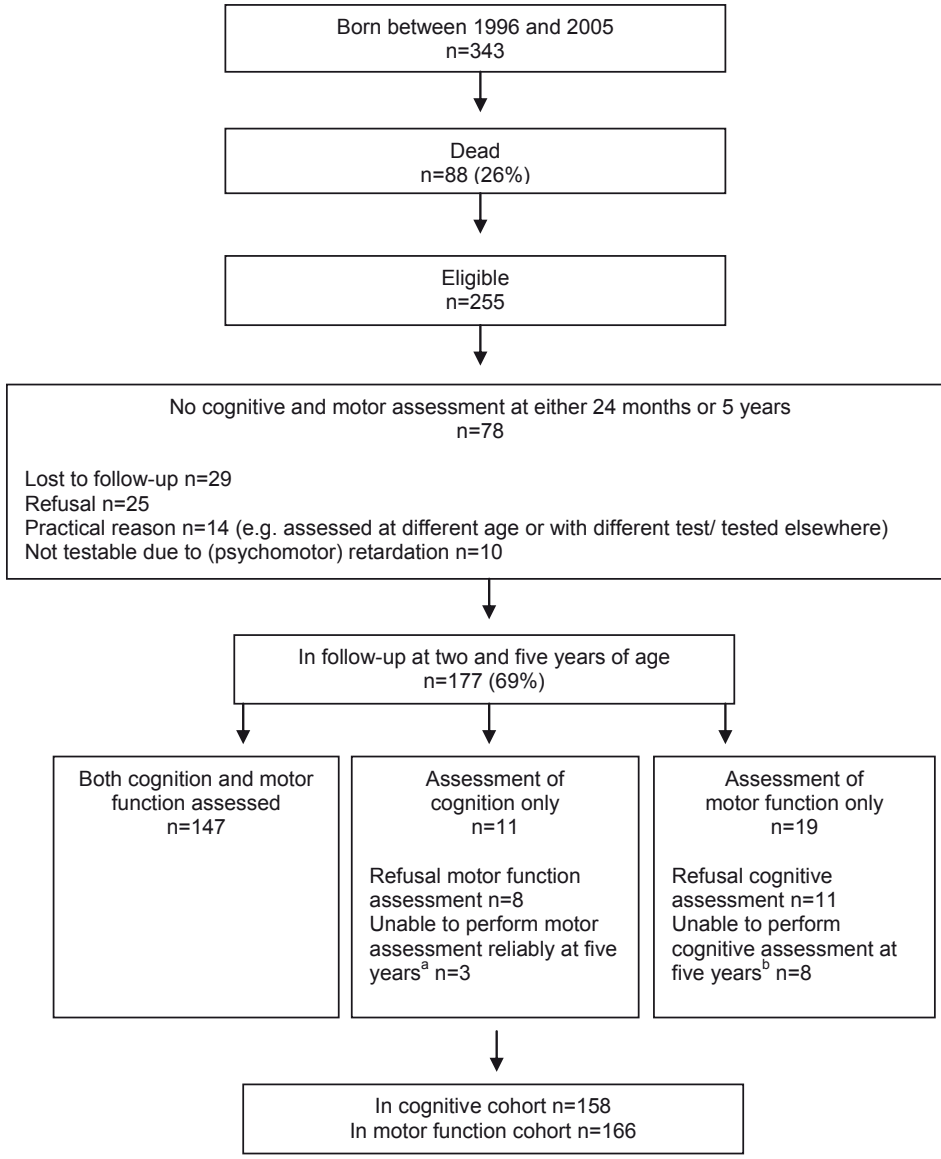


FIGURE 1 Inclusion flowchart

[a] = different test used: development disorder n=1; muscle tension problem n=1; broken arm n=1. [b] = different test used: comorbidity (e.g. anxiety or hearing problems) n=4; not testable n= 3; assessment elsewhere n=1.

TABLE 1 Medical and socio-demographic variables

		n=177
Diagnosis	MAS	96 (54)
	CDH	37 (21)
	Other	44 (25)
Birth weight in kg		3.5 (2.1-5.0)
Gestational age in weeks		40 (34-43)
Type of ECMO	VV ECMO	13 (7%)
	VA ECMO	162 (92%)
	VV conversion to VA	2 (1%)
ECMO time in hours		140 (24-369)
Duration of ventilation (including time on ECMO)		14 (1-68)
CLD	Yes	41 (23)
	No	129 (73)
	Missing	7 (4)
Abnormal CUS during ECMO	Yes	20 (11)
	No	155 (88)
	Missing	2 (1)
Gender	Male	94 (53)
	Female	83 (47)
Ethnicity	Dutch	142 (80)
	Non-Dutch	35 (20)
SES	High	54 (31)
	Moderate	68 (38)
	Low	52 (29)
	Missing	3 (2)

Results are presented as n (%) or median (range). MAS=Meconium Aspiration Syndrome; CDH=Congenital Diaphragmatic Hernia; Other=sepsis (n=13); persistent pulmonary hypertension of the newborn (n=21); cardiorespiratory insufficiency (n=2); pneumonia (n=2); congenital cystic adenomatoid malformation of the lung (n=2); respiratory syncytial virus (n=1); idiopathic respiratory distress syndrome (n=1); lunghypoplasia (n=1) and hypertrophic cardiomyopathy (n=1). ECMO=extra-corporeal membrane oxygenation; VV=venovenous; VA=venoarterial; CLD=Chronic lung disease defined by Jobe and Bancalari[18]; CUS=cerebral ultrasound; SES=socio-economic status.

At 2 years of age MDI mean (SD) scores were within normal range (101.7 (18.7); p=0.255) and PDI scores were below normal range (89.3 (17.7); p<0.001). Eighty-two percent (n=130) and 64% (n=106) scored normal on mental and motor development, respectively. The percentage of children with normal motor outcome on the BOS 2-30 (81%) differed significantly from the percentage on the BSID-II (54%, p<0.001). No differences were found for mental outcome (BOS 2-30: 81%/ BSID-II: 87%; p=0.261).

At five years of age IQ mean (SD) scores (100.1 (16.4); p=0.939) were within normal range. Percentages of children with normal motor outcome (73% versus 85% expected); borderline motor outcome (13% versus 10% expected) and motor problem outcome (15% versus 5% expected) on the MABC were significantly

different from normative data (p<0.001). Overall, 84% (n=133) and 73% (n=121) of five-year-olds scored normal on intelligence and motor function outcome, respectively.

Proportions of two-year-olds and five-year-olds with normal motor outcome differed significantly (64% versus 73%; p=0.012).

Table 2 shows mental (MDI and IQ) and motor (PDI and MABC) outcomes. Differences were found between the ECMO centers for PDI scores at 2 years ('delayed' motor outcome: Rotterdam n=15 (9%)/ Nijmegen n=45 (27%); p<0.001).

The Spearman rank correlation coefficients (r_s) between the MDI and IQ scores were 0.4 (p<0.001) and between the PDI and MABC percentile scores 0.3 (p<0.001).

TABLE 2 Mental and motor outcomes at 2 and 5 years of age

	5 years		
2 years	IQ ≥ 85	IQ < 85	total
MDI ≥ 85	118 (74)	12 (8)	130 (82)
MDI < 85	15 (10)	13 (8)	28 (18)
total	133 (84)	25 (16)	158 (100)
	P-MABC > 15	P-MABC ≤ 15	
PDI ≥ 85	92 (55)	14 (9)	106 (64)
PDI < 85	29 (18)	31 (18)	60 (36)
total	121 (73)	45 (27)	166 (100)

Data are shown as n (%). IQ= intelligence quotient measured with RAKIT at 5 years; MDI= mental developmental index; PDI = psychomotor developmental index (both indices measured with BOS2-30 or BSID-II-NL at 2 years); P-MABC=percentile score derived from total impairment score of the Movement Assessment Battery for Children.

Outcomes of the univariate and multivariate logistic analyses, to predict delayed intelligence and delayed motor function at five years, are shown in Table 3. The multivariate analyses were performed with 155 (98%) children for mental outcome and 163 (98%) children for motor outcome due to missing medical and/or socio-demographic variables. Multivariate logistic regression analyses revealed three predictive variables of delayed mental outcome (p-value of the goodness-of-fit test is 0.367) at five years (positive influence on the probability score; higher chance for delayed mental outcome): non-Dutch ethnicity, a low SES and <85 MDI at two years of age. A diagnosis of MAS was a predictor of normal mental outcome (negative influence on the probability score; lower chance for delayed mental outcome). For delayed motor outcome (p-value of the goodness-of-fit test is 0.336) at five years two variables were found predictive (positive influence on the probability score; higher chance for delayed motor outcome): low SES and <85 PDI at two years of age.

TABLE 3 Univariate and multivariate logistic regression

		Univariate	Multivariate	
		OR (95% CI)	OR (95% CI)	β
Mental outcome				
Diagnosis				
	MAS vs other diagnoses	0.44 (0.16-1.25)	0.17 (0.05-0.59)*	-1.754
	CDH vs other diagnoses	1.35 (0.44-4.13)		
Birth weight		1.00 (0.99-1.01)		
ECMO time in hours		1.01 (0.99-1.01)		
Presence of CLD		1.57 (0.59-4.17)		
Abnormal CUS during ECMO		3.82 (1.25-11.73)*		
Gender		1.09 (0.46-2.56)		
Non-Dutch ethnicity		4.44 (1.77-11.16)*	5.70 (1.68-19.38)*	1.740
SES				
	Low SES vs other SES	0.29 (0.06-1.43)	3.24 (1.09-9.64)*	1.176
	High SES vs other SES	2.61 (0.98-6.97)		
MDI <85		8.52 (3.29-22.06)*	10.50 (3.20-34.40)*	2.351
Motor outcome				
Diagnosis				
	MAS vs other diagnoses	0.88 (0.36-2.16)		
	CDH vs other diagnoses	2.98 (1.11-8.04)		
Birth weight		1.00 (0.99-1.00)		
ECMO time in hours		1.01 (1.00-1.01)*		
Presence of CLD		2.27 (1.06-4.88)*		
Abnormal CUS during ECMO		1.37 (0.48-3.91)		
Gender		0.57 (0.29-1.15)		
Ethnicity		1.59 (0.70-3.45)		
SES				
	Low SES vs other SES	0.56 (0.22-1.45)	2.76 (1.22-6.24)*	1.014
	High SES vs other SES	2.22 (0.99-4.99)		
PDI <85		7.03 (3.30-14.97)*	5.47 (2.47-12.11)*	1.699

MAS=meconium aspiration syndrome; CDH=congenital diaphragmatic hernia; ECMO=extra-corporeal membrane oxygenation; CLD=chronic lung disease defined by Jobe and Bancalari[18]; SES=socio-economic status; MDI=mental developmental index; PDI=psychomotor developmental index; β=regression coefficient of significant variables from the multivariate regression analysis; OR=odds ratio; CI=confidence interval. * P-value <0.05.

For mental outcome, a probability score (chance of delayed mental outcome at five years of age) was derived from the multivariate logistic regression analyses with the use of the following logistic regression equation:

$$P(delayed)\frac{e^{-2.480-1.754*diagnosis+1.740*ethnicity+1.176*SES+2.351*MDI}}{1+e^{-2.480-1.754*diagnosis+1.740*ethnicity+1.176*SES+2.351*MDI}}$$

For the regression equation, diagnosis is dichotomized for diagnosis in MAS (value of 1) and CDH or “other” (value of 0); for ethnicity in non-Dutch ethnicity (value of 1) and Dutch ethnicity (value of 0); for SES in low SES (value of 1) and moderate or high SES (value of 0); and for MDI in delayed (value of 1) and normal (value of 0). The cut-off probability score with the most effective sensitivity and specificity (e.g. balance between not inviting all children and lowest number of missed children with a delayed outcome at five years of age) was derived from a ROC curve calculated from the probability scores. For mental outcome the AUC (95% confidence interval (CI)) was 0.832 (0.728-0.937) (Figure 3A). With a sensitivity of 91% and a specificity of 47% we would have invited 91 of the 155 children, improving the efficiency of the follow-up by 41%. However, we would have wrongly predicted a normal intelligence outcome for 2 children (9% of the 23 children with delayed mental outcome at five years) and we would have unnecessarily tested 70 children (53% of the 132 children with normal mental outcome at five years). Figure 2 guides the decision whether a child should be scheduled for a follow-up assessment at five years of age.

The two children with delayed mental outcome at five years, who would have been predicted as ‘normal’ according to our prediction model, had attention problems (both were assessed at age eight years as well: one had a disharmonic intelligence profile, the other one suffered from dyslexia).

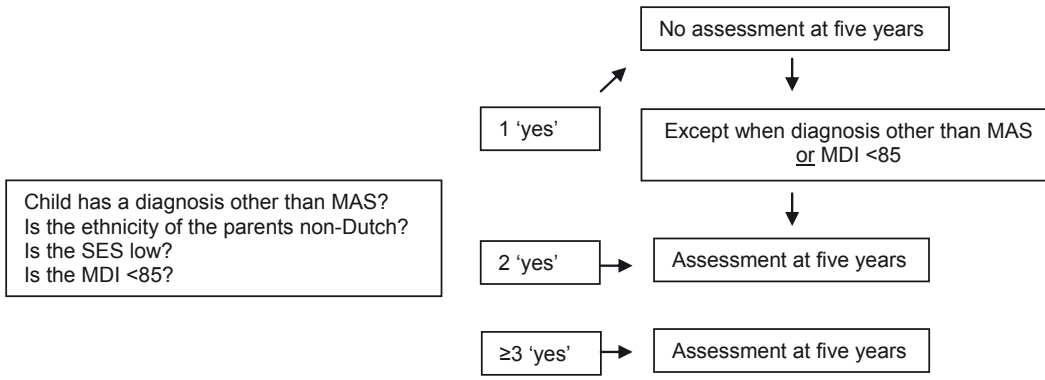


FIGURE 2 Algorithm for mental outcome testing at five years of age with 91% sensitivity and 47% specificity

MAS = meconium aspiration syndrome. SES = socio-economic status. MDI = mental developmental index at two years of age.

For motor outcome, a probability score (chance of delayed motor outcome at five years of age) was derived from the multivariate logistic regression analyses with the use of the following logistic regression equation:

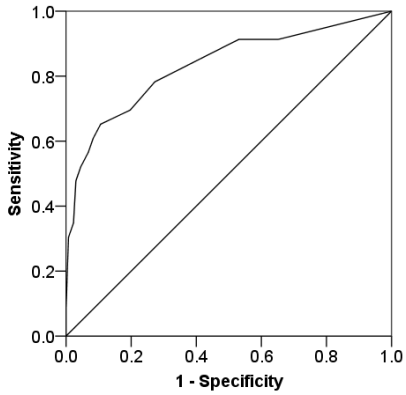
$$P(delayed)\frac{e^{-3.807+1.014*SES+1.699*PDI}}{1+e^{-3.807+1.014*SES+1.699*PDI}}$$

For the regression equation, SES is divided in low SES (value of 1) and moderate or high SES (value of 0); PDI is divided in delayed outcome (value of 1) and normal outcome (value of 0). With the use of these probability scores a ROC curve was calculated and the cut-off probability score with the most effective sensitivity and specificity (e.g. balance between not inviting all children and lowest number of missed children with a delayed outcome at five years of age) was derived from this ROC curve. For motor outcome the AUC (95% CI) was 0.756 (0.664-0.847) (Figure 3B). With a sensitivity of 77% and a specificity of 57% we would have invited 85 of the 163 children, improving the efficiency of the follow-up with 48%. However, we would have wrongly predicted a normal motor outcome at five years of age for 10 children (23% of the 44 children with delayed motor outcome at five years of age). We would have unnecessarily tested 51 children (43% of the 119 children with normal outcome at five years of age).

Two questions should be answered at two years follow-up: (1) is the PDI <85 or (2) is the PDI ≥85 but do the parents have a low SES? If the answer is ‘yes’ to any of the two questions; assessment at five years is indicated.

All but one of the 10 children with a wrong prediction of normal outcome at five years of age experienced borderline motor problems (P6 - P15) at five years of age (which was categorized as delayed outcome in our analysis). The one child with a definite motor problem (≤P5) had attentional problems during assessment at five years which might have negatively affected the outcome.

A



B

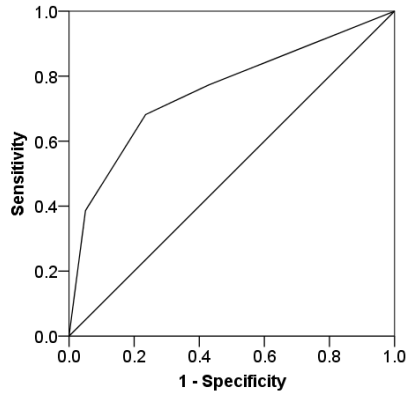


FIGURE 3 Receiver operating characteristics curves for delayed outcome at five years of age

A = Mental outcome at five years with an area under the curve (95% confidence interval) of 0.832 (0.728-0.937).
B = Motor outcome at five years with an area under the curve (95% confidence interval) of 0.756 (0.664-0.847).

DISCUSSION

Based on test results at two years of age for children treated with neonatal ECMO we developed prediction models both for mental and motor outcome at five years of age. We did so to increase the efficiency of the follow-up program by inviting only those children at risk for delayed outcome. Delayed mental outcome at five years of age was predicted by a diagnosis other than MAS, non-Dutch ethnicity of the parents, low SES of the parents and a MDI <85 at two years. Using these criteria, we would have improved the efficiency of the follow-up by 41%; however, we would have missed two children predicted to have normal outcomes but who in fact showed delayed outcome (9%). The predictive variables for delayed motor outcome at five years of age were: low SES of the parents and a PDI <85 at two years of age. Using these criteria, we would have improved the efficiency of the follow-up by 48%; however, we would have missed 10 children (23%) who had – all but one – a borderline motor performance at five years.

Overall MDI scores at two years of age fell within the normal range; with normal mental outcome in 82% of the children. Overall PDI scores fell below the normal range; with normal motor outcome in 64% of the children. Overall intelligence at five years was comparable to normative data; with normal intelligence in 84% of the children. Motor outcome was significantly different from normative proportions with

more children experiencing motor problems. These findings are comparable with the findings of others[1,3-12]. In addition, we found normal motor function in 73% of the children at five years, significantly higher than the proportion of children with normal motor outcome at two years of age.

The prediction models in the present study include predictive socio-demographic variables, such as ethnicity and SES based on maternal education. SES has been associated with outcome previously. For example, Stolar and coworkers reported that social disadvantage affected outcome in a cohort of children (mean age of 31 months) treated with ECMO[7]. And then, in their prediction study in a cohort of children with major anatomical congenital anomalies; our group found that SES added predictive value to outcome at five years of age[14]. Furthermore, Kumar and coworkers found that ethnicity was of influence on outcome at preschool age[25].
We were not surprised to find that medical variables, except for diagnosis, were not of predictive value to outcome at five years of age. In a cohort of preterm born children a prediction model for motor function revealed five predictive medical and background variables[13]. The fact that in the present study medical variables were not as predictive suggests that the course of development in neonatal ECMO survivors differs from that in prematurely born neonates. For example, we evaluated intelligence at eight years of age in a nationwide cohort of neonatal ECMO survivors and found that only the diagnosis of CDH was a significant predictor of low intelligence (Chapter 4, this thesis). Despite the fact that the overall intelligence was within the normal range children experienced more subtle problems with concentration and behaviour. Moreover, 41% of children needed extra support at regular education (Chapter 4, this thesis). The UK trial found that 68% (n=56 ECMO survivors) seven-year-olds experienced normal cognitive outcome with difficulties with spatial and processing tasks[26]. In their evaluation twenty percent of the ECMO cohort received special support at regular education and another 20% followed special education[26]. Furthermore, the UK trial reported normal motor development in 43% of the seven-year-old ECMO survivors and behavioral problems in 39%; most commonly hyperactivity[26]. Glass and coworkers, presenting US data, also reported that children treated with ECMO seem to be at increased risk for academic difficulties and behaviour problems at school age[9]. In a previous study the Dutch ECMO follow-up team reported motor problems combined with cognitive and behavioural problems

in their cohort of ECMO treated survivors and found that negative motor outcome was related to lower intelligence at school age[11]. It seems that children treated with neonatal ECMO experience cognitive as well as motor problems when they are required to execute more demanding tasks, which they are not yet required to be capable of at preschool age. Therefore, we assume that outcome at the age of two is not suitable to predict outcome at school age and in adolescence, but can be predictive for outcome at five years of age.
Still, the prediction models in the present study for both mental and motor outcome at five years are not perfect. We would have missed two children using the prediction model for mental outcome, both experiencing problems with concentration and/or sitting still during the assessment. These problems might have been of influence on the outcome at five years. At eight years of age one of them displayed a disharmonic intelligence profile and the other was diagnosed with dyslexia. Using the prediction model for motor outcome would have missed ten children. Most of these children experienced borderline motor problems at five years of age which could not have been predicted from the two years assessment. However, this provides evidence that these children might be at risk for further, more severe, motor problems at older age.

Because the maternal environment of the child is predictive of outcome at five years of age, parental motivation and cooperation in the follow-up assessments is important. Since the assessments are time-consuming for the parents, the child as well as the follow-up team, it would seem advisable to provide well-grounded reasons for inviting children to follow-up assessments. Parents may then be more motivated to cooperate so that eventually fewer of them will refuse their child's participation.
Efficiency of the follow-up program will be improved when we invite only those children with predicted delayed outcome. On the other hand, we should stay in touch with all families, e.g. by administering (online) questionnaires to get an update on the child's developmental status and any problems arising. Given the risk for more subtle cognitive, behaviour and educational problems at older age follow-up should be scheduled for all children at older school age.

Even though this was a multicenter, nationwide study in which standardized follow-up assessments were used, the prediction models should be validated in other centers before the models can be generalized. Furthermore, our cohort consisted of many

children with CLD whose pulmonary problems could lead to slower motor development. On the other hand, CLD was not of predictive value in any of the prediction models and its influence might not have been very high. Also, the differences in medical and socio-demographic variables between the two ECMO centers might have influenced the mental and motor outcomes. However, the multicenter structure might also have caused a more heterogenic cohort and is therefore more representive of the entire Dutch population. Of the variables that differed between ECMO centers; only ethnicity of the parents and PDI outcome at two years were of predictive value on the mental and motor outcome at five years. The differences in PDI scores between the two centers might be the result of the fact that while in Nijmegen only the BSID-II was used in Rotterdam no more than around 25% of the children were assessed with the BSID-II; the others were assessed with the BOS 2-30. This may have caused a bias in motor outcome because the proportion of children with normal motor outcome at two years of age differed between those tested with the BSID-II and BOS 2-30. Finally, only data from children who were able to fulfill the assessments were used in the prediction models and this might have resulted in biased (more positive) outcome results. On the other hand, the children who can not be tested tend to be the ones who already have the right medical, physical and psychological support due to severe delays and for whom prediction models are not of benefit.

CONCLUSIONS

We presented prediction models for both mental and motor outcome at 5 years of age for children treated with neonatal ECMO. Delayed mental outcome (IQ) was predicted by a diagnosis other than MAS, non-Dutch ethnicity, low SES of the parents and a delayed mental outcome at two years of age. Delayed motor outcome was predicted by a low SES of the parents and a delayed motor outcome at two years of age. These prediction models can improve the efficiency of the follow-up at preschool age by 41% and 52%, respectively. The children who are not invited for an assessment at five year of age should be assessed with (online) questionnaires and follow-up should be scheduled for all children at older school age.

Aknowledgements

This paper was written on behalf of the Dutch national ECMO follow-up team, consisting of pediatricians, psychologists, speech-language pathologists and pediatric physical therapists in both centers. The authors thank the entire team and specifically the ones not mentioned in the authors list: Saskia Gischler (pediatric intensivist), Marjolein Spoel (physician), Anne Zirar-Vroegindeweij and Annabel van Gils-Frijters (psychologists) from Erasmus MC- Sophia Children's Hospital and Jolanda Reuser (psychologist) and Sandra de Groot (speech-language pathologist) from Radboud University Nijmegen Medical Centre for their contribution to this study. We also thank Ria Nijhuis-van der Sanden who was involved in the initial set-up of the pediatric physical therapy follow-up program in Nijmegen.

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“THIS IS ME”

Boy, 6 years old

This is me at the hospital

This is me now

This is me when I am grown up

CHAPTER 3

Sensorineural hearing loss and language development following neonatal extracorporeal membrane oxygenation

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Pediatr Crit Care Med. 2013;14:62-69

ABSTRACT

Objective

To determine the prevalence of hearing loss in school-age children who have undergone neonatal extracorporeal membrane oxygenation (ECMO) treatment and to identify any effects of hearing loss on speech- and language development.

Design

Prospective longitudinal follow-up study within the framework of a structured post-ECMO follow-up program.

Setting

Outpatient clinic of a level III university hospital.

Results

Tone audiometry was performed by standardized protocol in 136 children aged 5 to 12 years. Hearing loss was considered clinically significant when >20dB. Hearing was normal in 75.7% of children. Five children (3.7%) had bilateral sensorineural or combined hearing loss; 3 of them received special audiological care (2.2% of total sample). Of the 24 children with congenital diaphragmatic hernia, 19 (79.2%) had normal hearing; and only 2 (8.3%) had mild SNHL, unilateral in one of them. Follow-up at 24 months of age had shown normal verbal and non-verbal developmental scores. Language development and intelligence median (range) scores at 5 years of age were also normal: receptive language development 104 (55-133); syntactical development 104 (68-132); and lexical development 101 (50-141) for 89 children; intelligence quotient was 104 (68-132) in 106 children. Scores did not differ between those with normal hearing, and those with mild hearing loss, or those with moderate to severe hearing loss (p=0.800, p=0.639, p=0.876, and p=0.886, for the respective developmental tests).

Conclusions

We found normal language development and intelligence in a cohort of neonatal ECMO survivors. The prevalence of bilateral sensorineural hearing loss was in accordance with that of larger series in the United States – which exceeds the prevalence in the normal population.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a supportive intensive-care technique to counteract acute reversible cardiorespiratory failure. ECMO provides prolonged cardiopulmonary bypass while allowing the lungs to rest using minimal ventilator settings[1]. A trial in critically ill neonates conferred a survival advantage of ECMO over conventional management – except in cases of congenital diaphragmatic hernia (CDH) – without a concomitant increase in severe disability[2].

Sensorineural hearing loss (SNHL) is one of the disabilities reported in patients who have undergone ECMO-treatment[3-5]. It was found in 28 of 371 ECMO-survivors (7.5%) from 6 different centers in North America[6], Frequencies per center ranged from 3 to 21%; follow-up from 1-10 years. Several groups have reported delayed onset of SNHL and therefore advocated ongoing follow-up testing[4-5,7]. A number of risk factors for SNHL after neonatal intensive care have been identified: presence of CDH [7], prolonged ventilatory support[8-9] prolonged ECMO[7,10], sepsis or bacterial meningitis[8,11], prolonged administration of aminoglycosides[7], severe birth asphyxia[9,11], cerebral bleeding or cerebral infarction[11], and clinical seizures prior to ECMO treatment[10].

Infants with hearing loss (HL) are at risk for delayed speech development and language acquisition, impaired academic achievement, and social/ emotional developmental problems[12-13]. Early identification of HL and appropriate intervention could prevent or minimize adverse effects on these developmental areas[14-15]. To our knowledge only one study – by Desai et al. – explored the relationship between hearing loss and language development of ECMO survivors; the relationship between neonatal brainstem audiometry results and delayed receptive language ability proved uncertain[16]. To shed more light on this issue we tested hearing as well as speech- and language development in survivors of neonatal ECMO-treatment. The following research questions were addressed: 1) What is the prevalence of SNHL after neonatal ECMO treatment?; 2) Does HL affect speech- and language development and intelligence?

PARTICIPANTS AND METHODS

Participants

A cohort of children, now aged between 5 and 12 years, who had received neonatal veno-arterial (VA) ECMO support between January 1992 and February 2005, and mainly consisting of children living in the referral area of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. The large majority had been treated in this hospital an additional four in the Radboud University Nijmegen Medical Center (Nijmegen, the Netherlands), and one in the University Hospitals Leuven (Leuven, Belgium). Inclusion criteria and treatment protocols did not differ between these centers. ECMO was initiated in case of reversible severe respiratory failure and an estimated mortality risk of higher than 80% using the entry criteria reported by Stolar et al.[17].

Entry criteria and exclusion criteria were previously described by our group[18] and did not change during the study period. Cerebral ultrasound examinations were performed prior to treatment with ECMO, daily during ECMO treatment, and before discharge from our hospital. All subjects of the study reported here participate in a prospective post-ECMO follow-up program that provides for regular assessments of lung function, growth and developmental parameters until 18 years of age[19]. Based on the national consensus on neonatal follow-up and the Dutch Ministry of Health's requirement to provide relevant data, the assessment protocol is the standard of care following ECMO treatment. As a consequence IRB approval was waived. Parents of all children studied were informed about the study and gave written informed consent to evaluate data collected during routine care.

Procedures and study design

The following clinical characteristics were recorded prospectively: underlying condition, gestational age, birth weight, age at onset of ECMO, duration of ECMO support, mean airway pressure (MAP) and highest oxygenation index[14] prior to ECMO, duration of mechanical ventilation before ECMO, total duration of mechanical ventilation (including ECMO), duration of oxygen dependency, and prevalence of chronic lung disease (CLD). CLD was defined as oxygen dependency at day 28[20]. The assessment protocol encompasses hospital consultations at 6, 12, 24 months and 5, 8 and 12 years of age. Audiometry is routinely performed at 5 years of age.

However, because the program started in 2001, some children entered not until 8 or 12 years of age. In those cases audiometry was performed during their first visit (Figure 1).

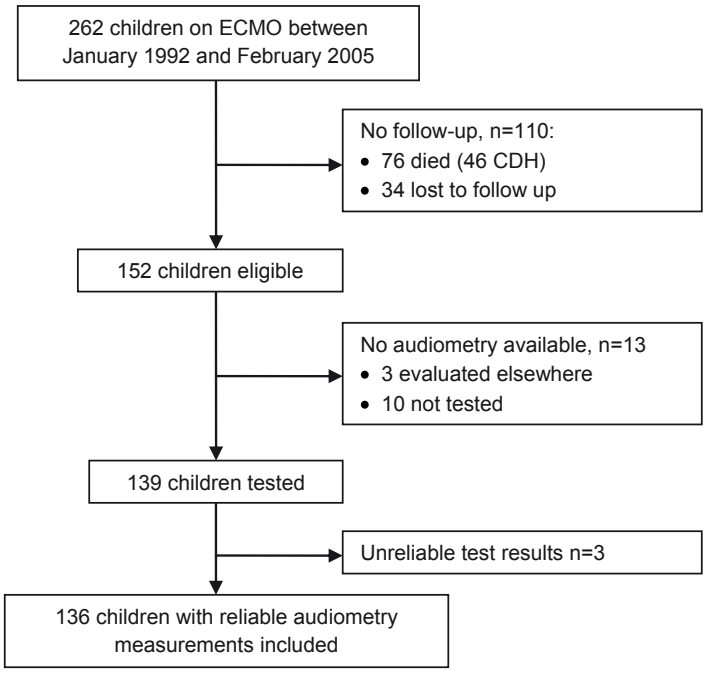

FIGURE 1 Flowchart

CDH = congenital diaphragmatic hernia

Hearing assessment

Audiometry was performed with a Madsen clinical audiometer (OB822; Madson Electronics, Denmark) according to the standard procedure used in the Netherlands, including both air conduction and bone conduction measurements. Tympanometry was done with an Interacoustics AT 235 h device (Interacoustics USA, Eden Prairie, Minnesota), with a 226-Hz probe stimulus.

Assessment of language development and intelligence

Within the framework of the follow-up program, the Dutch translation of the Bayley Developmental Scales (BOS 2-30) had been administered at age 2 years. This standardized instrument assesses both verbal and non-verbal development of 2 to 30-month-old children[21]. From December 2003, a new version of the BOS 2-30 was

used: the Bailey Scales of Infant Development – Second Edition – Dutch version (BSID-II-NL)[22]. The BOS 2-30 and the BSID-II-NL share the same background and are substantially related to each other[22]. The BSID-II-NL was administered to 8 children.

At 5 years of age the Reynell Test (receptive language development), the Schlichting Test (syntactical and lexical expression), and the short version of the Revised Amsterdam Intelligence Test were administered to assess language development and intelligence, as described previously[19].

Data analysis

Hearing assessment

In consultation with the audiologist (A.G.) the audiograms were interpreted as follows. Two frequency bands were distinguished: low and high. For the low frequency band the mean HL was calculated at 500, 1000 and 2000 kHz; for the high frequency band at 2000, 4000 and 8000 kHz. HL severity was categorized in terms of clinical consequences. HL <20 dB is “not significant”, thus “normal”; 20-40 dB is “mild”; and >40 dB is “moderate to severe”.

HL was considered symmetrical if it was of the same category in both ears for both frequencies.

We distinguished between “conductive HL” (>10 dB difference between the bone conduction response and the air conduction response) and “SNHL only” (difference ≤10 dB). If both were present HL was labelled as: combined. Tympanometry was used to confirm conductive HL.

Language development and intelligence

Language developmental and intelligence scores below 85 (<-1 SD) were categorized as "below average"; scores between 85 and 115 (≥ -1 SD and ≤ +1 SD) as "average"; and scores above 115 (>+1 SD) as "above average".

Statistical methods

Group comparisons were tested with the Kruskal-Wallis H test. The Mann-Whitney test with Bonferroni correction was used for post-hoc analysis. Proportions were compared using the Chi-square test. Data on HL and developmental tests for two

subgroups – underlying condition CDH or meconium aspiration syndrome (MAS) – were analyzed separately. These two subgroups were considered of special interest. CDH is associated with abnormal lung development with severe pulmonary hypertension and increased prevalence of HL[7,23-24]; infants with MAS form the largest homogeneous subgroup of children treated with ECMO. The other subgroups are small and more heterogeneous with respect to underlying disease. Data are presented as mean (SD) or median (range). Statistical significance was accepted at a two-sided 5% level for all tests. Statistical analyses were performed using SPSS 17.0 for Windows.

RESULTS

Between January 1992 and February 2005 a total of 257 neonates received ECMO in our center and 5 children from our referral area elsewhere; 76 patients died at neonatal age (29%; CDH n=46 (61%)). Of the remaining patients, 34 did not participate in the follow-up program (parents' refusal n=17; other reasons n=17), and 13 did not undergo audiometry for different reasons (Figure 1). One of them, a girl who had suffered from severe birth asphyxia, had been diagnosed with severe bilateral SNHL at the age of 6 months and wore hearing aids. She was evaluated elsewhere. Two other children who had been evaluated elsewhere had normal hearing. In 8 others who were not tested (7 for practical reasons and 1 with Down syndrome and ENT follow-up elsewhere) HL was not suspected by members of the follow-up team or the parents. Information on HL was lacking in the 2 remaining children: One was suffering from mental retardation and autism and lacked cognitive ability for audiometry; one, seen at age 5 years before audiometry was introduced into our program, had died of multiple congenital anomalies before the next scheduled visit.

Thus, 139 children underwent audiometry. We excluded the results of three 5-year-old participants because they could not be tested reliably (Figure 1). Therefore, the results of 136 children were analyzed; 104 of them (76%) were tested at age 5 years, 20 (15%) at 8 years, and 12 (9%) at 12 years.

Data on language development and intelligence at age 5 years had not been obtained in 28 children born before 1996 (because the follow-up program started in 2001) and in two 5-year-olds born after 1996 (due to parental refusal). Thus,

developmental evaluation at 5 years was performed in 106 children (audiometry in 104 because in 2 of them audiometry was performed at 8 years); for 66 of these children developmental data at 2 years were also available. The Reynell receptive language development test and the Schlichting subtests for syntactical and lexical development were not administered to 17 children (practical reasons n=10; poor cognitive competence n=3; insufficient command of the Dutch language n=3; and language development tested elsewhere n=1). Of these 17 children, 12 had normal hearing, 2 had moderate to severe unilateral HL (one sensorineural and one conductive), 1 had mild conductive unilateral HL and 2 had mild conductive bilateral HL. For 7 children tested at 5 years a reliable intelligence score could not be calculated (poor cognitive competence n=5; recent assessment elsewhere with intelligence within normal range n=1; assessment with non-verbal test due to hearing problems with intelligence in normal range n=1).

The baseline characteristics of all participants are shown in Table 1. None of the baseline characteristics differed between children included in the analysis and those who were excluded or lost to follow-up (data not shown). The subgroup of 106 children who underwent developmental assessment at 5 years did not differ from the total study group (data not shown).

TABLE 1 Baseline and ECMO characteristics of participants

	n = 136
Boys/girls, n (%)	73/63(54/46)
Diagnosis, n (%)	
CDH	24 (18)
MAS	73 (54)
Other	39 (29)
Gestational age, weeks, mean (SD)	39.6 (1.8)
Birth weight, kg, mean (SD)	3.37 (0.57)
Age at start ECM), hours, median (range)	25 (4-600)
Oxyenation index prior to ECMO, median (range)	43 (13-130)
Highest mean airway pressure, cm H_2O, median (range)	20 (11-45)
Time on ECMO, hours, median (range)	133 (47-510)
Duration of ventilation including ECMO, days, median (range)	12 (2-130)
Oxygen requirement post extubation, n (%)	
1 day-1 week	54 (40)
1 week-1 month	50 (37)
>1 month	18 (13)
unknown	14 (10)
Chronic lung disease, n (%)	
no	100 (74)
yes	27 (20)
unknown	9 (7)

CDH = congenital diaphragmatic hernia; MAS = meconium aspiration syndrome; remaining diagnoses consist of: persistent pulmonary hypertension n=18, sepsis n=8, pneumonia n=4, birth asphyxia n=2, cardiac disease n=2, other n=3. Chronic lung disease was defined as oxygen dependency at day 28.

Of the 136 children tested audiologically, 103 (75.7%) had normal hearing and 33 (24.3%) had a significant HL. Eleven children had SNHL only (8.1%); one child suffered from combined HL (0.7%); the remaining 21 children (15.4%) had conductive HL.

Five children had bilateral SNHL (3.7% of the study population); in 2 of them (1.5%) SNHL was mild, symmetrical, and of high frequencies only. Three children (2.2%) had moderate to severe bilateral SNHL, symmetrical in 2 of them, with loss of both high and low frequencies. The characteristics of these 5 children are described in Table 2. All had normal cerebral ultrasound during ECMO treatment. Three needed special education; 2 of them for learning difficulties (Patient 1 with severe birth asphyxia and Patient 2 with mental retardation due to a partial chromosome X-duplication), and one for hearing problems (Patient 4). The other 2 children received regular education with extra support for hearing problems and attention deficit disorder (Patient 3) or language support (Patient 5, who was not a native Dutch speaker).

SNHL in the remaining 7 children (5.1%) was unilateral; in 2 children it had resolved at follow-up. In 2 of the other 5 it was mild, but 3 children (2.2% of the study population) had completely impaired hearing in one ear (ipsilateral cerebral infarction n=1; bacterial meningitis at age 1 month n=1; unknown cause n=1). All three had abnormal audiological examinations within the first months of life and HL had been diagnosed early. The patient with bacterial meningitis suffered from severe combined HL.

Hearing was normal in 19 of the 24 CDH patients (79.2%); only 2 of the 24 CDH patients (8.3%) had mild SNHL, which was unilateral in one of them. The other 3 CDH patients had conductive HL. The proportions of children with normal hearing, SNHL or conductive HL did not differ between the three diagnosis categories (p=0.84, Chi-square test).

At 2 years of age the median verbal and non-verbal developmental scores were in the normal range (Table 3). The verbal developmental scores differed between children with normal hearing, mild hearing loss, and moderate to severe hearing loss (p=0.028; Kruskal-Wallis H-test). Post-hoc testing revealed that the verbal developmental score for children with a normal hearing was significantly lower than that for children with mild hearing loss (p=0.007; Mann-Whitney test). The non-verbal scores did not differ between the three hearing groups (p=0.363; Kruskal-Wallis H-test). The results are shown in Table 3.

At 5 years of age the median language and intelligence scores were in the normal range (Table 3). Receptive language development, syntactical language expression and lexical language expression did not differ between children with normal hearing, mild hearing loss, and moderate to severe hearing loss (p=0.800, p=0.639, p=0.876, respectively; Kruskal-Wallis H-test). The same was true for intelligence (p=0.886; Kruskal-Wallis H-test).

TABLE 2 Characteristics of five children with bilateral sensorineural hearing loss

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Hearing loss					
Description	Right ear: 40 dB at 4 kHz, 80 dB at 8 kHz; left ear: cup-shaped HL 45 dB at 2 kHz	70 dB at 8 kHz	20 dB at 250 Hz; 40-70 dB at 500 Hz-8 kHz	30- 50 dB at 250 Hz; 70- 100 dB at 500 Hz-8 kHz	Max. 30 dB
Neonatal screening	NA; brainstem normal at 5 years	NA	Abnormal	Normal	?
Age diagnosis HL	8.0 years	8.0 years	0.2 years	1.1 years	5.3 years
Risk factors					
Diagnosis	Severe asphyxia	CDH	MAS, asphyxia	PPHN	MAS
Comorbidity	Pre-ECMO seizures	-	-	-	-
Medication	Furosemide Phenobarbital Tobramycin (single dose)	Phenobarbital	Furosemide (continuously) Phenobarbital Erythromycin Fluconazol	Furosemide Phenobarbital Vancomycin	Furosemide
Age start ECMO	25 hours	20 hours	9 hours	284 hours	27 hours
ECMO duration	96 hours	120 hours	184 hours	288 hours	137 hours
Ventilation duration	12 days	37 days	22 days	36 days	9 days
Outcome					
Hearing aids	No	No	Yes	Yes	No
Speech therapy	At 8 years	At 8 years	At 2 years (articulation) and 5 years	At 5 years	None
Language development	Below average*	Below average*	Average	Average	Below average
Intelligence (IQ)	62*	62*	85	99	74

CDH: congenital diaphragmatic hernia; MAS: meconium aspiration syndrome; PPHN: persistent pulmonary hypertension of the newborn; CLD: chronic lung disease; ADHD: attention deficit hyperactivity disorder; NA: not available, i.e. not performed; language development measured with the Reynell and Schlichting language tests; IQ: intelligence quotient measured with the RAKIT intelligence test. * Assessment at 8 yrs (born before 1996): language development at 8 years measured with verbal subtests of the Wechsler Intelligence Scale.

TABLE 3 Developmental results at 2 and 5 years following neonatal ECMO

2 years	**Median (range)**
Verbal score (n=66)	98 (50-136)
Mild hearing loss (n=13)	118 (51-134)
Moderate to severe hearing loss (n=5)	96 (65-136)
Normal hearing (n=48)	94 (50-134)
Non-verbal score (n=66)	106 (48-133)
Mild hearing loss (n=13)	112 (60-130)
Moderate to severe hearing loss (n=5)	92 (64-1330
Normal hearing (n=48)	103 (48-132)
5 years	
Reynell (n=89)	95 (56-138)
Mild hearing loss (n=18)	99 (56-127)
Moderate to severe hearing loss (n=4)	99 (85-108)
Normal hearing (n=67)	95 (62-138)
Schlichting syntactical language expression (n=89)	101 (50-141)
Mild hearing loss (n=18)	107 (55-122)
Moderate to severe hearing loss (n=4)	95 (84-115)
Normal hearing (n=67)	101 (50-141)
Schlichting lexical language expression (n=89)	104 (55-133)
Mild hearing loss (n=18)	112 (67-121)
Moderate to severe hearing loss (n=4)	101 (96-119)
Normal hearing (n=67)	102 (55-133)
Intelligence quotient (n=99)	104 (68-132)
Mild hearing loss (n=20)	115 (68-131)
Moderate to severe hearing loss (n=5)	107 (90-132)
Normal hearing (n=74)	103 (69-132)

*significantly lower than scores in children with mild hearing loss (p=0.007; Mann-Whitney test)

DISCUSSION

In this study we found that 75.7% of children had normal hearing 5 to 12 years after neonatal VA-ECMO treatment; 15.4% of children had conductive HL. SNHL was established in 12 of the 136 children (8.8%). SNHL was bilateral in 5 (3.7%); three of them wore hearing aids and/or received special audiological care (2.2% of the total sample). Overall, the children's language development and intelligence at 2 and 5 years were normal. Language development and intelligence results of children with HL were not worse than those of children with normal hearing.

Few epidemiologic data on hearing impairment in the normal pediatric population are available. In the United States it is estimated to occur in 1.1 per 1000 infants[25]; a study in the Netherlands found that 0.78 per 1000 infants had permanent hearing

impairment[1-3]. Recently, Cone and co-workers reported a 0.88% prevalence of SNHL in primary school-aged children[26]. In 2009, Mehra and co-workers concluded from audiometric screening studies that 3.1% of children and adolescents in the United States suffer from unilateral or bilateral hearing impairment (>20 dB). Those screening studies took place between 1958 and 1993 and most children were between 6 and 19 years old[25]. We found an eightfold higher prevalence of HL (24.3%), mainly of conductive origin. A high prevalence of conductive HL within the first 24 months of life has been reported in very low birth weight infants, especially in those with chronic lung disease (up to 54.5%)[27]. Nasally-placed tubes for ventilatory assistance and disturbed local immunity might be associated with chronic otitis media with effusion in infants up to two years of age[28]. Although all of our patients had been ventilated neonatally, it is unclear whether nasal tube placement and disturbed immunity explain our results at the age of 5 years, because our population was not born prematurely and the prevalence of conductive HL seems to decrease with age. Another possible explanation is that the 5-year-old children in our study may have suffered from recurrent respiratory tract infections with concomitant conductive HL. However, all these assumptions are speculative and do not seem to fully explain the discrepancy in findings. Further evaluation by ENT-surgeons will be needed to uncover the origin and clinical course of conductive HL in ECMO-treated patients.

Regarding SNHL, Cheung and Robertson[6] reported a 7.5% overall prevalence of SNHL in ECMO survivors, ranging from 3 to 21% in six different ECMO centers in the United States. All reviewed studies had been published before 1996. Fligor and co-workers found a 26% prevalence of bilateral SNHL in ECMO survivors born between 1986 and 1994[7]. Almost half of the children had delayed-onset SNHL, and 72% had progressive HL. Cheung and co-workers also reported normal clinical neonatal screening results in children who developed SNHL. The prevalence of bilateral SNHL in our population is in accordance with data published on larger series in the United States[29-30]. One child with severe bilateral SNHL, who would have been eligible for the follow-up program, was evaluated elsewhere and her data had been excluded from our analysis. Should we have included her data, the prevalence of SNHL would have been 9.5% (13 of 137 cases) with bilateral HL in 4.4% (6 of 137 children).
In our study neonatal screening data were not available for 3 of 5 children with bilateral SNHL. One child failed to pass the neonatal screening and was referred for

audiological care at an early stage. In one child who passed the neonatal screening test successfully, SNHL was diagnosed at 13 months, indicating delayed-onset SNHL.

A high prevalence of SNHL has been reported in children with CDH, even those not treated with ECMO[7,23-24]. Two of the 24 CDH patients in our study had mild SNHL (one patient with bilateral HL also had a partial chromosome X duplication). Similarly, Morando and co-workers[31] reported one patient with SNHL in a cohort of 26 CDH survivors not treated with ECMO. CDH is not the only risk factor for SNHL after ECMO treatment. Other reported factors are: treatment with aminoglycosides[7,32], furosemide, muscle relaxants[32], initiation of ECMO-treatment after >160 hours[7], prolonged ECMO treatment, and pre-ECMO seizures[10]. A nationwide study in the Netherlands revealed that the only independent risk factors for HL in neonates receiving intensive care were severe birth asphyxia and assisted ventilation for ≥5 days[9]. The small number of children with bilateral SNHL in the present study did not allow for multivariate analysis. Yet, all 5 patients with bilateral SNHL had between 2 and 5 of the above-mentioned risk factors.

All our patients were treated with VA-ECMO. During this procedure deoxygenated blood is removed from the right internal jugular vein and oxygenated blood is returned through a cannula placed in the right carotid artery. Veno-venous (VV) ECMO is a technique that has now gained more acceptance – also in our institution - for use in patients with an isolated pulmonary disease without the need for cardiac support[33]. Using this technique, the carotid artery need not be sacrificed and the normal pulsatility to the systemic flow is maintained. The risk for central nervous system complications (bleeding, microthrombi or infarct) seems to be less in VV-ECMO than in VA-ECMO[33]. The question is whether VV-ECMO could have reduced the prevalence of SNHL. Significant differences in mean cerebral blood flow velocities between VV- and VA-ECMO have been reported with higher blood flow velocities in the basilar artery during VA-ECMO[34]. This observation seems to contradict the hypothesis that VA-ECMO has a negative influence on cochlear perfusion. Taking into account that the aetiology of SNHL in ECMO-treated patients is unclear and that many different factors may play a role, we assume that VV-ECMO likely would not have reduced HL prevalence. However, additional studies are needed to confirm this assumption.

In the present study, results of language development and intelligence testing after neonatal ECMO treatment were favourable. Developmental test results of children with impaired hearing did not differ from those of children with normal hearing. Because children with unilateral HL may suffer from conductive hearing impairment in their best ear during upper airway infections, we related the developmental data to HL severity and not to HL laterality or origin. However, the small number of patients with HL does not allow for conclusions on the impact of early HL. Others have found that even mild bilateral HL compromises the development of language, communication skills and behavior at school age[35-36]. It seems, therefore, to be important to detect HL at an early stage and provide early intervention.

For the main purpose of this study we described the characteristics of 5 children with purely bilateral SNHL (Table 2). Interestingly, two with profound SNHL diagnosed at an early age (at 0.2 years and 1.1 years respectively; patients 3 and 4 in Table 2) and wearing hearing aids showed normal intelligence and language development. The other three children had been diagnosed later, and showed worse intelligence and language development. In all three, however, language development and/or intelligence might have been affected by comorbidity: Two had an underlying problem associated with impaired intelligence: severe birth asphyxia (patient 1; Table 2) and a partial duplication of chromosome X with mental retardation (patient 2; Table 2), respectively. The third was not a native Dutch speaker (patient 5; Table 2).

CONCLUSIONS

In this cohort of survivors of neonatal ECMO the prevalence of SNHL was 8.8% which approximated that of larger series in the United States. Overall, these children demonstrated normal language development and intelligence, and children with HL did not perform worse. In addition to the common practice of neonatal hearing screening and audiological follow-up of patients with severe birth asphyxia or[9] meningitis, we suggest that adequate information for parents and caregivers and close follow-up of all children after neonatal ECMO treatment is important. Prompt referral to an ENT-department with expertise in profound audiological evaluation in children should be considered even at minor signals suspicious of hearing impairment.

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CHAPTER 4

Neurodevelopmental, educational and behavioural outcome at eight years after neonatal ECMO: a nationwide multicenter study

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ABSTRACT

Purpose

Reporting neurodevelopmental outcome of 8-year-old children treated with neonatal extra-corporeal membrane oxygenation (ECMO).

Methods

In a follow-up study in 135 8-year-olds who received neonatal ECMO between 1996 and 2001 we assessed intelligence (Revised Amsterdam Intelligence Test), concentration (Bourdon-Vos), eye-hand coordination (Developmental Test of Visual-Motor Integration) and behaviour (Child Behaviour Checklist and Teacher Report Form).

Results

Intelligence fell within normal range (mean IQ:99.9, SD:17.7; n=125) with 91% of the children following regular education. Significantly more children attended special education (9%) or received extra support in regular education (39%) compared with normative data. Slower working speed (χ^2 =132.36, p<0.001) and less accuracy (χ^2 =12.90, p<0.001) were found on the Bourdon-Vos (n=123) compared with normative data. Eye-hand coordination fell within normal range (mean:97.6, SD:14.3; n=126); children with congenital diaphragmatic hernia scored lowest but still normal (mean:91.0, SD:16.4; n=28). Mothers (n=117) indicated more somatic and attention behaviour problems; teachers (n=115) indicated more somatic, social, thought, aggression and total problems compared with normative data. Mothers indicated more somatic problems than teachers (p=0.003); teachers reported more attention problems than mothers (p=0.036; n=111). A diagnosis of congenital diaphragmatic hernia (β= -0.350, p=0.008) was a significant predictor of intelligence.

Conclusions

Eight-year-old children treated with neonatal ECMO fall in the normal range of intelligence with subtle problems on concentration and behavior. Long-term follow-up for children treated with neonatal ECMO should focus on early detection of subtle learning deficits.

INTRODUCTION

Neonatal extracorporeal membrane oxygenation (ECMO) is a supportive intensive care technique for severe (cardio)respiratory failure. In the past decades it was most frequently applied in children with persistent pulmonary hypertension due to meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), or sepsis[1,2]. The estimated survival rate for neonatal ECMO is 75%[3] and is higher compared to conventional management[4]. A randomized trial in the United Kingdom (UK-trial) showed no associated increase of severe disability till the age of seven years[5-7]. Still, ECMO –particularly venoarterial ECMO- might affect cerebral blood flow[8] and increases the risk for intracranial hemorrhage and intracranial infarction[9,10]; possibly resulting in neurodevelopmental problems.

Neuromotor and neurodevelopmental problems at age five years are reported for children treated with neonatal ECMO[5,11-13]. Social, attention and visuo-spatial problems may occur too, often combined with other cognitive and behavioral problems[5,13-15]. These, sometimes subtle, cognitive deficits can put children at a twofold risk for school failure when compared to healthy children[14,15]. Overall, many children surviving neonatal ECMO have difficulties with cognitive skills at later ages, without apparent disability[7,16].

The present paper evaluates long-term neurodevelopmental outcome of eight-year-old children treated with neonatal ECMO. We systematically evaluated intelligence, concentration, eye-hand coordination and behaviour in a nationwide study in the Netherlands. The goals were:

1. to compare these children's neurodevelopmental outcome with normative data.
2. to evaluate the predictive influence of underlying diagnosis and other medical and background variables on these children's neurodevelopmental outcome.

MATERIALS AND METHODS

Population

We included eight-year-olds who received ECMO support between January 1996 and December 2001 at the intensive care unit of the two designated ECMO centers in the Netherlands: the Erasmus Medical Center-Sophia Children's hospital in Rotterdam and the Radboud University Nijmegen Medical Center in Nijmegen. ECMO support was initiated in case of reversible severe respiratory failure and an estimated mortality risk > 80% using the criteria reported by Stolar and colleagues[17]. Treatment protocols were similar in both centers and included cerebral ultrasound (CUS) once prior to and daily during ECMO-treatment. Entry criteria and exclusion criteria were previously described[11,13,18] and did not change during the study period. The study was part of a structured prospective post-ECMO follow-up program initiated in 2001 in Rotterdam and Nijmegen in which lung function, growth and developmental parameters are regularly assessed until 18 years[11,13].The assessment protocol is the standard of care in the Netherlands. The Medical Ethical Review Board Erasmus MC stated that "Medical Research in Human Subjects Act (in Dutch: "WMO") does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed". Therefore IRB approval was waived. All parents were informed about the study and provided permission to use the data for research purposes.

Design

Parents completed questionnaires on socio-economic status (SES; based on mother's education)[19] and their child's education and behaviour. With parental permission, teachers completed a parallel questionnaire concerning the child's behaviour. The children underwent a structural psychological assessment under supervision of a developmental psychologist in either Rotterdam or Nijmegen.

Assessment

Intelligence

The Revised Amsterdam Intelligence Test (RAKIT) short form was used consisting of three subtests (mean:15, standard deviation (SD):3) representing 'perceptual

reasoning' and 'visuo-spatial skills' (exclusion; discs, and hidden figures); two subtests representing 'verbal learning' (word meaning and learning names); one subtest representing 'verbal speed' and 'visuo-spatial skills' (idea production); and one subtest representing 'memory' (memory-span)[20].

The intelligence quotient (IQ) was defined as above average (IQ>115; 16% of normative data), average (IQ:85-115; 68% of normative data), or below average (IQ<85; 16% of normative data). Good reliability and validity have been reported[20] and the RAKIT has been referred to in international publications[21].

Concentration

The Bourdon-Vos is a paper-and-pencil test measuring sustained selective attention and concentration in terms of working speed and accuracy. Good validity, sensitivity, reliability and Dutch normative data have been described[22].

Eye-hand coordination

Developmental Test of Visual-Motor Integration (Beery VMI) is a sequence of 30 geometric forms to be copied with paper and pencil. The Beery VMI assesses the extent to which individuals can integrate their visual and motor abilities (eye-hand coordination) and scores can be compared with Dutch normative data (mean: 100; SD: 15)[23].

Mother-reported and teacher-reported behaviour

The Dutch version of the Child Behaviour Checklist (CBCL) and Teacher's Report Form (TRF) was completed by mothers and teachers. Both questionnaires are standardized for Dutch children aged 4-18 years and scores can be compared to Dutch reference samples[24-26]. A clinical (psychopathology) score in 10% of the children for the Total, Internalising and Externalising problems (T-score >63), and in 2% of the children for the problem behaviour scales (T-score >70) served as cut-off points for comparison with reference samples[25,26].

Data analysis

Differences in medical and sociodemographic variables between the two ECMO centers were tested with Mann-Whitney tests.

Mean IQ and eye-hand coordination scores between diagnosis groups were evaluated with one-way analysis of variance (ANOVA). Type of education was compared to Dutch normative data using chi-square tests[27,28]. Differences in mean scores of intelligence and eye-hand coordination were compared with normative data using one-sample t-tests. Differences in proportions for outcome categories of intelligence, type of education, concentration (working speed; accuracy) and eye-hand coordination were calculated using chi-square tests (both for comparison with normative data and between diagnosis groups).

Differences in mean scores of the CBCL and TRF for the ECMO group and the reference samples were assessed with Mann-Whitney tests due to skewness of data distribution. The percentages of children with a clinical CBCL and TRF T-score were compared between the ECMO group and the reference samples using Binomial tests; and between mothers and teachers using Fisher exact tests.

Multiple linear regression analyses served to assess predictive influences of medical variables (diagnosis (MAS/CHD/other); birth weight; prevalence of chronic lung disease (CLD: yes/no)[29]; the need for morphinomimetics or other sedatives (<1 week/ 1 week-1 month/ > 1 month); the use of muscle relaxants (no/ perioperative only/ ICU 1 day- 1 week/ ICU >1 week) and abnormal CUS (yes/no)) on continuous outcome variables (intelligence, eye-hand coordination and behaviour). Influence of medical variables on dichotomous outcome variables (concentration; working speed and accuracy) was calculated using binary logistic regression analysis. Predictive influences of background variables were analysed separately from the medical variables; using linear (categorical outcome variables) and binary logistic (dichotomous outcome variables) regression analyses. The background variables were categorized: gender (male/female); SES (low/moderate/high); type of education (regular education/regular education with support/special education); grade repetition (yes/no) and parents' ethnicity (Dutch/at least one of the parents non-Dutch). Normal probability plots of the residuals were evaluated to examine the applicability of the model and the assumptions for linear regression analysis. Assumptions of the binary logistic regression model were checked with the Hosmer & Lemeshow test. Multicollinearity was evaluated using the criteria that variance inflation factors should not exceed 2.5[30]. All statistical tests were two-sided, and p-values less than 0.05 were considered statistically significant. Bonferroni correction for multiple comparisons was applied for the regression analyses of the six medical variables (p

<0.008) and the five background variables (p <0.01). The analyses were performed using SPSS version 20.

RESULTS

Between January 1996 and December 2001 235 children were treated with neonatal ECMO (Figure 1). Fifty-five children died during their first hospitalization (23%). Of the 180 survivors, 141 (78%) were invited for follow-up assessment at eight years. In 135 children (96%) assessment was possible. Of these 135 children the medical and sociodemographic variables were evaluated (Table 1) with differences in variables between Rotterdam and Nijmegen for ventilation time (median (range); Rotterdam: 13 days (6-70)/ Nijmegen: 16 days (7-45); p=0.011), CLD ('yes': Rotterdam n=54 (83%)/ Nijmegen n=47 (67%); p=0.027), and ethnicity (Dutch: Rotterdam n=43 (66%)/ Nijmegen n=62 (89%); p=0.002).

Intelligence

In 3/135 (2%) children, intelligence was not assessed (Figure 1). Data of seven other children who were administered a different intelligence test due to organisational reasons were excluded (four of them had IQ below average). Thus, IQ could be calculated for 125 children.

Their mean IQ was 99.9 (SD: 17.7) and did not differ from normative data (t= -0.035, p=0.972). Twenty-three children (18%) had below average IQ scores, 80 children (64%) had average IQ scores, and in 22 children (18%) IQ was above average. These percentages did not differ significantly from normative data (χ^2 =0.944, p=0.662). All subtest scores were within the range of normative data (data not shown).

No significant differences were found in mean (SD) IQ scores between MAS (n=63; 101.5 (17.0)), CDH (n=29; 96.6 (18.6)) and the other diagnoses (n=33; 102.4 (17.4) with F=2.474, p=0.088. CDH patients had the lowest IQ scores but these scores were still in the range of normative data.

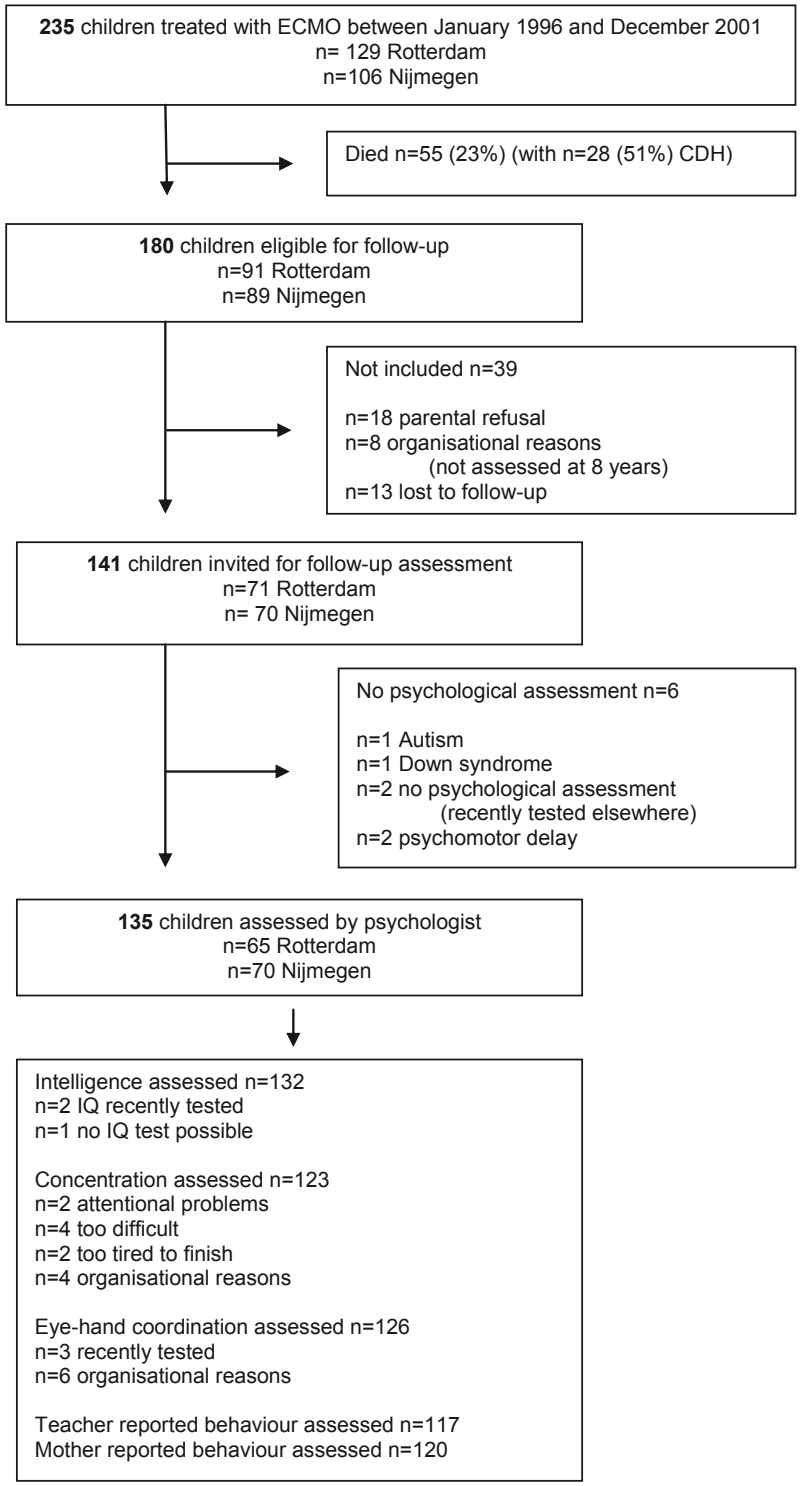

FIGURE 1 Flowchart ECMO cohort

ECMO = extra-corporeal membrane oxygenation; CDH = congenital diaphragmatic hernia

TABLE 1 Medical and socio-demographic variables

		n=135
Gender	Male	77 (57)
	Female	58 (43)
Diagnosis	MAS	71 (53)
	CDH	30 (22)
	Other	34 (25)
Birth weight (kilograms)		3.4 (2.2-4.8)
Gestational age in weeks		40 (34-42)
Type of ECMO	VA ECMO	135 (100)
ECMO time in hours		161 (63-369)
Ventilation time in days		18 (6-70)
Oxygen dependency after ECMO	1 day- 1 week	65 (48)
	> 1 week- < 1 month	54 (40)
	> 1 month	9 (7)
	Missing	7 (5)
Abnormal cerebral ultrasound during ECMO	Yes	24 (18)
	Missing	1 (1)
Morphinomimetics and sedatives	< 1 week	6 (4)
	1 week- 1 month	108 (80)
	> 1 month	19 (14)
	Missing	2 (2)
Need for drug therapy to prevent withdrawal symptoms	Yes	46 (34)
	Missing	1 (1)
Use of muscle relaxants	No	17 (13)
	Perioperative only	9 (7)
	ICU 1 day- 1 week	85 (63)
	ICU > 1 week	23 (17)
	Missing	1 (1)
Incidence of CLD	Yes	33 (24)
	No	101 (75)
	Missing	1 (1)
Ethnicity	Dutch	105 (78)
	Non-Dutch	30 (22)
SES	High	30 (22)
	Moderate	46 (34)
	Low	53 (39)
	Missing	6 (5)
Type of education	Regular	65 (48)
	Regular + extra support	53 (39)
	Special	12 (9)
	Missing	5 (4)
Grade repetition	None	87 (68)
	Group 2/ preschool	24 (18)
	Group 3/ first grade	6 (4)
	Group 4/ second grade	6 (4)
	Missing	12 (9)

Results are presented as n (%) or median (range). MAS=meconium aspiration syndrome; CDH=congenital diaphragmatic hernia; other=sepsis (n=13) or persistent pulmonary hypertension of the newborn (n=19) or pneumonia (n=2); ECMO=extra-corporeal membrane oxygenation; ventilation time=ventilation time including ECMO; CLD=chronic lung disease[29]; SES=socio-economic status. Abnormal cerebral ultrasound during ECMO: n=16 primary hemorrhage; n=6 vessel occlusion; n=2 “other” with n=6 right sided; n=11 left sided; n=3 bilateral and n=4 missing.

Education

Type of education was known for 130 children: 91% (n=118) followed regular education, with 39% (n=53) needing extra support. Nine percent (n=12) followed special education. The percentage of children attending special education (χ^2 =9.3, p=0.002) and the percentage of children receiving extra support in regular education (χ^2 =30.6, p<0.001) differed significantly from normative data. No differences were found for type of education between diagnoses groups (χ^2 =2.731, p=0.582; data not shown).

Concentration

For 123 children, the Bourdon-Vos was assessed (Figure 1). Thirty percent (n=37) scored normal-to-high on working speed and 70% (n=86) scored slow-to-very-slow. Sixty-one percent (n=75) scored normal-to-high on accuracy and 39% (n=48) scored low-to-very-low (Figure 2). Compared with normative data, working speed was significantly slower (χ^2 =132.36, p<0.001) and accuracy was significantly less (χ^2 =12.90, p<0.001).

When concentration was compared between diagnoses no significant differences were found (working speed: χ^2 =2.729, p=0.283 and accuracy: χ^2 =0.597, p=0.772; data not shown).

Eye-hand coordination

The Beery VMI was assessed in 126 children (Figure 1). The mean score of 97.6 (SD: 14.3) was within the normal range (t= -1.908, p= 0.059). Twenty percent (n=25) scored below average; 70% (n=88) had an average score; 10% (n=13) scored above average (Figure 3). The proportions did not differ from normative data (χ^2 =4.208, p=0.122).

A significant difference in VMI scores was found between diagnoses (F=4.165, p=0.018). Post-hoc testing revealed a significant difference in VMI mean (SD) score between the diagnosis of MAS (n=65; 99.9 (11.6)) and CDH (n=28; 91.0 (16.4)), p=0.016. Children with CDH scored lower, but within normal range.

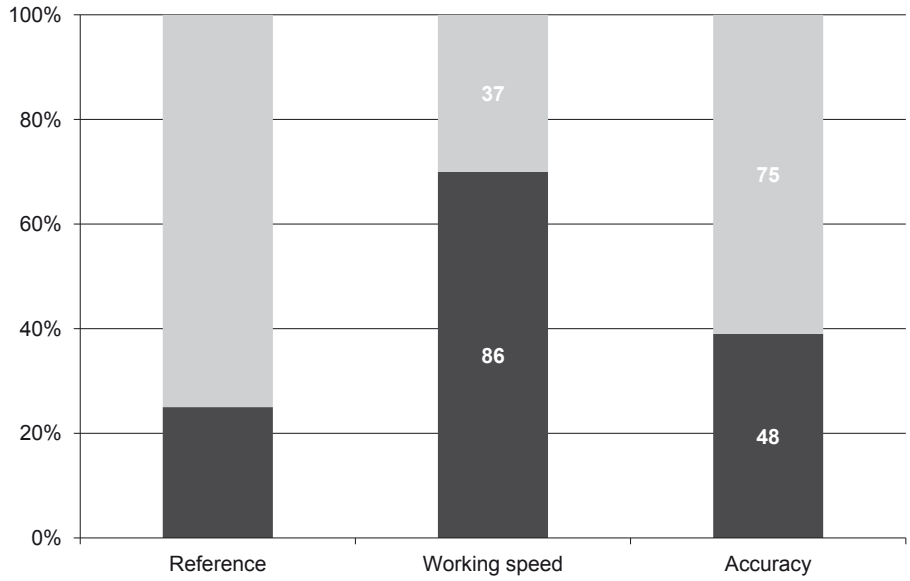

FIGURE 2 Concentration for the entire ECMO group

Working speed = working speed during task. Accuracy = accuracy of working during task. Numbers in bars represent number of patients in each category. In dark-grey = below average eye-hand coordination and (s)low-to-very-(s)low concentration. In grey = average eye-hand coordination. In light-grey = above average eye-hand coordination and normal-to-high concentration

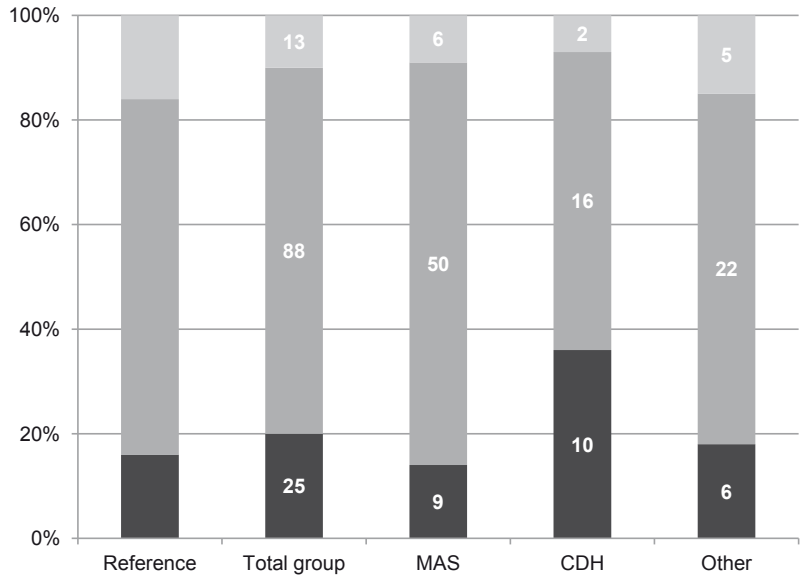

FIGURE 3 Eye-hand coordination for the entire ECMO group

MAS = meconium aspiration syndrome; CDH = congenital diaphragmatic hernia; Other = sepsis, persistent pulmonary hypertension of the newborn and pneumonia. Numbers in bars represent number of patients in each category. In dark-grey = below average eye-hand coordination and (s)low-to-very-(s)low concentration. In grey = average eye-hand coordination. In light-grey = above average eye-hand coordination and normal-to-high concentration

Mother-reported and teacher-reported behaviour

A CBCL was obtained for 117, a TRF for 115, and both a TRF and a CBCL for 111 children (Figure 1). SES distribution was similar in the ECMO group and the reference sample (data not shown). We therefore assumed that SES did not confound CBCL and TRF outcomes.

Mothers of the ECMO group reported significantly higher scores for somatic problems ($p<0.001$) and attention problems ($p=0.020$) but significantly lower scores for thought problems ($p=0.022$) and rule breaking problems ($p=0.043$) when compared to the reference sample (Table 2). They reported internalising problems in 19% (n=22) of children, externalising problems in 12% (n=14), and total problems in 17% (n=20). Compared with normative percentages (10% with clinical score), the mothers in the ECMO group indicated significantly more internalising problems ($p=0.003$) and total problems ($p=0.012$).

On the TRF behaviour scale, teachers of the ECMO group indicated significantly higher scores for somatic problems ($p<0.001$), social problems ($p=0.004$), thought problems ($p<0.001$), aggressive problems ($p=0.022$) and total problems ($p=0.035$) when compared to the reference sample (Table 2). Clinical problem behaviour was indicated by teachers in 10% (n=12) for internalising problems, in 5% (n=6) for externalising problems and in 5% (n=6) for total problems. These proportions did not differ significantly from normative percentages (10% with clinical score).

On the behaviour scales, mothers (mean=2.2; SD=2.2) indicated significantly higher scores for somatic problems ($p=0.003$) than did teachers (mean=1.5; SD=1.9). Teachers (mean=7.3; SD=6.5) indicated significant higher scores for attention problems ($p=0.036$) than did mothers (mean=5.1; SD=4.0). Mothers significantly more frequently than teachers indicated clinical social problems (CBCL: n=6 (5%); TRF: n=0 (0%), $p= 0.029$); attention problems (CBCL: n=7 (6%); TRF: n=0 (0%), $p= 0.014$) and total problems (CBCL: n=20 (18%); TRF: n=6 (5%), $p= 0.006$).

No significant differences on CBCL or TRF scale scores for the internalising-, externalising- and total problem T-scores were found for the different diagnoses groups (data not shown).

TABLE 2 Mother- and teacher-reported behaviour

	Child behaviour checklist Mean total problem scores			**Teacher report form** Mean total problem scores		
Scales	ECMO n=117	Reference n=767	Difference p-value	ECMO n=115	Reference n=633	Difference p-value
Anxious/depressed	3.6 (4.3)	3.3 (3.2)	0.378	3.3 (3.9)	3.0 (3.5)	0.904
Withdrawn/depressed	1.7 (2.2)	1.9 (2.1)	0.078	1.8 (2.2)	2.0 (2.5)	0.969
Somatic complaints	2.2 (2.2)	1.5 (2.0)	**<0.001**	1.4 (1.9)	0.5 (1.3)	**<0.001**
Social	2.8 (2.9)	2.6 (2.5)	0.980	2.6 (2.9)	1.9 (2.6)	**0.004**
Thought	1.8 (2.1)	2.2 (2.4)	**0.022**	1.4 (1.9)	0.6 (1.3)	**<0.001**
Attention	5.1 (4.0)	4.1 (3.3)	**0.020**	7.3 (6.4)	8.9 (8.9)	0.657
Rule-Breaking	1.4 (1.8)	1.7 (1.9)	**0.043**	1.0 (1.4)	1.2 (1.9)	0.664
Aggressive	5.1 (5.8)	4.9 (4.5)	0.297	4.0 (5.6)	3.3 (5.3)	**0.022**
Internalising	7.4 (7.3)	6.7 (5.8)	0.901	6.4 (6.2)	5.5 (5.9)	0.133
Externalising	6.5 (7.3)	6.5 (5.9)	0.105	4.9 (6.7)	4.5 (6.8)	0.113
Total	27.2 (21.5)	25.9 (17.7)	0.877	24.8 (18.9)	22.1 (20.4)	**0.035**

ECMO=extra-corporeal membrane oxygenation. **Bold**: significant p-value for difference between ECMO group and normative data with Mann-Whitney Test.

Medical and background variables associated with outcome

Diagnosis of CDH was a significant predictor of lower intelligence (β= -0.350, p=0.008). Also, special education (β= -0.345, p<0.001) and non-Dutch ethnicity (β= -0.258, p=0.004) were significantly associated with lower intelligence. Special education (β= -0.359, p<0.001) was significantly associated with lower eye-hand coordination, whereas extra support in regular education was significantly associated with more behavioural problems on the CBCL (β= 0.324, p=0.001) and TRF (β= 0.336, p=0.001) (Table 3).

TABLE 3 Regression models for medical and socio-demographic variables associated with outcome

	Intelligence	Concentration		Eye-hand coordination	Behaviour	
		Working-speed	Accuracy		CBCL	TRF
Medical variables						
Diagnosis (difference CDH vs. other)	**β= -0.350**	OR= 1.8 (0.6-5.7)	OR= 0.7 (0.2-1.8)	β= -0.262	β= -0.099	β= -0.055
	p=0.008	p=0.919	p=0.735	p=0.043	p=0.488	p=0.709
Sociodemographic variables						
Type of education (difference regular with support vs. regular)	β= -0.076	OR= 1.4 (0.5-3.5)	OR= 1.3 (0.6-3.1)	β= -0.130	**β= 0.324**	**β= 0.336**
	p= 0.387	p= 0.523	p= 0.508	p= 0.153	**p= 0.001**	**p= 0.001**
(difference special vs. regular)	**β= -0.345**	OR= 0.0 (0.0)	OR= 2.6 (0.2-33.6)	**β= -0.359**	β= 0.174	β= 0.108
	p <0.001	p= 0.999	p= 0.461	**p <0.001**	p= 0.086	p= 0.283
Non-Dutch ethnicity	**β= -0.258**	OR= 0.5 (0.2-1.8)	OR= 1.0 (3.5-1.3)	β= 0.011	β= -0.082	β= -0.103
	p= 0.004	p= 0.324	p= 0.971	p= 0.905	p= 0.411	p= 0.305

Medical variables were separately analysed from the sociodemographic variables with multiple linear regression for intelligence, eye-hand coordination and behaviour; and with binary logistic regression for concentration (working speed/ accuracy). Predictive values were reported with β (standardized regression coefficient) for multiple linear regression and with odds-ratios (OR with 95% confidence interval) for binary logistic regression. Diagnosis: other=sepsis, persistent pulmonary hypertension of the newborn and pneumonia; CDH=congenital diaphragmatic hernia. We applied Bonferroni correction for the multiple comparison of 6 medical variables (p <0.008) and 5 sociodemographic variables (p <0.01). **Bold**=significant predictor/association.

DISCUSSION

This cohort of eight-year-old children treated with neonatal ECMO showed normal intelligence with 91% attending regular education. However, more children attended special education and more children attending regular education received extra support when compared to the Dutch population. Furthermore, these children had a significantly slower working speed and worked significantly less accurately when compared to normative data. Their eye-hand coordination was within normal range, although CDH patients had significantly lower scores than patients with other diagnoses. Furthermore, the mothers of these children reported significantly more somatic and attention problems, and the teachers more somatic, social, thought, aggressive and total problems when compared to the reference sample. However, when mothers and teachers were compared (n=111), mothers indicated significantly more somatic problems and teachers indicated significantly more attention problems.

Normal range IQs at school age have been reported for children treated with neonatal ECMO[7,9,16,31]. However, more children in our cohort attended special education or received extra support at school compared to the 4% and 21%, respectively, in the Dutch population[27,28]. This suggests that those children without apparent delays remain at risk for subtle cognitive deficits.

In a concentration test the children needed more time to finish a task and had more trouble performing the task accurately than children in the Dutch population. Children studied in the UK-trial also had below average concentration, however, teachers indicated an above average cooperation in class[7]. This suggests that impaired concentration was not caused by poor motivation.

McNally and coworkers reported problems with pattern construction and recall of designs[7]. In our study, the children scored normally in spatial ability, both on visuo-spatial skills subtests of the RAKIT and on the Beery VMI-test. Taking into account that the VMI has a moderate correlation with aspects of intelligence and academic achievement[23] the normal VMI outcome seems not surprising: we found overall intelligence in the normal range, and a significant negative association with attending special education on VMI scores.

Parents have reported behaviour disability in 7% of seven-year-old children treated with neonatal ECMO[7]. In a study by Hofkosh and coworkers both parents and teachers of 5-10-year-old ECMO survivors did not report behavioural problems[9]. In our study, the mothers reported significantly higher scores on somatic and attention domains when compared with the reference sample. They also indicated significantly more clinical behaviour on the internalising and total domains. Although teachers of our ECMO group indicated significantly higher scores on somatic, social, thought, aggressive and total problems than in the reference sample, the proportion of clinical behavior scores did not differ. This suggests only mild behavioural problems at school. However, mothers and teachers had significantly different outcomes, which is not unusual; Verhulst and coworkers showed that teacher reports were a stronger predictor of poor outcome than parents' reports[32]. In the present study, the negative influence of needing extra support at regular education on the CBCL and TRF total problem scores may indicate that children who experience difficulties at school might suffer from behavioural signs of e.g. fatigue at home.

We saw lower outcome for intelligence and eye-hand coordination in CDH patients although scores were still in the normal range. Subtle deficits in areas of cognition

seem present in children with CDH[9,33,34]. Our group already showed that ECMO-treated CDH patients had significantly lower IQ scores than those not treated with ECMO[36]. We assume that this reflects severity of disease rather than ECMO-treatment. This assumption is supported by the results of the UK-trial, although the majority of CDH patients in their study cohort died[7].

Bulas and Glass reported impaired language problems after mild brain injury during neonatal ECMO, whereas children with more severe brain injury in the focal right-sided hemisphere experienced greater deficits in visuo-spatial and visuo-motor skills[36]. Right-sided or bilateral hemisphere lesions occurred in our study in 9/24 (38%) patients with abnormal CUS during ECMO. Because we found no negative prediction of abnormal CUS on outcome in our study, we assume that these lesions were mild, causing subtle cognitive problems.

Interestingly, we also did not find an association between treatment with morphinomimetics or other sedatives and outcome. This is in line with observations by de Graaf and coworkers that continuous morphine administration in the neonatal period was not associated with neurodevelopmental outcome of children born preterm at 8-9 years[37].

A limitation of our study is that we used Dutch neuropsychological tests, which limits cross-cultural comparison. A strength is, that we could compare our data to Dutch normative data. Another limitation is that not every child could be tested and this might have resulted in a positive outcome bias, because most dropouts were the ones with delayed neuropsychological outcome (e.g., tested elsewhere because of problems already present or could not perform the assessment). However, the number of dropouts due to severe cognitive impairment was relatively low and - compared to other studies – the participation rate was high[9,10](Figure 1).

CONCLUSIONS

Eight-year-old children treated with neonatal ECMO have average intelligence with subtle cognitive problems in the areas of concentration and behavior. A larger proportion of them, compared to the Dutch population, attends special education or receives extra support in regular education. A diagnosis of CDH might predict negative outcome. Long-term follow-up should focus on early detection of subtle learning deficits and providing adequate intervention.

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CHAPTER 5

Congenital diaphragmatic hernia with(out) ECMO: impaired development at eight years

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ABSTRACT

Objective

Evaluating developmental and social-emotional outcomes at 8 years of age for children with congenital diaphragmatic hernia (CDH), treated with or without neonatal Extra Corporeal Membrane Oxygenation (ECMO) between January 1999 and December 2003.

Design

Structural prospective follow-up.

Setting

Level III University Hospital.

Patients

Thirty-five children (ECMO: n=16; non-ECMO: n=19) were assessed at 8 years of age.

Interventions

None.

Main outcome measures

Intelligence and motor function. Concentration, behaviour, school performance, competence and health status were also analysed.

Results

Mean (SD) intelligence for the ECMO group was 91.7 (19.5) vs. 111.6 (20.9) for the non-ECMO group ($p=0.015$). Motor problems were apparent in 16% of all participants and differed significantly from the norm (5%; $p=0.015$) without differences between treatment groups. For all participants, problems with concentration (68%, $p<0.001$) and with behavioural attention (33%, $p=0.021$) occurred more frequently than in reference groups, with no difference between treatment groups. School performance and competence were not affected.

Conclusions

Children with CDH – whether or not treated with neonatal ECMO – are at risk for long-term morbidity especially in the areas of motor function and concentration. Despite their impairment, children with CDH have a well developed feeling of self-competence.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is an anatomical congenital anomaly occurring in approximately 1 in 2500 births[1]. Mortality and morbidity are determined by associated anomalies and the extent of lung hypoplasia and pulmonary hypertension[1]. Ventilation strategies nowadays focus on minimizing barotrauma[1] and survival rates are approaching 80%[2]. Because more children survive the neonatal period, incidences of physical and neurodevelopmental morbidities at older ages are on the rise[3-5].

In the past decade many CDH patients, especially those with high risk CDH (respiratory insufficiency within the first six hours of life) were treated with neonatal Extra Corporeal Membrane Oxygenation (ECMO), the use of which is decreasing nowadays[6]. Some studies report an improved survival rate with the use of ECMO treatment[7], others a relatively unchanged rate[8-10]. Of all ECMO-treated neonates, patients with CDH are most prone for clinical complications during ECMO treatment and long-term morbidity[11-14]. ECMO treatment was found to be significantly associated with delayed neurodevelopmental outcome[3]. However, this might rather be the result of severe illness necessitating ECMO than of the ECMO treatment itself[15].

As all studies have different study designs it is hard to compare outcomes between CDH patients treated with or without neonatal ECMO. Also, most studies so far are limited to pre-school age. In this paper we present neurodevelopmental outcomes of 8-year-old children with CDH enrolled in our multidisciplinary follow-up program. We hypothesized that they would show developmental and social-emotional impairments and that outcomes would be worst in those treated with ECMO, who were more severely ill. The primary outcome parameters were intelligence and motor function. Secondary outcome parameters were school performance, concentration, sense of competence, health status and behaviour.

MATERIALS AND METHODS

Participants

A follow-up study was conducted in 8-year-old children who were diagnosed with CDH and treated in their neonatal period at the Intensive Care Unit of a level III

University Hospital between January 1999 and December 2003. Veno-arterial ECMO support was given to neonates who met the entry criteria[16], which did not change during the study period. Artificial ventilation was administered by conventional mechanical ventilation (Babylog 8000, Drager Medical, Lubeck, Germany) or high-frequency oscillatory ventilation (Sensormedics, Bilthoven, The Netherlands).

The study was part of a structural prospective follow-up program initiated in 1999 that provides for regular assessments of lung function, exercise capacity and development until 18 years of age[12,13,17-20]. The Medical Ethical Review Board of Erasmus MC waived IRB approval because “Medical Research in Human Subjects Act does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed”. All parents provided written permission to use the data for research purposes.

Study design

Before assessment, parents completed questionnaires on socio-economic status (SES[21]) and their child’s education and health status. The children underwent a structural psychological and psychomotor assessment by a developmental psychologist and a pediatric physical therapist.

Clinical and background characteristics were recorded and compared between the treatment groups (ECMO/ non-ECMO) (Table 1).

TABLE 1 Background and clinical characteristics of the treatment groups

	ECMO group n=16	Non-ECMO group n=19	p-value
Background characteristics			
Dutch etnicity	12 (75)	15 (79)	0.398
Missing	-	2 (11)	
SES			0.092
Low	6 (38)	4 (21)	
Moderate	5 (31)	1 (5)	
High	5 (31)	11 (58)	
Missing	-	3 (16)	
Male gender	10 (63)	8 (42)	0.315
Clinical characteristics			
Gestational age in weeks	40 (36-41)	39 (27-42)	0.507
Birth weight in grams	3200 (2800-3810)	3200 (1200-4000)	0.594
Defect side			0.608
Left	15 (94)	15 (79)	
Right	1 (6)	2 (11)	
Para-esophageal	-	2 (11)	
Repair with patch	10 (63)	12 (63)	0.968
Associated anomalies	3 (19)	5 (26)	0.700
Intracranial abnormalities	1 (6)	1 (5)	0.925
High risk	16 (100)	15 (79)	0.109
Oxygen dependency			<0.001*
1 day- 1 week	1 (6)	13 (68)	
1 week- 1 month	10 (63)	5 (26)	
> 1 month	5 (31)	1 (5)	
CLD			0.015*
No	7 (44)	14 (74)	
Mild	1 (6)	4 (21)	
Moderate	3 (19)	1 (5)	
Severe	5 (31)	-	
Duration of mechanical ventilation in days	27 (11-130)	7 (1-53)	<0.001*
Use of morphinomimetics and sedatives			0.002*
< 1 week	1 (6)	10 (53)	
1 week- 1 month	5 (31)	6 (31)	
> 1 month	10 (63)	2 (11)	
Missing	-	1 (5)	
Use of methadone			0.006*
Yes	8 (50)	1 (5)	
Missing	-	1 (5)	
Use of muscle relaxants			0.281
Peroperative only	10 (63)	12 (63)	
ICU < 1 day	5 (31)	2 (11)	
ICU 1 day- 1 week	1 (6)	4 (21)	
Missing	-	1 (5)	
Age at onset ECMO in hours	13 (4-252)	-	-
Duration of ECMO support in hours	164 (63-369)	-	-
Highest MAP prior to ECMO	17 (14-45)	-	-
Highest OI prior to ECMO	41 (13-98)	-	-

SES=socio-economic status; CLD=Chronic lung disease [23]; ECMO=Extra Corporeal Membrane Oxygenation; MAP=mean airway pressure prior to ECMO; OI=Oxygenation Index prior to ECMO; high risk=respiratory insufficiency within the first six hours of life; ICU=Intensive Care Unit. Data presented as median (range) or n (%). *Significant difference between treatment groups. Associated anomalies represent: Marfan syndrome (n=1); Cohen syndrome (n=1); cardiac anomalies (ventricular septal defect n=1 and atrial septal defect n=1) and situs inversus totalis (n=1). Intracranial abnormalities were diagnosed with ultrasound during the initial admission and represent: corpus callosum agenesis (n=1) and stroke (n=1).

Primary outcome parameters

Intelligence

A short version of the Revised Amsterdam Intelligence Test (RAKIT) was administered[22]. Except for patients born after 2001; the short version of the Wechsler Intelligence Scale for children (WISC-III-NL)[23] was administered to them. Both tests have good reliability and validity[22,23]. Intelligence quotient (IQ) was classified into above average (IQ>115), average (IQ:85-115) and below average (IQ<85).

Motor function

The Movement Assessment Battery for children (MABC) was administered[24]. Percentile scores were calculated for the total impairment score, which is the sum of the item scores, and scores in three different domains (manual dexterity, ball skills and balance); a percentile score ≤P5 is indicative of a motor problem, P6 to P15 of borderline performance, and >P15 of normal motor development.

Additional psychological assessment

Concentration

Concentration was measured with The Bourdon-Vos, which is a paper-and-pencil test measuring sustained selective attention and concentration in terms of speed and accuracy. It has good validity, sensitivity and reliability[25].

Self-perceived competence and health status

Self-perceived competence was measured with the Dutch adaptation of The Self Perception Profile for Children (SPPC) for 8 to 12-year-old children[26]. The SPPC assesses a child's sense of competence in cognitive, social, and physical domains and yields a measure of general self-worth. The internal consistency and test-retest reliability of the Dutch version are acceptable[27]. Fifteen percent of the healthy reference group scores below the normal range and this percentage was set as a cut-off point[27].

Health status was assessed with the Pediatric Quality of Life Inventory (PedsQL) as described previously[28]. A scale score of 1 SD below the healthy reference norm was taken to indicate an impaired health status[29].

Proxy-reported behaviour

The Dutch version of the Child Behavior Checklist (CBCL) - standardized for the Dutch population from 4 to 18 years - was completed by mothers[30]. A subclinical to clinical score in 16% of the children was used as a cut-off point for comparison with reference norms[30].

Data analysis

Normally distributed data were analysed with student's t-test. The χ^2 test or Fisher's exact test served to evaluate categorical data.

Influences of clinical variables (ECMO treatment (yes/no); gestational age; associated anomalies; type of repair and prevalence of chronic lung disease (CLD)[31]) prolonged use of morphinomimetics/sedatives (>1 month) and use of methadone (yes/no)) and background variables (gender; ethnicity and SES) on intelligence and motor function were calculated using multiple linear regression analysis. Normal probability plots were evaluated to test the applicability of the model and the assumptions for regression analysis. Multicollinearity was tested using the criterion that variance inflation factors should not exceed 2.5[32]. The medical variables were individually entered into 7 regression analyses to avoid the risk of multicollinearity. Data are presented as mean (SD) unless stated otherwise.

RESULTS

Sixty-five CDH patients were treated between January 1999 and December 2003. Thirty-five children (ECMO n=16; non-ECMO n=19) were eligible for assessment at 8 years. Psychological and motor function assessment was completed in 32 and 31 patients, respectively (Figure 1).

Primary outcome parameters

Intelligence

For 4 of the 32 children no IQ was calculated (Figure 1). For the remaining 28 children the mean total IQ was 101.6 (22.3) and within the reference norm. Mean IQ significantly differed between the ECMO group (IQ: 91.7 (19.5)) and non-ECMO group (IQ: 111.6 (20.9)) (t=-2.599, p=0.015). The proportions of children with above

average, average and below average IQ did not differ significantly between both groups (χ^2=6.305, p=0.052; Figure 2).

Motor function

Thirty-one children underwent motor function testing (Figure 1). Twenty-five children (81%; ECMO: n=10; non-ECMO: n=15) scored within normal range, 1 child (3%; ECMO) was classified as borderline and 5 children (16%; ECMO n=3; non-ECMO n=2) were classified as having a motor problem. These proportions differed significantly from the norm population (χ^2=9.171, p=0.015). No significant difference in motor development was found between treatment groups (Figure 3).

A percentile score within the normal range was obtained in 26 children for manual dexterity (84%; ECMO n=11, non-ECMO n=15), in 20 children for ball skills (65%; ECMO n=9, non-ECMO n=11) and in 26 children for balance skills (84%; ECMO n=11, non-ECMO n=15). Ball skills differed significantly from the norm population (χ^2=10.309, p=0.010). No significant differences in domain proportions were found between the treatment groups (Figure 3).

Combined intelligence and motor function development

Twenty-six children (ECMO n=13 and non-ECMO n=13) had both an intelligence and motor function assessment. The percentages of children with normal or impaired intelligence combined with normal or impaired motor function did not significantly differ between the treatment groups (χ^2=7.271, p=0.057) (Figure 4).

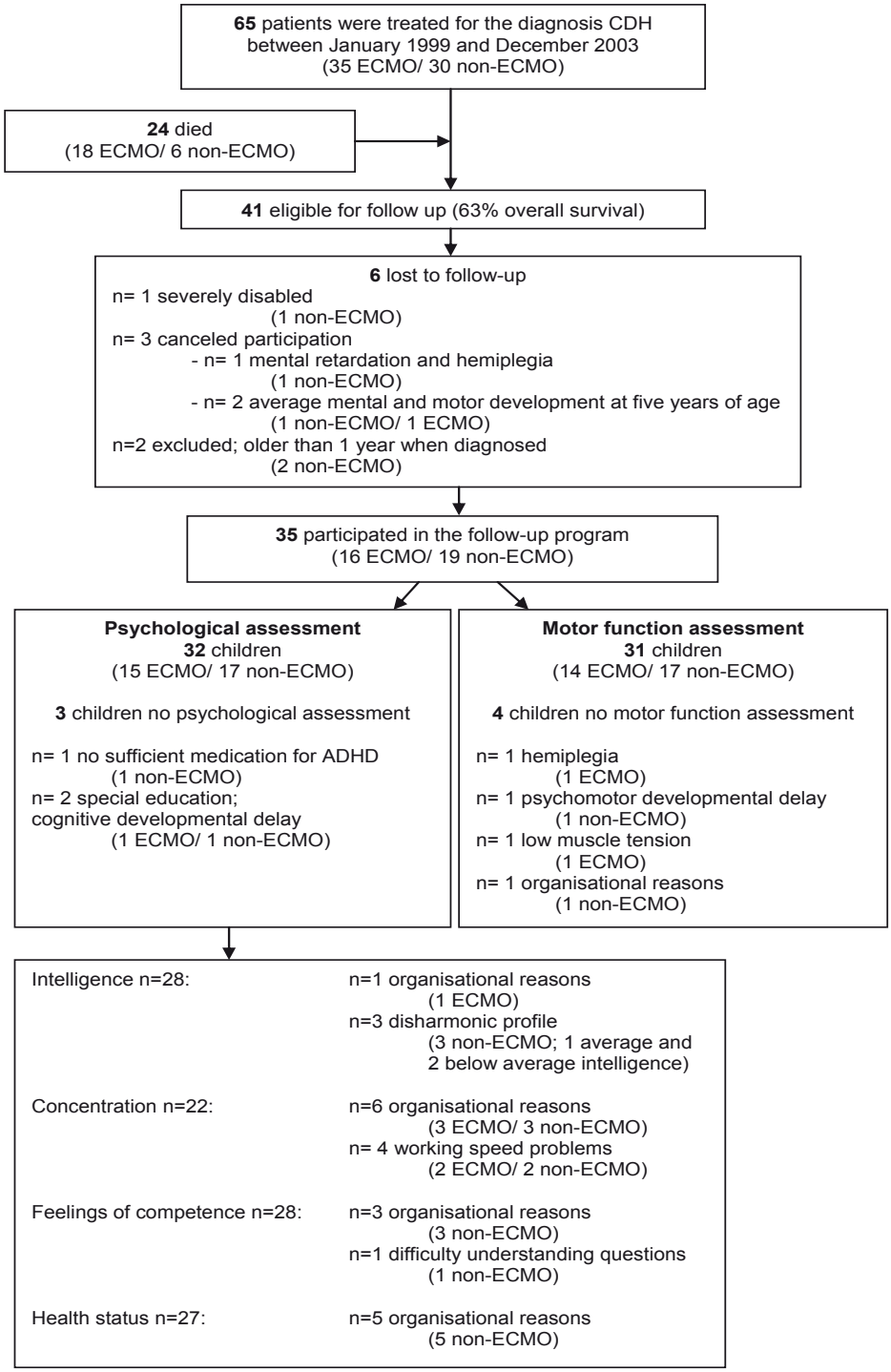

FIGURE 1 Flowchart

CDH = Congenital diaphragmatic hernia; ECMO = Extracorporeal Membrane Oxygenation; Non-ECMO = no Extra Corporeal Membrane Oxygenation; ADHD = Attentional Deficit Hyperactivity Disorder. Organisational reasons for no psychological assessment = the child arrived late at the follow-up appointment or was too tired to finish the entire assessment battery.

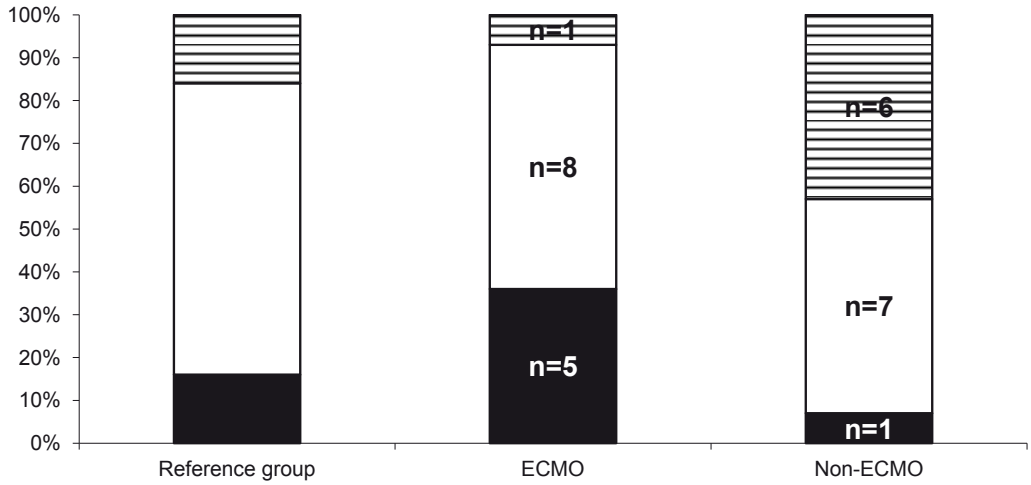

FIGURE 2 Intelligence in eight-year-old CDH-patients

Intelligence in eight-year-old CDH patients. In white with stripes = Above average intelligence. In white = Average intelligence. In black = Below average intelligence

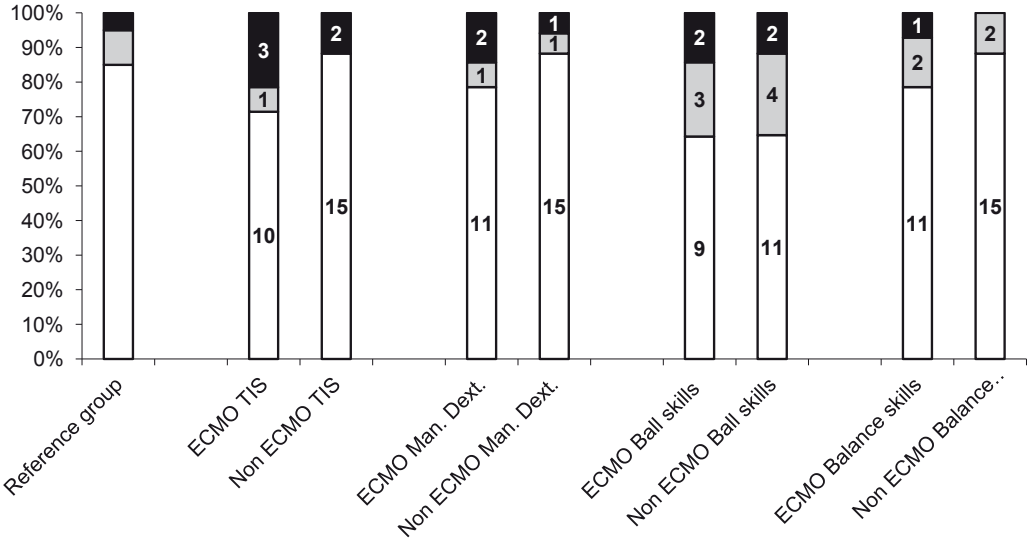

FIGURE 3 Motor function in eight-year-old CDH patients

Motor function in eight-year-old CDH patients. In white = Normal motor function. In grey = Borderline motor function problems. In black = Severe motor function problems. Number of patients is indicated in the bars

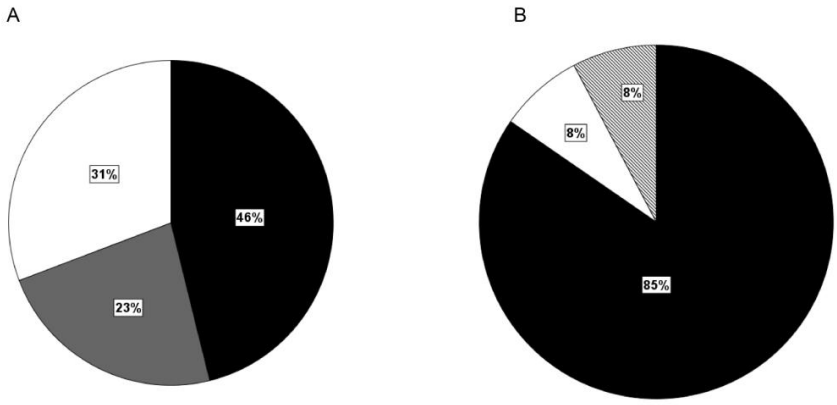

FIGURE 4 Combined intelligence and motor function development

A = Intelligence and motor function for ECMO group. B = Intelligence and motor function for non-ECMO group. In black = Both intelligence and motor function development are normal. In white = Both intelligence and motor function development are impaired. In grey = Only intelligence is impaired. In white with stripes = Only motor function is impaired

Additional psychological assessment

School performance

Of all 35 children, 33 followed regular education (94%; ECMO n=15, non-ECMO n=18); fourteen of those (42%; ECMO n=7, non-ECMO n=7) received extra support at school. Two children (6%; ECMO n=1, non-ECMO n=1) followed special education because they had cognitive and motor function problems.

Concentration

Concentration was assessed in 22 children (Figure 1). Fifteen of them (68%; ECMO n=7, non-ECMO n=8) had low to very low information-processing speed (χ^2=0.028, p=0.867). Eight had low-to-very low accuracy (36%; ECMO n=5 and non-ECMO n=3) (χ^2=1.473, p=0.387). Information-processing speed differed significantly (χ^2=21.879, p<0.001) from the reference population, but accuracy did not (χ^2=1.515, p=0.324).

Self perceived competence and health status

Four children did not complete the SPPC (Figure 1). Of the 28 children tested, a below normal range score was obtained in 29% for scholastic competence (ECMO n=4, non-ECMO n=4); 11% for social acceptance (ECMO n=2, non-ECMO n=1); 18% for athletic competence (ECMO n=3, non-ECMO n=2); 21% for behavioral

conduct (ECMO n=2, non-ECMO n=4) and 7% for global feeling of self-worth (ECMO n=2, non-ECMO n=0). None scored below normal for physical appearance. No significant differences were found for the entire group compared to reference norms, nor between the two treatment groups.

Twenty-seven children filled in a PedsQL (Figure 1). Overall, they had significantly lower health status scores than reference peers for total functioning (mean difference (md) -8.45, $p<0.001$), physical functioning (md -10.71, $p<0.001$), social functioning (md -11.14, $p<0.001$), school functioning (md -10.22, $p<0.001$) and psychosocial functioning (md -8.36, $p<0.001$), whereas emotional functioning was not significantly different (md -3.70, $p=0.208$). Comparison of the two treatment groups (ECMO n=12, non-ECMO n=15) revealed significantly lower scores for the ECMO group for total functioning (md -13.43, $p=0.024$), physical functioning (md -14.64, $p=0.044$), social functioning (md -16.42, $p=0.012$), school functioning (md -13.90, $p=0.038$) and psychosocial functioning (md -13.24, $p=0.027$). Other medical variables (e.g. presence of CLD) did not influence health status scores (not shown).

Proxy-reported behaviour

Twenty-seven mothers filled in the CBCL and the scores indicated borderline-to-clinical range for 7 children (26%; ECMO n=3, non-ECMO n=4) on the total scale, for 7 children (26%; ECMO n=3, non-ECMO n=4) on the internalizing scale and for 4 children (15%; ECMO n=2, non-ECMO n=2) on the externalizing scale; all proportions were not significantly different from the reference population. Nine children (33%; ECMO n=4, non-ECMO n=5) were assigned borderline-to-clinical range on the attention scale; this is significantly more than in the reference population ($\chi^2=6.036$, $p=0.021$). No significant differences between treatment groups were found.

Associations between outcome parameters

ECMO treatment ($R^2=0.206$, $p=0.015$), having associated anomalies ($R^2=0.190$, $p=0.020$), CLD ($R^2=0.107$, $p=0.049$) and prolonged use of morphinomimetics/ sedatives ($R^2=0.183$, $p=0.023$) negatively influenced intelligence. Having associated anomalies ($R^2=0.175$, $p=0.019$), CLD ($R^2=0.207$, $p=0.010$), and use of methadone

(R^2=0.176, p=0.021) negatively influenced motor function. High SES (R^2=0.285, p=0.035) positively influenced intelligence.

Five of the 6 children with below average intelligence indicated on the SPPC to be satisfied with their scholastic competence. Three of these five children plus one other, with borderline or definite motor function problems, were satisfied with their athletic competence.

DISCUSSION

In this study we hypothesized that ECMO-treated CDH children would have poorer developmental and social-emotional outcome than those without ECMO treatment. We found that intelligence was in the normal range for all children together, but ECMO-treated children had significantly lower IQ. For all children together motor function was significantly worse compared to reference peers, with no differences between treatment groups. To our knowledge this is the first study comparing outcome in 8-year-old children with CDH with and without ECMO-treatment within a similar time period and in one centre.

In an earlier study we found below normal intelligence for 8-to12-year old CDH children treated with neonatal ECMO before 1999[33]. The children in the present study had normal intelligence, in line with other studies in CDH patients without ECMO treatment[5,34]. Nevertheless, intelligence scores in the ECMO group were significantly lower than those in the non-ECMO group. Ultrasound examinations revealed intracranial bleeding and infarctions in only a few children in both treatment groups. These do not seem to explain the difference in IQ; perhaps we should assume that children needing ECMO were more severely ill[15]. However, we found subtle cognitive deficits such as concentration problems in both treatment groups. Also, mothers indicated more attention problems for their children when compared to reference parents. Subtle deficits in specific areas of intelligence seem apparent in children with CDH[5,35,36] and support the findings that CDH survivors – even those without ECMO treatment – are at risk for attention and concentration deficits[5,34]. The fact that 42% of our cohort needs extra support in regular education vs. 21% in the Dutch reference population[37] also points at subtle cognitive problems.

Motor problems have been reported in 60% of one-year-old and in 73% of 3-year-old children with CDH treated with and without ECMO[4,17]. The present study found motor problems with ball skills particularly affected in the total CDH group, as we previously found in 5-year-old CDH children[12,20]. We assume that CDH patients get little physical activity during infancy and have few opportunities to practice ball skills[20]. Because both treatment groups showed motor problems, evaluation of motor function is important for all CDH children, irrespective of previous ECMO treatment.

When we combined intelligence and motor function outcome (n=26) we found no significant difference between the two treatment groups. However, we might have been unable to reach statistical significance due to small sample sizes. On the other hand, proportions of children with combined normal intelligence and normal motor function does seem to be higher for the non-ECMO group. This supports the idea that ECMO-treated children were more severely ill and thus experience more morbidity. We assume that for CDH patients, without severe hemorrhagic or thromboembolic complications, it need not to be the ECMO treatment itself that result in worse outcome. Severity of illness, necessitating ECMO treatment, should rather be considered the main determining factor in long-term outcome.

We found a significantly lower health status for the entire cohort (with the lowest scores for ECMO-treated patients) with only emotional functioning not affected. Like emotional functioning, feelings of competence were not affected overall. It is not an unusual finding that children with objectively impaired intelligence or motor function experience normal feelings of competence[38].

The small sample sizes per treatment group in this study can be seen as a limitation, possibly precluding reaching statistical significant difference when comparing intelligence and motor functioning outcomes. Small sample sizes are not uncommon when analysing this rare diagnosis group (supplement Table 1). As a second limitation, data for a number of children in different neuropsychological assessments are missing (differentiated between the ECMO and non-ECMO-treated groups). The fact that children experiencing severe morbidity were the ones who were unable to complete the assessments might have resulted in a bias. This bias also shows the importance of long-term follow-up of CDH children (supplement Table 2 presents

long-term outcome); as more of them survive the neonatal period incidences of severe CDH-related morbidity are on the rise. This phenomenon has increasingly been identified in other studies[3,4,14,17].

CONCLUSIONS

Children with CDH – whether or not treated with ECMO – are at risk for long-term morbidity especially in the areas of motor function, concentration and health status. Intelligence seems within the normal range for all CDH children, with significantly lower scores for the children treated with ECMO. Despite their impairment, children with CDH have a well developed feeling of self-competence. Collecting long-term follow-up data in a multi-center CDH registry[39] will facilitate collaborative efforts to evaluate the efficacy of clinical care practices and to decrease morbidity.

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SUPPLEMENT

TABLE 1 Developmental studies at school age for patients with congenital diaphragmatic hernia

	Patients	Age at follow-up	Intelligence	Motor function
Bouman[1] 2000	n=11 no ECMO birth year NA	8.4-11.8 years	Mean IQ: 85 (below normal range) Below average IQ scores n=5 (45%)	-
Rasheed[2] 2001	n=9 ECMO post surgical repair birth year 1984-1989	9 years	Median (range) IQ: 92 (66-104) (normal)	Gross motor mean (SD): 93 (24) (normal) Fine motor mean (SD): 86 (23) (below normal range)
	n=6 ECMO prior surgical repair birth year 1989-1994	5 years	No IQ could be calculated due to hearing impairment	Gross motor mean (SD): 92 (25) (normal) Fine motor mean (SD): 86 (18) (below normal range)
Jakobson[3] 2009	n=15 no ECMO birth year NA	10-15.9 years	Mean (SD) IQ: 101 (14) (normal) Except for two children with full scale IQ: 40 and 49	-
Peetsold[4] 2009	n=31 no ECMO birth year 1987-1999	6-16 years	Mean (SD) IQ: 100 (13) (normal) Except for four children (IQ score < -1 SD)	-

[1] Bouman NH, Koot HM, Tibboel D, et al. Children with congenital diaphragmatic hernia are at risk for lower levels of cognitive functioning and increased emotional and behavioral problems. Eur J Pediatr Surg 2000;10:3-7. [2] Rasheed A, Tindall S, Cueny DL, et al. Neurodevelopmental outcome after congenital diaphragmatic hernia who did not receive extracorporeal membrane oxygenation. J Pediatr Surg 2001;36:539-44. [3] Jakobson LS, Frisk V, Trachsel, D, et al. Visual and fine-motor outcomes in adolescent survivors of high-risk congenital diaphragmatic hernia who did not receive extracorporeal membrane oxygenation. J Perinatol 2009;29:630-6. [4] Peetsold MG, Huisman J, Hofman VE, et al. Psychological outcome and quality of life in children born with congenital diaphragmatic hernia. Arch dis child 2009;94:834-40. NA=not available.

SUPPLEMENT

TABLE 2 Long-term mental and psychomotor outcome for all congenital diaphragmatic hernia patients

	Mental				Psychomotor			
Patient	12 months	24 months	5 years	8 years	12 months	24 months	5 years	8 years
	MDI	MDI	IQ	IQ	PDI	PDI	MABC total	MABC total
ECMO								
1	104	87	106	93	81	96	P38[c]	P89
2	107	110	107	112	99	114	P93	P89
3	126	94	-	-	122	115	-	P65
4	123	120	91	90	90[c]	110	P10	P79
5	71[a,b]	92[a,b]	-[b]	82	68[c,e]	50[c,d,e]	-[c,d,e]	-[c,e]
6	127[a]	134	138	145	75	115	P89	P84
7	118[a]	98	73	67	94	100	P29	P84
8	50	50	71	80	50	68	P1[c]	P16[c]
9	77	50	80	85[a]	50[c]	60[c]	P13	P7
10	92[a]	120	113	99	59	-	P29	P54
11	94	97	98	84	105	117	P9	P3
12	67[a]	109[a]	69	86	100[c]	81[c]	P1	P5
13	115	97	95[a]	85[a]	50	86[c]	P86	P45
14	115[a]	86[a]	88	72	50[c]	-[c]	P1[c]	P1
15	127	110	126	106	110	94	P62	P65
16	50[a]	50[a]	-[a]	-	75[c]	51[e]	-[c,d,e]	-
Non-ECMO								
17	133	120[b]	110	125	85	101	P15	P26[c]
18	149	118	-♣	102	112	90	P38	P54
19	112	100	85	-♣	90	86	P19	P79
20	123	102	121[b]	116[b]	119	115	P96	P70
21	-	-	-♣	57	-	-	P5[c]	P1[c,d]
22	126	116	130	131	105	104	P79	P70
23	118	134	130	109	94	100	P84	P96
24	120	125	103[a]	-♣	92	-	P9	P65
25	120	82[a]	101[a,b]	-[a,b]	119	103	P29[c]	P70
26	107	113	-	121[b]	93	97	-	P54
27	107	120	105	108	94	90	P29	P89
28	106	96	114	132	85	100	P67	P45
29	117	124	104[a]	111[b]	131	121	P67	P36
30	111	-	-	100	99	-	-	P70
31	141	125	128	145	119	108	P79	P93
32	120	-	110	95	75	-	P16	P5
33	-	-	-	-♣	-	-	-	P18[c]
34	104	-	-	110	98	-	-	-
35	98[a]	-[a]	-	-[a,b]	50[c]	-[c,d]	-	-[c,d]

MDI=mental development index; PDI=psychomotor development index; IQ=intelligence quotient; MABC total=movement assessment battery for children, total percentile score. Support: [a]Speech Therapy; [b]Psychologist/social work; [c]Physiotherapy; [d]Occupational Therapy; [e]Rehabilitation Therapy.♣ No IQ calculated due to a disharmonic profile. - No follow-up data available.

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CHAPTER 6

Memory skills, executive functioning and emotional/behavioural outcome after neonatal ECMO: preliminary findings at 18 years of age

ABSTRACT

Objective

Reporting preliminary outcome in 19 adolescents treated with neonatal extracorporeal membrane oxygenation (ECMO) between 1991 and 1995.

Methods

Memory was assessed with two subtests of the Kaufman Adolescent and Adult Intelligence Test (n=14); one subtest of the Wechsler Adult Intelligence Scale (n=7); and Rey's Auditory-Verbal Learning Test (n=13). Executive function (EF) was assessed with the Tower Test (n=15); Stroop (n=7); Trail Making Test (TMT) (n=7); and parent-reported Behavior Rating Inventory of Executive Function (BRIEF) (n=12). In addition: self-esteem (Self Perception Profile for Adolescents: n=19); behaviour (Youth Self Report: n=18); and health status (Pediatric Quality of Life Inventory: n=17) were assessed. Six adolescents' intelligence and concentration had been assessed at ages eight and twelve years as well.

Results

Fifty percent of the patients had problems with immediate and delayed recall of visual memory, 57% with delayed recall for stories, 46% and 57% respectively, with immediate recall for words and for numbers; all significantly more than expected from the norm population ($p \leq 0.02$). Planning skills (Tower Test, $p=0.721$), inhibition (Stroop, $p=0.462$) and cognitive flexibility (TMT, $p=0.902$) were in the normal range. Significantly more problems were found for working-speed (TMT; in 57% of patients, $p=0.015$). Parent-reported EF skills (BRIEF) and self-reported self-esteem, behaviour and health status were within normal range. Two of the six adolescents assessed earlier showed below average intelligence, and three and four adolescents had working-speed problems at age eight and twelve years, respectively.

Conclusions

Memory problems and decreased working-speed seem to be long-term problems in adolescents following neonatal ECMO. Future studies in neonatal ECMO survivors need to focus on the longitudinal outcome of specific cognitive skills such as memory skills and working-speed.

INTRODUCTION

Neonatal extracorporeal membrane oxygenation (ECMO) stabilizes and supports critically ill newborns with acute, and potentially reversible, respiratory failure[1,2]. It is commonly used to treat neonates with congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS) and sepsis[2,3]. Internationally, the reported overall survival rate for neonates treated with ECMO has been 75%[3].

We previously reported subtle cognitive problems in the areas of concentration and behaviour, with increased need for special education or extra support at regular education, in a cohort of eight-year-old neonatal ECMO survivors with overall normal intelligence (see Chapter 4). These problems are not unusual for children treated with neonatal ECMO[4-7]. In another cohort, i.e. eight-year-old CDH patients treated with or without ECMO, we found overall normal intelligence with significantly lower intelligence for the children treated with ECMO. All CDH patients (with and without ECMO) experienced concentration and behavioural attention problems[8]. Considering neurodevelopmental outcomes until school age, long-term follow-up into adolescent age is warranted in survivors of neonatal ECMO.

To develop academic, behavioural and social functioning, interrelated neuro-cognitive processes – called executive functioning (EF) – are needed[9,10]. These skills are developed in early childhood, but not entirely before young adulthood[11]. Because EF is important to respond to new and unexpected stimuli, poor EF may cause problems with functioning in a complex and demanding environment[12]. EF skills consist of: inhibitory control (i.e. suppression of responses to irrelevant stimuli), working-memory (i.e. capacity to store and manipulate information), cognitive flexibility (i.e. alternation between mental strategies when resolving a problem), planning (i.e. development of strategies to resolve a problem) and fluency (i.e. generating as many solutions as possible for a particular problem)[13-15]. Problems with attention and EF have been found in neonatal intensive care unit survivors at school age[16-18]. Because children treated with neonatal ECMO seem to experience problems with concentration and attentional behaviour[4-8], without an overall cognitive deficit, poor EF may contribute to their problems. To confirm this assumption, we

evaluated neuropsychological outcome in terms of EF for adolescents treated with neonatal ECMO. We do not know of any other follow-up study in a similar cohort.
The aim of the present study was two-fold. First, we wanted to – cross-sectionally – evaluate neuropsychological functioning in terms of memory, EF skills and social-emotional functioning of all participants. Second, we wanted to evaluate the longitudinal outcome (from age eight to 12 to 18 years) of six of them whose intelligence and concentration had also been assessed at ages eight and 12 years.

MATERIALS AND METHODS

Population

A follow-up study was conducted in the years 2009-2013 for patients who had received veno-arterial neonatal ECMO support between February 1991 and December 1995 at the intensive care unit of the Erasmus MC-Sophia Children's Hospital in Rotterdam. ECMO support was given in case of reversible severe respiratory failure and an estimated mortality risk of higher than 80% using the criteria reported by Stolar and colleagues[19]. Treatment protocol included cerebral ultrasound (CUS) once prior to and daily during ECMO-treatment. Inclusion and exclusion criteria were previously described[20-22] and did not change during the study period. The study was part of a structured prospective post-ECMO follow-up program initiated in 2001 in which lung function, growth and developmental parameters are regularly assessed until 18 years of age[20,22].The assessment protocol is the standard of care in the Netherlands. The Erasmus MC Medical Ethical Review Board stated that "Medical Research in Human Subjects Act (in Dutch: "WMO") does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed". Therefore IRB approval was waived. All participants and their parents were informed about the study and provided permission to use the data for research purposes.

Design

At follow-up parents completed questionnaires on socio-economic status (SES; based on maternal education)[23] and ethnicity (Dutch/ (if one of parents is) non-Dutch). The adolescents underwent a structural psychological assessment performed by a licensed developmental psychologist. The following clinical data were retrieved

from the medical records: underlying diagnosis (categorized as: CDH, MAS, other diagnoses); gestational age; birth weight; age at start ECMO; time on ECMO in hours; highest oxygenation index prior to ECMO, highest mean airway pressure prior to ECMO, duration of ventilation in days; oxygen dependency after extubation; presence of chronic lung disease (CLD) defined according to Jobe and Bancalari[24]; abnormal CUS during ECMO; the need for morphinomimetics or other sedatives (<1 week/ 1 week-1 month/ > 1 month); the use of muscle relaxants (no/ Intensive care unit (ICU) < 24 hours/ ICU 24 hours- 1 week/ ICU >1 week); presence of convulsions (no/ clinical but not tested/ confirmed on EEG); use of anti-epileptic drugs (no/ prophylactically/ therapeutically < 1 month/ therapeutically > 1 month).

The entire population (n=19) was assessed at 18 years, but not all were administered the same tests. Before the year 2012 we based the follow-up assessments on individual needs. In January 2012 we started with a structural assessment battery aimed at memory and EF, used in all patients at 18 years of age. In addition, we longitudinally evaluated intelligence and concentration in six of them who had been examined also at ages eight and 12 years).

Instruments used at age 18 years

Cognitive tests and behavioural questionnaires developed for children and adolescents were administered to assess skills in three domains[25-33]. All tests and questionnaires were administered in their Dutch versions:

1. **Memory skills**: four subtests of the Kaufman Adolescent and Adult Intelligence Test (KAIT; verbal memory for symbols immediate and delayed recall and auditory memory for stories immediate and delayed recall), Rey Auditory-Verbal Learning Test (AVLT; immediate and delayed recall), one subtest of the Wechsler Adult Intelligence Scale Third Edition (WAIS-III; digit span forward and backward).
2. **Executive functioning**: Tower Test (planning), Stroop Color-Word Test (Stroop; color-word score represents working-speed; interference score represents inhibition); Trailmaking Test (TMT A + B represent working speed; TMT B-A represents cognitive flexibility); Behavior Rating Inventory of Executive Function (BRIEF; parent-report).

3. **Social-emotional outcome**: Self Perception Profile for Adolescents (SPPA; self-esteem), Youth Self Report (YSR; behaviour), Pediatric Quality of Life Inventory (PedsQL; health status).

Instruments used at ages 8 and 12 years

Intelligence was assessed with the Revised Amsterdam Intelligence Test (RAKIT)[34] at eight years and the Wechsler Intelligence scale - third edition[35] at 12 years. Concentration (working-speed and accuracy) was assessed with the Bourdon-Vos at both ages; as previously described[8].

Data analysis

For the subtests of the KAIT, WAIS-III and Tower Test a subtest score ≤7 was indicative of a problem/ impaired outcome (16% in norm population). For the AVLT, TMT and Stroop a T-score of ≤40 was indicative of a problem/ impaired outcome (16% in norm population). For the BRIEF a T-score >65 was indicative of a problem/ impaired outcome (9% in norm population). For the YSR a T-score of >70 on the behavioural scales (2% norm population) and a T-score of >63 on the three domain scales was indicative of a problem/ impaired outcome (10% norm population). For the SPPA a percentile score of <15 was indicative of a problem/ impaired outcome (16% norm population). For the PedsQL a score of -1 SD compared to the reference sample[27] was indicative of a problem/ impaired outcome.

Mean subtest scores were compared to Dutch normative data with the Wilcoxon signed rank test. Percentages of subtest scores were compared to normative proportions using Fisher's-exact tests or binomial tests.

Patients

Between February 1991 and December 1995 54 children were treated with neonatal ECMO. Seventeen (31%) had died (n= 9 CDH/ n=3 MAS/ n=9 other diagnosis). Eleven of the 37 survivors (30%) were excluded from follow-up for different reasons (n=4 follow-up elsewhere, n=1 late death (CDH), n=4 refusal, n=2 moved). Twenty-six were eligible for follow-up at age 18 years, which represents 70% of the surviving cohort. However, seven adolescents were not available for assessment (n=3 refusal, n=1 moved (he attended special education at 12 years of age), n=3 not testable or

tested elsewhere because of problems). Medical and socio-economic characteristics were evaluated for all 19 children who underwent neuropsychological assessment (Table 1). Medical characteristics did not differ between participants and non-participants (data not shown). As not all adolescents were administered the same tests we report for each test the number of participants. One patient with CDH and with retardation (chromosome X-duplication) could only fill in questionnaires on self-esteem, behaviour, and health status.

TABLE 1 Medical and socio-demographic variables

	n=19
Diagnosis	
MAS	10 (53%)
CDH	4 (21%)
Other	5 (26%)
Gestational age in weeks	40 (36-43)
Birth weight in grams	3360 (2180-4980)
Age start ECMO in hours	28 (12-226)
Time on ECMO in hours	124 (47-192)
Highest oxygenation index prior to ECMO	54 (33-95)
Highest mean airway pressure prior to ECMO	20 (14-26)
Duration of ventilation in days	10 (4-37)
Oxygen dependency after extubation	
1 day- 1 week	9 (47%)
>1 week- 1 month	2 (11%)
>1 month	6 (32%)
missing	2 (11%)
CLD	
yes	6 (32%)
no	11 (58%)
missing	2 (11%)
Abnormal cerebral ultrasound during ECMO	
Yes	1 (5%)
Missing	2 (11%)
Morphinomimetics and sedatives	
< 1 week	6 (32%)
1 week- 1 month	10 (53%)
> 1 month	3 (16%)
Use of muscle relaxants	
No	1 (5%)
ICU < 24 hours	7 (37%)
ICU 24 hours- 1 week	8 (42%)
> 1 week	3 (16%)
Convulsions	
No	14 (74%)
Clinical, but not tested	4 (21%)
Confirmed on EEG	1 (5%)
Use of anti-epileptic drugs	
No	9 (47%)
Prophylactically	5 (26%)
Therapeutically < 1 month	3 (16%)
Therapeutically > 1 month	2 (11%)
Male gender	9 (47%)
Dutch ethnicity	12 (63%)
SES	
High	1 (5%)
Moderate	6 (32%)
Low	10 (53%)
Missing	2 (11%)

Results are displayed as n (%) or median (range). MAS = meconium aspiration syndrome; CDH = congenital diaphragmatic hernia; other = pneumonia (n=1), persistent pulmonary hypertension in the newborn (n=3), pulmonary hypoplasia due to kidney failure (n=1); ECMO = extracorporeal membrane oxygenation; CLD = chronic lung disease as defined by Jobe and Bancalari[24]; SES = socio-economic status based on maternal education[23]. Abnormal CUS = watershed injury.

CROSS-SECTIONAL EVALUATION OF ALL ADOLESCENTS (n=19)

Memory skills

Visual memory for symbols (KAIT subtests n=14)

When compared to normative data, the adolescents scored significantly lower on the symbols immediate recall memory subtest (median (Interquartile range (IQR): 8 (1-12); p= 0.022) but not on the symbols delayed recall memory subtest (median (IQR): 8 (1-14); p= 0.093) (Figure 1 A). Seven adolescents (50%) had problems both with immediate recall memory and delayed recall memory and this percentage was significantly greater compared to normative data (p=0.003 for each test).

Auditory memory for stories

Results of both auditory memory subtests (median (IQR)) score for immediate recall: 9 (1-12); p=0.038 and delayed recall: 6 (1-13); p=0.012) were significantly lower compared to normative data (Figure 1 B). Five (36%) adolescents scored below -1 SD for immediate recall memory (p=0.059). Problems with delayed recall memory were present in eight (57%) adolescents and this percentage was significantly greater compared with norm population proportions (p=0.001).

Auditory memory for words (AVLT n=13)

Scores on the immediate recall subtest differed from normative data (median (IQR) T-score: 41 (15-63); p=0.028) but scores on the delayed recall subtest did not (median (IQR) T-score: 50 (0-78); p=0.824). On the immediate recall subtest, six adolescents (46%) experienced problems and this percentage was significantly greater than the normative proportion (p=0.020). Three adolescents (23%) experienced problems with delayed recall memory (p=0.707) (Figure 1 C).

Auditory memory for numbers (WAIS-III subtest n=7)

Scores on the WAIS-III subtest did not differ from normative data (median (IQR): 7 (3-18); p= 0.344). However, four adolescents (57%) had an impaired outcome on auditory memory for numbers and this percentage was significantly greater compared to normative proportions (p=0.015) (Figure 1 D).

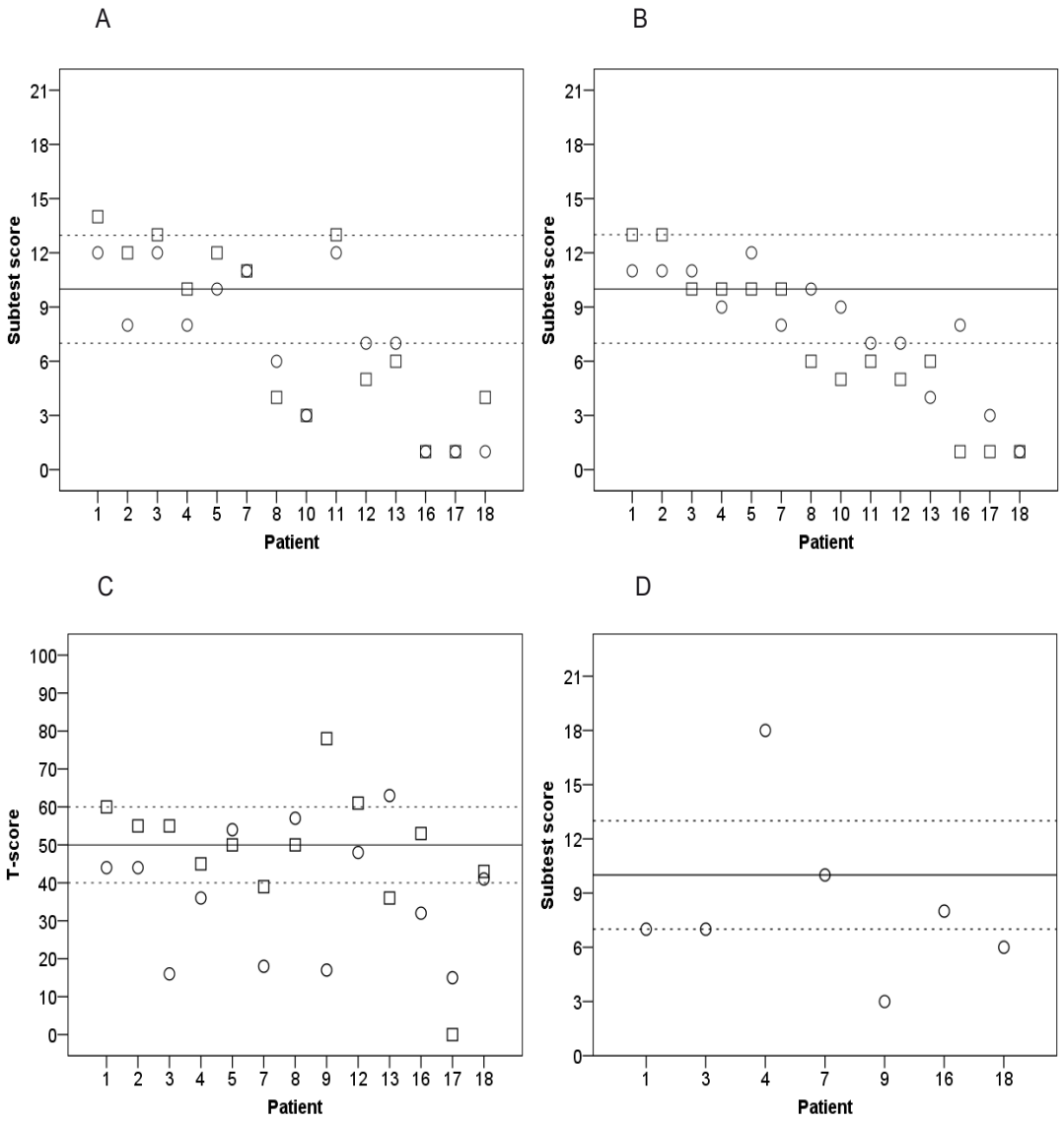

FIGURE 1 Memory

A = visual memory for symbols. B = auditory memory for stories. C = auditory memory for words. D = auditory memory for numbers. Line represents population mean, dotted lines represent -1 SD and +1 SD (of the normative population); circles represent immediate recall memory; squares represent delayed recall memory Numbers on the x-axis represent patient numbers, with each number representing the same patient for each figure.

Executive functioning

Planning (Tower Test n=15)

Scores on the Tower Test did not differ from normative data (median (IQR): 10 (3-12); p= 0.064). Three adolescents (20%) experienced problems with planning (p=0.721) (Figure 2 A).

Inhibition (Stroop n=7)

Working-speed did not differ from normative data (median (IQR) T-score: 46 (37-59); p=0.173), neither did the interference-score (median (IQR) T-score: 45 (36-70); p=0.462). Three (43%) adolescents had an impaired working-speed outcome (p=0.173), while one (14%) adolescent experienced an inhibition problem; both percentages did not differ from normative proportions (p=0.462) (Figure 2 B).

Cognitive flexibility (TMT n=7)

TMT A did not differ from normative data (median (IQR) T-score: 29 (17-69); p=0.091), neither did TMT B (median (IQR) T-score: 37 (25-57); p=0.075). TMT B-A also did not differ from normative data (median (IQR) T-score: 49 (33-54); p=0.246). For working speed (both TMT A and B), four adolescents (57% in both) had an impaired outcome and these percentages were significantly greater than normative proportions (p=0.015 for both). One adolescent (14%) experienced problems with cognitive flexibility (p=0.902) (Figure 2 C).

Parental observations of EF (BRIEF n=12)

The parents indicated significantly lower T-scores compared to normative data for planning and organization (median (IQR) T-score: 41 (36-60), p=0.012) and organization of materials (median (IQR) T-score: 41 (32-58), p=0.013). Impaired outcome was reported for inhibition (8%), initiative (8%), meta-cognition (8%), emotional regulation (25%), behaviour regulation (8%), cognitive flexibility (17%) and total problems (8%). These percentages did not different significantly from normative proportions (Figure 2 D).

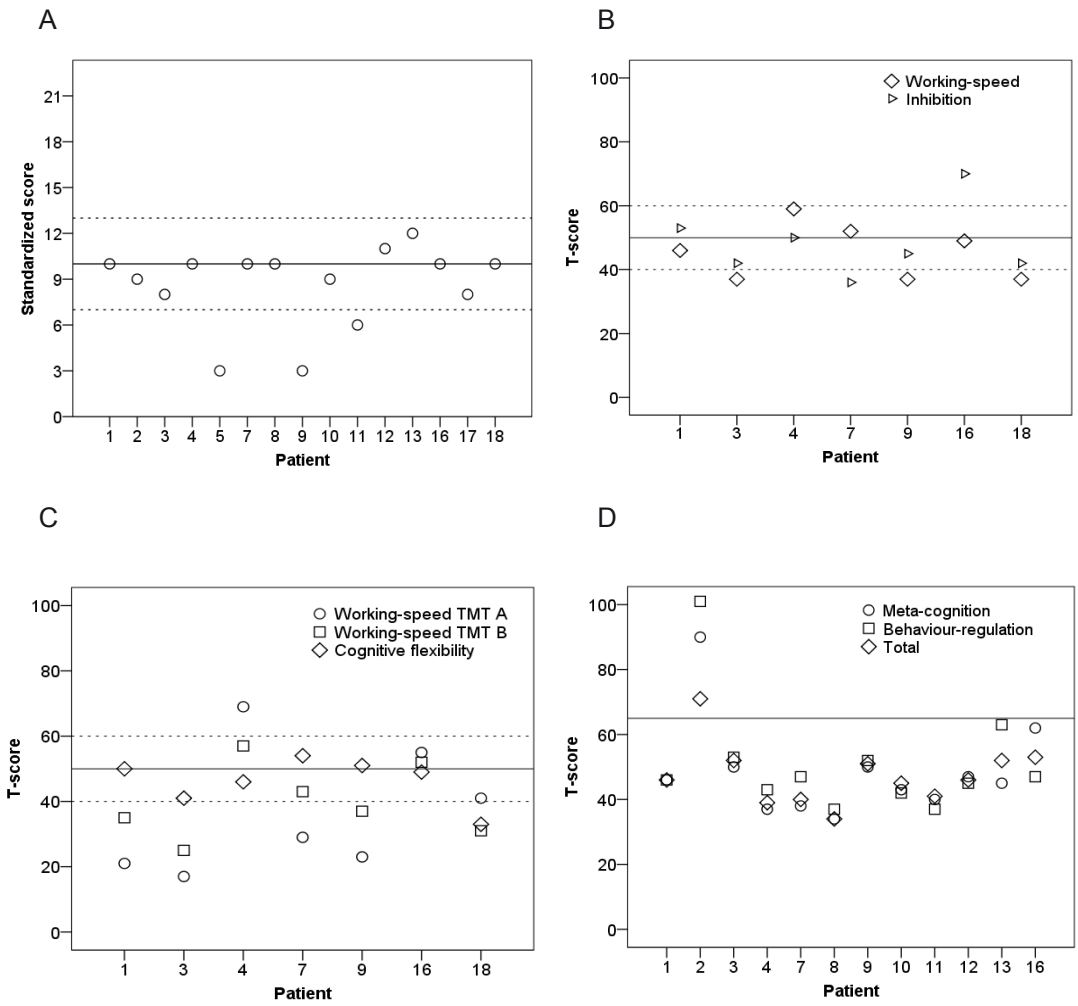

FIGURE 2 Executive function

A = planning (Tower Test). B = working-speed and inhibition (Stroop). Squares represent color-word scores; triangles represent interference scores. C = working-speed and cognitive flexibility (TMT). Circles represent TMT A scores; squares represent TMT B scores; triangles represent TMT B-A scores. Line represents population mean, dotted lines represent -1 SD and +1 SD (of the normative population). D = parent-reported executive functioning (BRIEF). Circles represent meta-cognition; squares represent behaviour regulation; triangles represent total functioning. Line represent cut-off (from the norm population) for psychopathological behaviour (T-score >65). Numbers on the x-axis represent patient numbers; with each number representing the same patient for each figure.

Social-emotional outcome

Self-esteem (SPPA n=19)

The proportions of adolescents with impaired self-esteem outcome did not differ from normative data for all domains: social skills: 16% (p=0.923), social acceptance: 26% (p=0.190), sportive skills: 26% (p=0.190), physical appearance: 11% (p=0.757), behaviour: 5% (p=0.343), friendships: 26% (p=0.190) and feeling of self-worth: 11% (p=0.757).

Self-reported emotional/ behaviour problems (YSR n=18)

On the externalising domain one adolescent (6%) scored a psychopathological score which did not differ from normative proportions (9% expected, p=0.176). For all other domains no psychopathological scores were reported.

Health status (PedsQL n=17)

The health status median (IQR) scores did not differ from normative data for all domains; physical functioning: 84 (44-100), p=0.794; emotional functioning: 80 (55-100), p=0.406; social functioning: 95 (30-100), p=0.916; school functioning: 80 (65-100), p=0.162; psychosocial functioning: 87 (50-100), p=0.381; and total functioning: 86 (45-100), p=0.381.

LONGITUDINAL EVALUATION AT EIGHT, 12 & 18 YEARS (n=6)

Table 2 provides an overview of the outcomes of the six patients whose intelligence and concentration had been assessed at ages eight and 12 years as well. At eight years of age two of them (33%) had a below average IQ and that was still true at 12 years of age. Slow working-speed was found in four (67%) and three (50%) of them at eight and 12 years, respectively.

TABLE 2 Longitudinal assessment of six patients

	Patient 1	*Patient 3*	*Patient 4*	*Patient 7*	*Patient 16*	*Patient 18*
Diagnosis	MAS	MAS	PPHN	MAS	MAS	PPHN
Gender	male	female	male	female	female	male
8 years						
IQ	N	-2 SD	+1 SD	N	N	-1 SD
Working speed	N	-2 SD	+1 SD	-1 SD	-1 SD	-2 SD
Accuracy	+1 SD	+2 SD	N	+2 SD	-1 SD	-2 SD
12 years						
IQ	N	-2 SD	N	N	N	-2 SD
Working speed	N	-1 SD	N	-2 SD	+1 SD	-1 SD
Accuracy	+1 SD	+1 SD	+1 SD	N	+1 SD	-2 SD
18 years						
Memory problems	yes	no	no	yes	no	no
Visual memory						
Immediate	N	-1 SD	N	-2 SD	N	-2 SD
Recall	N	-1 SD	N	-2 SD	+2 SD	-2 SD
Auditory memory						
Stories						
Immediate	N	-2 SD	N	N	-1 SD	-2 SD
Recall	N	-1 SD	N	-2 SD	-1 SD	-2 SD
Numbers	-1 SD	-1 SD	+2SD	N	N	-1 SD
Words						
Immediate	N	-2 SD	-1 SD	-2 SD	-1 SD	N
Recall	N	N	N	-1 SD	N	N
Executive functioning						
Planning	N	N	N	N	N	N
TMT						
Working-speed (TMT A)	-2 SD	-2 SD	N	-2 SD	N	N
Working-speed (TMT B)	-1 SD	-2 SD	N	-1 SD	N	-1 SD
Cognitive flexibility	N	N	N	N	N	-1 SD
STROOP						
Working-speed	N	-1 SD	N	N	N	-1 SD
Inhibition	N	N	N	-1 SD	+1 SD	N
BRIEF problems	no	no	no	no	emotional regulation	-

N= normal range (within -1 and +1 SD); SD=standard deviation; MAS = meconium aspiration syndrome; PPHN = persistent pulmonary hypertension of the newborn; IQ = intelligence quotient. TMT=Trail Making Test; BRIEF= Behavior Rating Inventory of Executive Function. At 8 and 12 years: working-speed and accuracy is measured with the Bourdon-Vos. At 18 years: memory problems are self-reported by the adolescent. Planning is measured with the TOWER. For TMT: working speed is measured with TMT A and TMT B; cognitive flexibility is measured with TMT B-A. For Stroop: working speed is measured with the color-word score. Inhibition is the 'interference effect' of the Stroop test. BRIEF problems are proxy-reported by the parents on the BRIEF questionnaire.

DISCUSSION

We presented preliminary outcome of memory skills, EF and social-emotional outcome in a cohort of adolescents treated with neonatal ECMO. To our knowledge, this study is the first to evaluate neuropsychological outcome at this age in this population.

McNally and coworkers (United Kingdom randomized Trial) reported for a cohort of seven-year-old neonatal ECMO patients specific patterns of learning difficulties with global cognitive loss, poor spatial and processing skills as well as difficulties with reading comprehension and visual and auditory memory. They concluded that poorer processing skills combined with poor spatial abilities might have resulted in the low scores in visual memory testing. Overall, at seven years of age the children experience difficulties with both visual and spatial information-processing[7]. Previously we found average intelligence overall in eight-year-olds treated with neonatal ECMO, however, with subtle problems in the area of concentration. The children had slower working-speed and they were less accurate on a concentration test (see Chapter 4). In line with McNally and coworkers, we found visual memory problems for both immediate and delayed recall of symbols in the present study. We also found auditory memory problems for delayed recall for stories, immediate recall for number and immediate recall for words. Concerning EF: planning, inhibition and cognitive flexibility seem within normal range, however, the adolescents seem to experience problems with working-speed. This is in line with what we found for eight-year-olds (see Chapter 4). In the present study, parents reported EF skills in the normal range on the BRIEF. Since the level of agreement between the BRIEF and well-established EF cognitive tasks is at best modest[36], the BRIEF provides unique information in addition to the structured assessment of EF skills and is specifically sensitive to EF skills in every-day life.

Positively, self-reported emotional and behavioural functioning seems not affected. Self-esteem and emotional-behaviour problems were not more frequent in these adolescents when compared with Dutch normative data. Also, health status outcome was not different from healthy Dutch adolescents. This is not an unusual finding. In a study with adolescent preterm born children, the vast majority reported to be satisfied

with their activities and participation in society even though most of them where neither at school or employed at age 19[37]. In studies in children with congenital anomalies treated with or without neonatal ECMO, we also found that self-reported emotional-behaviour was not affected[8,38].

We additionally evaluated the separate longitudinal outcome of six patients (from the entire cohort) from the age of eight to 12 to 18 years. At eight years of age two of them had a below average IQ and that was still true at 12 years of age. Most of them showed slow working-speed on a concentration test at eight and/or 12 years. Like the other adolescents in the cohort these six showed a trend of problems with memory skills for both immediate and delayed recall at 18 years of age. Two of them explicitly reported memory problems in daily life. Most EF skills – with the exception of working-speed – were within normal range. Parents reported emotional regulation problems in daily life for one patient. Emotion regulation/control reflects the ability to control emotions. These regulatory processes are not only important for the organization of a cognitive activity, but are also essential for social-adaptive behaviour[9]. One of the behaviour problems of non-regulated emotions is impulsive behaviour[9]. Attentional behaviour problems, specifically hyperactivity, are not uncommon findings in children treated with neonatal ECMO[7].

Further research should identify whether these adolescents experience more immediate recall than delayed recall problems. If they do, there is a good chance that the capacity of the working-memory as well as working-speed/ information-processing speed is the underlying cause for their memory problems. Research has shown that more information must be stored in the working-memory and information must be processed faster when a task gets more demanding[39-41]. It might well be that children/adolescents treated with neonatal ECMO have a limited capacity to store, integrate and manipulate information in their working-memory and process information across the brain at lower speed. This might explain why the neonatal ECMO survivors seem to experience increasing – subtle – academic problems as they get older.

A limitation of this study is the small cohort size. This is why we consider the outcomes of this study as ‘preliminary’. Still, this is a pioneer study because we are

the first to report on neuropsychological outcome at adolescent age for this population. The outcomes will serve to provide guidelines for the content of future long-term follow-up assessments in neonatal ECMO survivors. Furthermore, only data of adolescents able to perform the assessments were used in the present study. Five of the 26 eligible patients had serious learning disabilities (four of them were not assessed; one could only fill in questionnaires on emotional/ behavioural outcome). This might have led to selection bias. Since this cohort represents those patients treated at the beginning of the neonatal ECMO era (1991-1995) they received ECMO treatment at a later stage than current practice, and – concomitantly –they may have suffered from prolonged hypoxia. However, from the available data in the medical records (e.g. oxygenation index prior to ECMO or age at the start of ECMO) it is hard to find convincing evidence to support this assumption. Future, prospective studies should focus on evaluating which medical factors cause cerebral damage (and therefore cause delayed neurodevelopmental outcome) and in what way 'severity of illness' at neonatal age is of influence on the development of the brain. For children born preterm (who experience similar outcome problems as neonatal ECMO survivors) abnormal image phenotype is associated with impaired mental outcome at two years of age[42]. Standardized registration of baseline characteristics may help elucidate which factors contribute to long-term neuropsychological problems.

CONCLUSION

Preliminary outcomes suggest problems with memory skills and working-speed in adolescents of 18 years of age who received ECMO treatment at neonatal age. Self-esteem, emotional/ behaviour and health status might not be affected at this age. Considering the outcome at school age and the preliminary findings at adolescent age; future studies in neonatal ECMO survivors need to focus on the longitudinal outcome of specific cognitive skills such as memory skills and working-speed.

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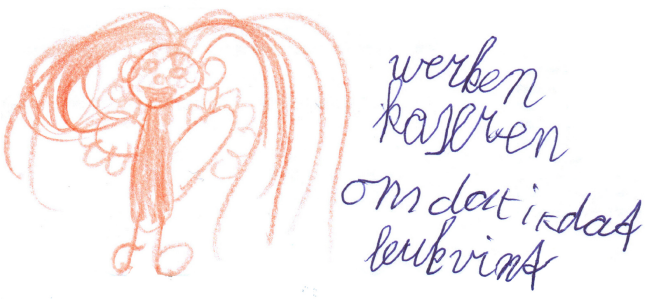
“THIS IS ME”

Girl, 5 years old

This is me at the hospital

This is me now



This is me when I am grown up

PART 2

Psychological functioning

CHAPTER 7

Follow-up of children treated with extracorporeal membrane oxygenation: impaired health at 5 years of age

Marlous J. Madderom, Saskia J. Gischler, Hugo Duivenvoorden, Dick Tibboel, Hanneke IJsselstijn

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ABSTRACT

Objective

Children treated with neonatal Extra Corporeal Membrane Oxygenation (ECMO) may show physical and mental morbidity at later age. We compared the health-related quality of life (HRQOL) of these children with normative data.

Design and setting

Prospective longitudinal follow-up study in a outpatient clinic of a III level university hospital.

Patients and measurements

Ninety-five 5-year-olds who had received neonatal ECMO support between January 1999 and December 2005 were administered the Pediatric Quality of Life Inventory (PedsQL).

Main results

The mothers (n=74) as proxy-reporters assigned significantly lower HRQOL scores for their children than did the parents in the healthy reference group for the total functioning scale of the PedsQL (mean difference:8.1, $p<0.001$). Mothers' scores for 31 children (42%) were indicative of impaired HRQOL (≥-1 SD below the reference norm). The children (n=78) themselves scored significantly lower than did their healthy peers on total functioning (mean difference:11.0, $p<0.001$). Thirty-two children (41%) indicated an impaired HRQOL themselves. For the mother proxy-reports, duration of ECMO support ($R^2=0.009$, $p=0.010$) and the presence of chronic lung disease ($R^2=0.133$, $p=0.002$) were negatively related to total functioning. Children with a disabled health status for neuromotor functioning, maximum exercise capacity, behavior and cognitive functioning at five years of age had a higher odds ratio of also having a lower HRQOL. Health status had no influence on reported emotional functioning.

Conclusions

Overall, children treated with ECMO in the neonatal period reported low HRQOL at 5 years of age. Because only emotional HRQOL was not associated with health status, the PedsQL might be a measure of health status rather than of HRQOL. In contrast with conclusions from others we found that 5-year-old children might be too young to rate their own HRQOL.

INTRODUCTION

Neonatal extracorporeal membrane oxygenation (ECMO) is used to stabilize and support critically ill newborns with acute, and potentially reversible, respiratory failure. Neonatal ECMO treatment has been shown effective in, for example, meconium aspiration syndrome (MAS) and sepsis[1,2]. Its use in congenital diaphragmatic hernia (CDH) is disputed[3] because CDH survivors are at high risk of developing secondary morbidity such as chronic lung disease and persistent pulmonary hypertension[4-6]. However, morbidity at later age seems to illustrate the severity of the underlying conditions rather than the effect of ECMO treatment[2]. Therefore, it is imperative to evaluate morbidity for these patients.

One way to evaluate morbidity is to assess the health status (HS) and the health-related quality of life (HRQOL). HS is defined as the ability to function normally in everyday live; HRQOL is defined as the impact of the HS on the quality of life[7]. The Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales measures HRQOL in children[8]. The PedsQL uses the three health dimensions (physical functioning, mental functioning and social functioning) as indicated by the World Health Organization[9]. In addition, school functioning can be assessed[10]. The PedsQL is either filled in by the children themselves (self-report for ages 5 to 18 years) or by the parents (proxy-report for ages 2 to 18 years).

A PedsQL study in 5 to 18-year-old children with a chronic disease indicated lower physical, emotional, social, and school functioning compared to healthy age peers[11]. However, the medical diagnoses of these children differ from those of children treated with ECMO. Impaired functioning in physical and psychosocial domains was reported by parents for 8 of 22 children (mean age 7.2 years) treated with neonatal or pediatric ECMO, mainly for cardiac failure[12]. A study in our own institution evaluated symptoms and impairments in addition to HRQOL in children with primarily the diagnosis of CDH; analysis indicated that symptoms and impairments are imperfect predictors of HRQOL and that not every impairment results in a lower HRQOL[13].

The aim of the present study was to determine the HRQOL of children treated with ECMO in the neonatal period using both PedsQL parent proxy-reports and child self-reports at 5 years of age. In addition, we evaluated (dis)agreement between parents' and children's reports. Following on to previous HRQOL studies, we also evaluated the influence of the HS of these children on their HRQOL.

MATERIALS AND METHODS

Population

A follow-up study was conducted in neonates who received ECMO support between January 1999 and December 2005 at the intensive care unit of the Erasmus Medical Center-Sophia Children's Hospital in Rotterdam. ECMO support was given in case of reversible severe respiratory failure and an estimated mortality risk of higher than 80% using the entry criteria reported by Stolar and colleagues[14]. Entry criteria and exclusion criteria were previously described by our group[15-17] and did not change during the study period. The study was part of a structured prospective post-ECMO follow-up program initiated in 2001 in which lung function, growth and developmental parameters are regularly assessed until 18 years of age[15,17]. The assessment protocol is the standard of care in the Netherlands. The Medical Ethical Review Board Erasmus MC stated that “Medical Research in Human Subjects Act (in Dutch: "WMO”) does not apply to this study, since subjects are not being submitted to any handling, nor are there rules of human behaviour being imposed”. Therefore IRB approval was waived. All parents were informed about the study and provided written permission to use the data for research purposes.

The following medical characteristics were recorded prospectively: underlying diagnosis, gestational age, birth weight, age at onset of ECMO, duration of ECMO support, highest mean airway pressure (MAP), highest oxygenation index (OI) prior to ECMO, total duration of mechanical ventilation (including ECMO), duration of oxygen dependency and presence of chronic lung disease (CLD) according to the definition of Jobe and Bancalari[18].
Sociodemographic variables were gender of the child; ethnicity of the parents and socioeconomic status (SES; based on education of the primary caregiver divided by low, moderate and high socioeconomic status)[19].

The children’s HS at 5 years of age was classified into eight clinical domains (cognitive ability, behavior, neuromotor skills, maximum exercise capacity, general health, scoliosis, hearing and vision), adapted from the outcome classification table of the United Kingdom Collaborative Randomized Trial (UK trial)[1].

Assessment of HS

Cognitive ability

The short version of the Revised Amsterdam Intelligence Test (RAKIT) was administered. The RAKIT is a Dutch standardized instrument with good psychometric properties and has been used in previous studies with ECMO-treated children[15]. Children with an IQ≥85 and following regular education were classified as normal.

Behaviour

The Dutch version of the Child Behavior Checklist and the Teacher's Report Form were completed by parents and teachers, respectively. Both have been standardized for the Dutch population from 4 to 18 years old, and the Child Behavior Checklist has been used previously[15,20]. Children with a total score <60 were classified as having normal behavior.

Neuromotor skills and maximum exercise capacity

Motor development was assessed with the Movement Assessment Battery for Children (M-ABC)[15,21]. It evaluated three domains: manual dexterity, ball skills, and three balance items. Using percentile normative data tables, the total impairment score (TIS) and the three domain scores were interpreted as percentile scores. TIS at or below the 5th percentile is indicative of a motor problem, TIS between the 6th and 15th percentile of a borderline motor problem, TIS above the 15th percentile is considered normal. Children with a TIS percentile score ≥16 and normal findings at neurological examination were classified as normal.

The maximum exercise capacity test consisted of a treadmill test according to the Bruce protocol. The maximal endurance time was used as criterion of exercise capacity and was compared to the Dutch norm[22]. The maximum exercise capacity was considered normal when a standard deviation (SD) score of -1 or higher was obtained.

General health, scoliosis, hearing and vision

Prior to the follow-up visit, the parents filled in questionnaires, which included questions on their children's use of visual or hearing aids and use of medication. During the visit, a complete medical assessment was done including tone audiometry

and evaluation of physical problems which may affect HS, e.g. neurological impairment or scoliosis.

Assessment of HRQOL

HRQOL was assessed with the PedsQL. The PedsQL encompasses 23 items on four scales: physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items). A psychosocial functioning scale can be derived from the emotional, social and school functioning items, All 23 items together provide the total functioning score. Each of the 23 items states a problem. The parent indicates on a 5-point Likert scale the frequency with which the child experiences the problem. Response categories are never (0), almost never (1), sometimes (2), often (3) and almost always (4). For the child self-report (age 5-7), the response scale was simplified to a 3-point faces scale; never (0), sometimes (2) almost always (4), with each response choice anchored with a happy to sad face. Feasibility, reliability and validity testing of the PedsQL yielded good results[23]. The Dutch version of the PedsQL has adequate psychometric properties and can be used as a HRQOL instrument in pediatric research in the Netherlands[24]. A scale score of 1 SD below the healthy reference norm was taken to indicate impaired HRQOL[25].

Design

Before the follow-up at 5 years of age, the parents were invited to complete questionnaires at home concerning sociodemographic status and the child's current general health, emotional and behavior problems and HRQOL. Parent couples were asked to fill in these questionnaires individually. During the follow-up assessment, the children themselves filled in the PedsQL under supervision of a developmental psychologist. For all the children the questions and answers were read out loud.

Data analysis

Perinatal and medical characteristics of the children participating in the follow-up were compared with those of the non-participating children (e.g. lost to follow-up, refusal to participate). When continuous data were not distributed normally, the Mann Whitney test was used and medians and interquartile range (IQR) were presented. Pearson χ^2 test or Fisher's exact test served to evaluate categorical data.

Independent sample t-tests evaluated the parent proxy-reports with published Dutch PedsQL population norms for parent proxy-reports[24]. The child self-reports were compared to published American PedsQL population norms because there are no Dutch reference norms for 5-year-old children's self-reports[26].

Differences between mother and father proxy-reports and between parent proxy-reports and child self-reports were tested by paired sample t-tests. Intraclass correlation coefficients (ICC) were calculated to evaluate the levels of agreement. The levels of agreement were designated as poor to fair (≤0.40), moderate (0.41-0.60), good (0.61-0.80) and excellent (0.81-1.00). Internal consistency of the scales for parents and child were calculated using Cronbach's alpha. A cut-off point of 0.70 was considered suitable[27].

Influences of the medical variables on the mother proxy- report total functioning scale of the PedsQL were calculated using linear regression analysis. The variables were individually entered in 8 regression analyses to avoid the risk of multicollinearity. The influences of the sociodemographic variables on the total functioning scale of the PedsQL were calculated using multiple linear regression analysis. Normal probability plots were evaluated to test the applicability of the model and the assumptions for regression analysis. Multicollinearity was tested using the criteria that variance inflation factors should not exceed 2.5[28] and the average variance inflation factor should not be substantially greater than 1[29].

The influence of the child's HS on HRQOL was calculated using odds-ratios. Crosstabs served to calculate the unadjusted odds-ratio of having disabled HS (impaired, mild disability, moderate disability and severe disability classifications combined) on any of the 8 domains and having impaired HRQOL (≥-1 SD below the reference norm) on any of the PedsQL scales. Logistic regression calculated the adjusted odds-ratios (adjusted for gender and SES).

A p-value smaller then 0.05 (two-tailed) was considered statistically significant.

RESULTS

Patient sample

A total of 171 children were treated with neonatal ECMO between January 1999 and December 2005 (Figure 1). Forty-six children (27%) died during their first hospitalization. Of the 125 children who survived, 103 participated in the follow-up

program. However, for 8 children PedsQL questionnaires were not available (neither child self-report nor parent proxy-report). Thus, data of 95 children were included.
Seventy-eight children completed the PedsQL self-report; 17 did not for the following reasons: different follow-up assessment provided (n=3); cognitive developmental problems (n=2); language developmental problems (n=4; for two children due to living abroad); recently tested elsewhere (n=2); organisational reasons (n=6, i.e., not enough time to complete entire assessment battery).
In total 128 parent proxy-reports were available: 54 father proxy-reports and 74 mother proxy-reports. For 17 children no parent proxy-report was available for different reasons (n=3 language barrier; n=4 refusal; n=10 organisational reasons). Thus, a total of 206 PedsQL's were available (see Figure 1). An overview and evaluation of perinatal and ECMO characteristics for participating and non-participating children is shown in Table 1.

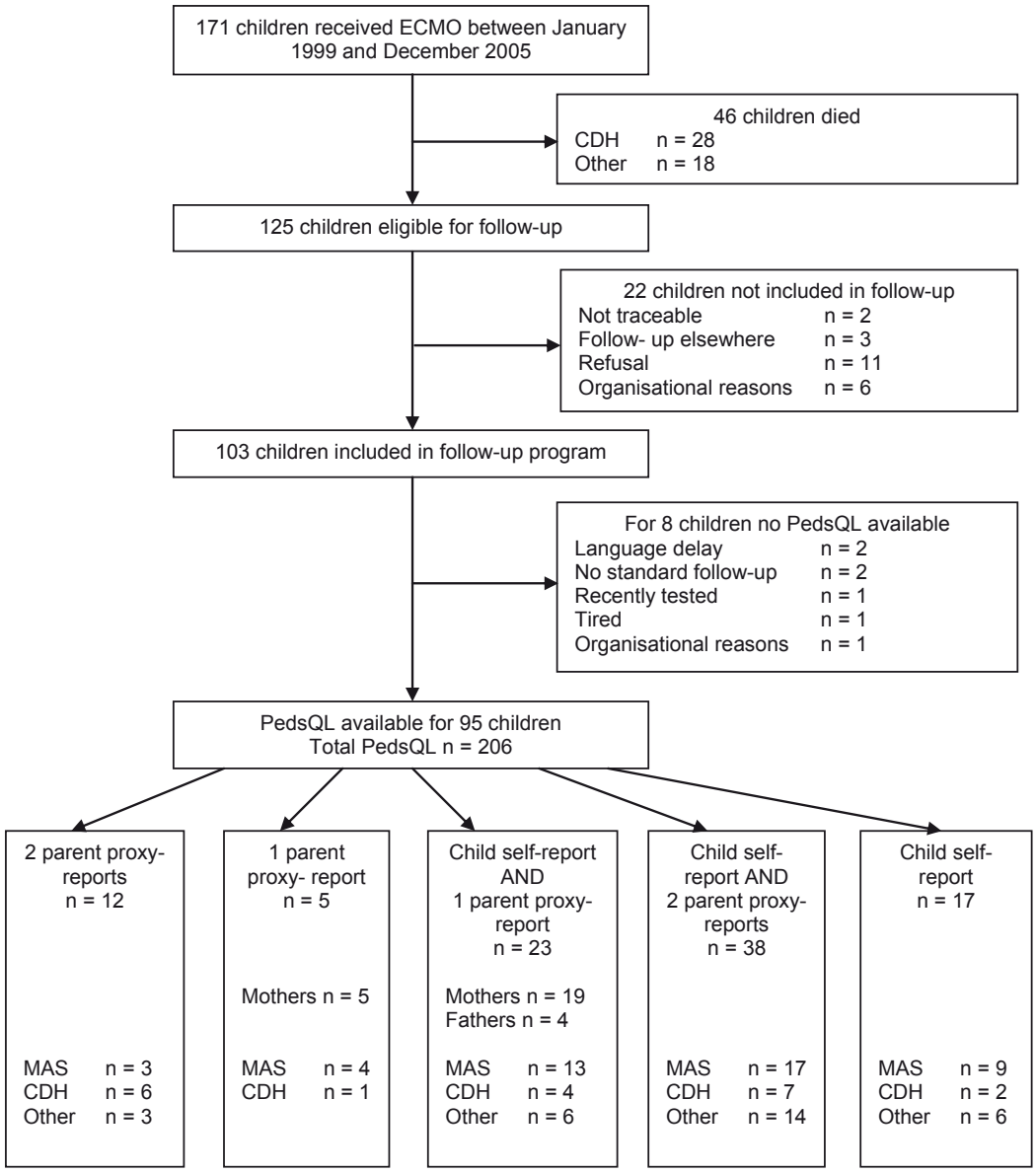

FIGURE 1 Flowchart

ECMO = Extra Corporeal Membrane Oxygenation; CDH = Congenital Diaphragmatic Hernia; Other = Sepsis, persistent pulmonary hypertension of the newborn, asphyxia, respiratory syncytial- infection, cardiorespiratory failure and pneumonia; PedsQL = Pediatric Quality of Life Questionnaire; MAS = Meconium Aspiration Syndrome

TABLE 1 Background characteristics

	Participating	Non-participating	p-value
Number of subjects	95	30	
Diagnose			0.987
MAS	46 (48%)	15 (50%)	
CDH	20 (21%)	6 (20%)	
Other	29 (31%)	9 (30%)	
Gestational age in weeks[a]	40 (39-41)	40 (38-41)	0.028
Birth weight in grams[a]	3500 (3000-3750)	3000 (2802-3300)	0.004
Age at start ECMO in hours	24 (14-58)	24 (14-51)	0.719
Duration of ECMO support in hours	120 (84-171)	154 (109-196)	0.084
Mean airway pressure in cmH_2O	19 (17-22)	20 (18-22)	0.454
Oxygenation index	40 (30-50)	45 (32-56)	0.279
Ventilation time in days (including ECMO)[a]	11 (8-19)	19 (12-29)	0.003
Duration of oxygen dependency			0.693
1 day- 1 week	44 (46%)	11(37%)	
1 week- 1 month	29 (31%)	11 (37%)	
> 1 month	10 (11%)	3 (10%)	
Unknown	12 (14%)	5 (17%)	
CLD[a]			0.035
Yes	17 (18%)	12 (40%)	
No	71 (75%)	13 (43%)	
Unknown	7 (9%)	5 (17%)	
Male gender	47 (50%)	18 (60%)	0.314
Dutch ethnicity	59 (62%)	na	-
SES			-
Low	24 (25%)	na	
Moderate	35 (37%)		
High	24 (25%)		
Missing	12 (13%)		

Data are presented as median (interquartile range) or n (%). MAS=meconium aspiration syndrome; CDH=congenital diaphragmatic hernia; other=sepsis; persistent pulmonary hypertension in the newborn; asphyxia, respiratory syncytial-infection, cardiorespiratory failure and pneumonia; CLD=chronic lung disease; SES=socioeconomic status. na=data not available. [a]Significantly different between participants and non-participants.

Comparing HRQOL with the healthy reference group

Parent-proxy reports

Before comparing the parent proxy-reports with their reference group, we analyzed the difference in PedsQL scores reported by the mothers and fathers. For 50 children both parents filled in a PedsQL report (a total of 100 PedsQL's). For all scales, scores of mothers and fathers differed to some extent, with the fathers being the more positive evaluators: physical functioning (mean difference (md):6.8, p<0.001); emotional functioning (md:4.6, p=0.06); social functioning (md:1.1, p=0.55); school functioning (md:3.8, p=0.09); psychosocial functioning (md:3.2, p=0.07) and total functioning (md:3.9, p=0.02).

In addition, the ICC was calculated to indicate the extent of agreement on the individual PedsQL questions. The ICC between mothers and fathers for physical functioning (ICC:0.52) and school functioning (ICC:0.42) indicated moderate agreement. Emotional functioning (ICC:0.27), social functioning (ICC:0.34), psychosocial functioning (ICC:0.25) and total functioning (ICC:0.28) showed poor agreement between mothers and fathers.

Because of the above-mentioned differences and low agreement between mothers and fathers proxy-reports, and also because the Dutch healthy reference group consisted of almost 90% mother proxy-reports, we decided to only compare the 74 mother proxy-reports with the reference group. Overall, for 31 children (42%) the mothers indicated a score of ≥-1 SD below the reference mean on the total functioning scale of the PedsQL. These children were considered to have impaired HRQOL.

Mothers scored significantly lower than the parents from the healthy reference group on physical functioning (md:10.5, $p<0.001$), social functioning (md:9.3, $p<0.001$), school functioning (md:14.0, $p<0.001$), psychosocial functioning (md:7.7, $p<0.001$) and total functioning (md:8.1, $p<0.001$). No significant difference was found for emotional functioning (md:0.3, $p=0.99$).

Child self-reports

Overall, 32 of 78 children (41%) scored ≥-1 SD below the reference mean for the total functioning scale of the PedsQL and were considered to have impaired HRQOL. The children scored significantly lower than the healthy children on physical functioning (md:10.8, $p<0.001$), emotional functioning (md:8.9, $p<0.001$), social functioning (md:10.0, $p<0.001$), school functioning (md:16.4, $p<0.001$), psychosocial functioning (md:11.8, $p<0.001$) and total functioning (md:11.0, $p<0.001$). An overview of PedsQL scores for the child self-report and mother and father proxy-reports is shown in Figure 2.

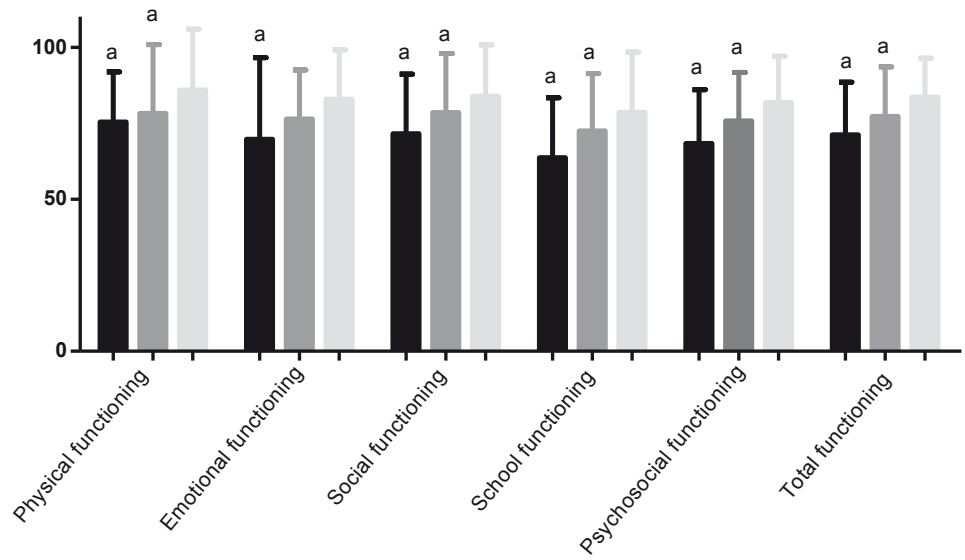

FIGURE 2 Health-related quality of life scores

Bars indicate mean and standard deviation scores. In black: child self-report n=78; in dark grey: mother proxy-report n=74; in light grey: father proxy-report n=54. Father proxy-reports were not compared with a healthy reference group. [a] Significantly different from healthy reference group at p<0.001.

Comparing proxy-reports with child self-reports

For 57 children both a child self-report and a mother proxy-report were filled in (in total 114 PedsQL's). Mothers indicated significantly higher scores than the children on physical functioning (md:7.2, p=0.02), emotional functioning (md:9.7, p=0.017), social functioning (md:9.5, p=0.006), school functioning (md:12.4, p<0.001), psychosocial functioning (md:10.5, p<0.001) and total functioning (md:9.2, p=0.002). The ICC between mother proxy-report and child self-report indicated poor agreement on all scales: physical functioning (ICC:0.18); emotional functioning (ICC:0.18); social functioning (ICC:0.10); school functioning (ICC:0.16); psychosocial functioning (ICC:0.12) and total functioning (ICC:0.12).

Mother proxy-reports showed suitable Cronbach's alpha scores for physical functioning (0.90); emotional functioning (0.75); social functioning (0.79); school functioning (0.81); psychosocial functioning (0.90) and total functioning (0.93). Child self-reports showed suitable Cronbach's alpha scores for emotional functioning (0.73); psychosocial functioning (0.79) and total functioning (0.82). Low Cronbach's alpha scores were found for physical functioning (0.55), social functioning (0.46) and school functioning (0.52). When we analysed internal consistency of the child self-

reports, Cronbach's alpha scores proved similar only for children with an IQ≥85 (n=62) (data not shown).

Influence of medical variables and HS on HRQOL

For the mother proxy-reports, linear regression analysis showed that duration of ECMO support (R^2=0.090, p=0.010) and the presence of CLD (R^2=0.133, p=0.002) were negatively related to the scoring on the total functioning scale. Diagnosis was not related to total functioning. Multiple linear regression showed no significant influences of sociodemographic variables on the total functioning scale.

The outcome status, functional ability on eight clinical domains, for 103 children was categorized according to the classification table adapted from the UK trial[1] (Table 2). Disabled functioning on the cognitive domain was found for 37% of the children in our study versus 30% of the children treated with ECMO in the UK trial (n=56). On the behavioral domain we found 42% with disabled functioning versus 39% in the UK trial. For the neuromotor domain, we found 19% disabled functioning versus 55% in the UK trial. On the general health domain, we found 19% of the children had a disabled functioning versus 25% in the UK trial. On the hearing domain 22% had disabled functioning versus 28% in the UK trial. For the vision domain 6% had disabled functioning versus 17% in the UK trial. The extended table in our study showed 25% disabled functioning on the maximum exercise capacity domain and 5% disabled functioning on the scoliosis domain.

TABLE 2 Health status

	Cognitive ability	Neuromotor skills	General health	Behavior	Vision	Hearing	Scoliosis	Maximum exercise capacity
Normal	**64 (62.1%)**	**77 (74.8%)**	**83 (80.6%)**	**50 (48.5%)**	**96 (93.2%)**	**80 (77.7%)**	**98 (95.1%)**	**58 (56.3%)**
Impairment	**13 (12.6%)**	**2 (1.9%)**	**10 (9.7%)**	**12 (11.7%)**	**6 (5.8%)**	**19 (18.4%)**	**5 (4.9%)**	**16 (15.5%)**
	IQ ≥ 85 + regular education with help	Abnormal signs on neurologic examination but normal function and/or total MABC score between p5 and p15	Medical condition requiring medication most days	Borderline T-score ≥ 1 scale of the CBCL	Abnormal eye movements or squint or correction needed (normal vision achievable)	Unilateral hearing loss with normal hearing in good ear	Visible but no functional disability and/or Cobb's angle <10 degrees	No complaints; Bruce protocol between -1 and -2 SD
Mild disability	**15 (14.6%)**	**11 (10.7%)**	**10 (9.7%)**	**24 (23.3%)**	**-**	**2 (1.9%)**	**-**	**3 (2.9%)**
	IQ between 84 and 70	Total MABC score between p5 and p15 or <p5 including 2 subtests MABC <p5 but able to walk without support	Chronic medical condition requiring >1 admission in 6 months and/or epilepsy with >1 fit/month	Clinical T-score ≥ 1 scale of the CBCL	Correction needed (moderate disabled visual acuity in best eye)	Normally wears hearing aids	Cobb's angel >10 degrees + expectative treatment	No complaints; Bruce protocol < -2 SD
Moderate disability	**4 (3.9%)**	**1 (1.0%)**	**-**	**7 (6.8%)**	**-**	**2 (1.9%)**	**-**	**2 (1.9%)**
	IQ between 69 and 50	Total MABC score < p5 and/or 3 subtests MABC <p5 and walks with assistive devices but able to sit without support	Continuous need for stoma and/or tube feeding or intensive care at hospital admission	Clinical T-score ≥ 1 scale of the CBCL + specialist intervention	Correction needed (severe disabled visual acuity in best eye)	Hearing impairment (school, conversation) despite correction with hearing aids.	Cobb's angle >20 degrees + conservative treatment	Functional disability in everyday live; Bruce protocol < -2 SD
Severe disability	**6 (5.8%)**	**6 (5.8%)**	**-**	**-**	**-**	**-**	**-**	**5 (4.9%)**
	IQ < 50	Unable to perform MABC test due to neuromotor disease and/or limited self-mobility or no means of independent mobility	Need for continuous home oxygen or home parenteral nutrition and/or frequent seizures-difficult to control	Behavioral disturbance requiring constant supervision	Gross movement/ light and dark only	Severe hearing loss with persistent and continuous hearing impairment despite correction	Cobb's angle >20 degrees + operation needed	No ability to reach maximum exercise level due to neurological and/or cardiopulmonary disability
Missing	**1 (1.0%)**	**6 (5.8%)**	**-**	**10 (9.7%)**	**1 (1.0%)**	**-**	**-**	**19 (18.4%)**

Data are presented as number (percentage) of children in each health status domain. Total number of children n=103.

TABLE 3 Impact of health status on health-related quality of life

		Odd-Ratio (95% CI) unadjusted	Odd-Ratio (95% CI) adjusted
Lower physical functioning	**Exercise capacity**	**9.2** (2.7 to 31.7)	**14.3** (3.3 to 62.4)
	Neuromotor skills	**8.0** (2.0 to 32.8)	**7.0** (1.6 to 30.6)
	Behavior	3.0 (1.0 to 8.8)	3.4 (1.0 to 10.8)
	Scoliosis	2.6 (0.4 to 16.9)	2.5 (0.3 to 17.8)
	General health	1.9 (0.6 to 6.0)	2.3 (0.7 to 3.3)
	Cognitive ability	1.4 (0.5 to 3.7)	0.3 (0.3 to 2.6)
	Hearing	0.8 (0.3 to 2.4)	0.9 (0.3 to 3.0)
	Vision	0.6 (0.5 to 0.7	0.0
Lower emotional functioning	Exercise capacity	5.5 (1.0 to 22.2)	6.2 (1.4 to 26.6)
	Behavior	3.3 (0.8 to 13.7)	3.4 (0.8 to 14.2)
	Cognitive ability	2.7 (0.8 to 8.7)	4.1 (1.1 to 16.3)
	Neuromotor skills	2.1 (0.5 to 8.3)	2.5 (0.6 to 10.6)
	General health	2.0 (0.5 to 7.7)	1.9 (0.5 to 7.6)
	Scoliosis	1.1 (0.1 to 10.5)	1.1 (0.1 to 11.0)
	Vision	0.8 (0.7 to 0.9)	0.0
	Hearing	0.5 (0.1 to 2.3)	0.5 (0.1 to 2.3)
Lower social functioning	**Behavior**	**8.1** (2.5 to 26.1)	**8.9** (2.7 to 29.7)
	Neuromotor skills	**4.6** (1.3 to 17.0)	**4.4** (1.1 to 16.9)
	Exercise capacity	2.5 (0.8 to 7.5)	2.2 (0.7 to 7.0)
	Cognitive ability	2.4 (0.9 to 6.3)	2.9 (0.9 to 8.8)
	Scoliosis	2.3 (0.4 to 14.9)	2.3 (0.3 to 15.1)
	Vision	1.5 (0.1 to 24.7)	1.2 (0.6 to 24.5)
	General health	1.1 (0.3 to 3.7)	1.0 (0.3 to 3.4)
	Hearing	0.5 (0.2 to 1.5)	0.5 (0.1 to 14.3)
Lower school functioning	**Neuromotor skills**	**12.0** (1.5 to 98.4)	**15.0** (1.6 to 138.6)
	Cognitive ability	**5.4** (1.8 to 16.9)	**11.4** (2.6 to 50.0)
	Behavior	**3.7** (1.3 to 10.4)	**4.5** (1.4 to 14.0)
	General health	1.9 (0.5 to 6.8)	1.7 (0.4 to 6.3)
	Exercise capacity	1.4 (0.5 to 4.3)	1.2 (0.4 to 4.1)
	Scoliosis	1.0 (0.2 to 6.5)	0.9 (0.1 to 6.6)
	Hearing	0.8 (0.3 to 2.4)	0.7 (0.2 to 2.2)
	Vision	0.6 (0.5 to 0.7)	0.0
Lower psychosocial functioning	**Neuromotor skills**	**6.8** (1.7 to 27.8)	**6.7** (1.5 to 29.0)
	Behavior	**6.5** (2.1 to 19.8)	**8.2** (2.4 to 26.8)
	Exercise capacity	**5.4** (1.7 to 17.6)	**4.8** (1.4 to 16.2)
	Cognitive ability	**2.8** (1.0 to 7.3)	**4.7** (1.4 to 16.1)
	Scoliosis	2.2 (0.3 to 14.0)	2.3 (0.3 to 16.0)
	General health	1.5 (0.5 to 4.8)	1.4 (0.4 to 4.7)
	Vision	1.4 (0.1 to 23.3)	0.6 (0.0 to 11.8)
	Hearing	0.6 (0.2 to 1.9)	0.7 (0.2 to 2.2)
Lower total functioning	**Neuromotor skills**	**6.8** (1.7 to 27.8)	**6.0** (1.4 to 25.6)
	Behavior	**4.2** (1.5 to 12.4)	**4.7** (1.5 to 14.3)
	Exercise capacity	**4.2** (1.4 to 13.5)	**3.8** (1.2 to 12.5)
	Cognitive ability	2.2 (0.8 to 5.6)	2.7 (0.9 to 8.5)
	Scoliosis	2.2 (0.3 to 14.0)	2.2 (0.3 to 15.5)
	General health	1.5 (0.5 to 4.8)	1.4 (0.4 to 4.8)
	Vision	0.6 (0.5 to 0.7)	0.0
	Hearing	0.6 (0.2 to 1.9)	0.7 (0.2 to 2.2)

CI = confidence interval. In **bold**: the odd-ratios that have a significant influence on the health related quality of life scores. Adjusted for gender and socioeconomic status

Next, we compared the mother proxy-report PedsQL scale scores with the different HS domains to analyse if disabled HS would also indicate a lower HRQOL score. For the purpose of analysis, the mother proxy-reports were divided into two groups: indicating normal HROQL and indicating lower HRQOL (a score of ≥-1 SD compared with the reference group). The HS domains were classified into normal functioning and disabled functioning (impaired, mild disability, moderate disability and severe disability classifications combined). The calculated odds-ratios indicated that for all PedsQL scales, except emotional functioning, disabled HS resulted in a higher chance of having a low HRQOL indicated by the mother (Table 3). Disabled functioning on the neuromotor domain significantly influenced the functioning on all scales, except emotional functioning. Disabled functioning on the maximum exercise capacity domain significantly influenced the physical functioning, psychosocial functioning and total functioning scales. Disabled functioning on the behavior domain significantly influenced the social functioning, school functioning, psychosocial functioning and total functioning scales. Disabled functioning on the cognitive domain significantly influenced the school functioning and psychosocial functioning scales (Table 3).

DISCUSSION

To our knowledge, HRQOL of 5-year-old children treated with neonatal ECMO has not been studied before using both parent proxy-reports and child self-reports. Ratings of 42% of the mothers on the total functioning scale of the PedsQL were indicative of their child having impaired HRQOL. Only emotional functioning was not affected. The children themselves indicated a lower HRQOL on all PedsQL functioning scales when compared to a healthy reference group. Ratings of 41% of the children were indicative of impaired HRQOL. These two percentages are not far apart, but mothers' responses did not agree with the children's responses. Disagreement between parents and children is not an unusual finding[30]. Agreement might increase with the child's age, as verbal skills may facilitate communication between the child and parents[30]. However, it is debatable whether 5-year-old children can reliably fill in the PedsQL. Indeed we found low internal consistency scores for the child self-reports, even when we analysed only the subset of children without cognitive delay. The American reference group, however, showed adequate internal

reliability for all PedsQL scales[31], perhaps because they completed the PedsQL, which had been sent by post, under parental guidance. The children in our study may have had a better opportunity to rate their HRQOL more honestly because they completed the questionnaire independently.

Next, we evaluated the children's HS to gain insight into the effect of long-term morbidity on their HRQOL. Several cross-sectional studies have reported on morbidity following neonatal ECMO. However, reports on neurodevelopmental outcome in ECMO-treated patients may be difficult to compare because the study populations were born years and decades apart. Roy and coworkers showed that the ECMO-treated population born in 1997 differed from the populations born between the 1980s and 1990s; the neonates treated in 1997 could benefit from new therapies, appeared to be healthier, and were cared for in centers that reported fewer ECMO cases per year[32]. Interestingly, both Hofkosh and coworkers[33] and Glass and coworkers[34] – who both studied a cohort born in the 1980s – reported lower neurodevelopmental morbidity rates than we did. We assume that with advances in ECMO technology newborns who would have died in earlier years will nowadays survive. In the UK trial, morbidity rates for 7-year-old children born between 1993 and 1996 were higher than we found in our study[1]. A lower oxygenation index prior to ECMO and a younger age at the start of ECMO may – at least partly – explain these differences. Both factors have been recognized as predictors of poor outcome in non-CDH neonates treated with ECMO[35]. Also, the mentioned percentages in our cohort could be an underestimation of morbidity due to significantly different perinatal and ECMO characteristics between participants and non-participants in our study. The small differences in gestational age and birth weight might not have been of clinical influence. However, the difference in ventilation time (which was not caused by a difference in diagnosis) could have resulted in bias.

For the mother proxy-reports, delayed neuromotor development, cognitive and behavior problems and a disabled maximum exercise capacity significantly affected the outcome of HRQOL. Interestingly, the emotional functioning scale of the PedsQL was not affected by the children's HS. This suggests that HS and HRQOL seem to be partly independent, in line with findings from another study[13]. In our study, having disabled HS does not imply decreased emotional HRQOL.

The influence of the HS, in our study, on the other functioning scales of the PedsQL might indicate that the PedsQL measures HS rather than HRQOL. The concept of HS refers to the ability to function normally in everyday life. However, HRQOL is assessed when individuals rate the effects of their functioning and their health on their (emotional) wellbeing[7]. When a HS measure is used as a HRQOL measure, the conclusions can be misleading and should be drawn cautiously[36]. In this view, we have reason to believe that the conclusions in our study concerning HRQOL in fact concern HS. Thus we should conclude that the HS of 5-year-old children treated with ECMO in the neonatal period is affected, and that they show long-term morbidity

With regard to long-term morbidity at 4 to 5 years of age following neonatal ECMO, the following problems have been reported: neurological disorders, cognitive delay, abnormal motor functioning and behavioral problems[15,37]. The morbidity is highest in children with CDH[17], notably during the first year of life. Survivors after the first year of life show major additional physical morbidity in the long term[38]. In our study, the diagnosis of CDH did not significantly negatively influence HRQOL at 5 years of age, but this could be due to the small sample size. On the other hand, prolonged ECMO treatment as well as the presence of CLD negatively influenced the total functioning scale of the PedsQL (as indicated by the mother).

Long-term morbidity is not found only in children treated with ECMO[1,2]. The focus of the unique study of the UK trial – for example – was to analyse the extent to which ECMO treatment contributes to morbidity. This study confirmed that it is not ECMO treatment, but rather the underlying disease that seems to cause morbidity[1].In line with the findings of the UK trial, Frisk and coworkers found that children with CDH not treated with ECMO are also at substantial risk for neurodevelopmental problems in late childhood and adolescence[39]. Rais-Bahrami and coworkers reported that poor neurodevelopmental outcome was equally prevalent in ECMO-treated patients and in those who were critically ill but did not reach the ECMO criteria at age 5 years[40]. Also preschool children who had received neonatal intensive care had poorer HS and HRQOL in different life domains compared to healthy children[41]. Therefore, we should not only follow children treated with ECMO but all children admitted to an intensive care unit after birth. Our data do not allow estimating the effect of ECMO treatment itself, because we lack data on HRQOL in similar patient groups who did not receive ECMO treatment. For future studies, it would be interesting to compare

groups of patients treated in ECMO centers with similar patients treated in centers without ECMO facilities

A limitation of our study is that we were able to evaluate HRQOL of no more than 95 of the 125 survivors (76%). Only 78 of those 95 children (82%) filled in a child self-report and 74 mothers (78%) filled in a proxy-report. This may limit the broader implications of our findings. Another limitation is that we compared the children's scores with those of an American reference group, which might have caused bias due to cultural differences. We did so because Dutch reference norms for child self-reports at 5 years of age were not available. A third limitation is that – during evaluation of the proxy reports – we only used mother proxy-reports with the healthy reference group. Even though the reference group consisted mostly of mothers, a few father proxy-reports were included. As we had only 4 father proxy-reports available from fathers as single informant (figure 1), we considered the mothers as primary caretakers and decided to analyse their reports only. However, the fact that mothers tended to score more negatively than fathers did, may have resulted in a negative bias.

CONCLUSIONS

We found low HRQOL at five years of age for children treated with neonatal ECMO. However, the negative influence of disabled HS on the HRQOL might indicate that the PedsQL is more a measure of HS than of HRQOL. Still, the HS for the children in our study indicates that long-term morbidity is present five years after being treated with neonatal ECMO. Because problems detected at a younger age are of predictive value at older age and also might have an increasing effect on the children as they get older[1], we recommend HS and HRQOL of children treated with neonatal ECMO are separately assessed at different age stages. Professionals should be aware that the concepts of HS and HRQOL differ, and should choose their questionnaires carefully in accordance with what they intend to measure (HS or HRQOL). Considering the low internal consistency for half of the PedsQL scales in this study, the use of child self-reports at 5 years of age seems to be unreliable.

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CHAPTER 8

Measuring health status with a health-related quality of life questionnaire

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Submitted

ABSTRACT

Objective

Comparing two health-related quality of life (HRQOL) questionnaires in children with anatomical congenital anomalies and/or extra corporeal membrane oxygenation treatment. We hypothesised that these two questionnaires would not present the same results because one questionnaire does not yield the childrens' evaluation and should be defined as a health status (HS) questionnaire.

Design and setting

Prospective longitudinal follow-up study in a outpatient clinic of a III level university hospital.

Patients

115 children born between January 1998 and April 2004.

Main outcome measures

The Pediatric Quality of life Inventory (PedsQL) and the DUX-25 were parallel assessed at 8 (n=71) and 12 (n=44) years. Also, two competence questionnaires were assessed.

Results

Correlation between paired scales of the PedsQL and DUX-25 ranged from small (r=0.24) to large (r=0.68) at both ages. The PedsQL concluded impaired HRQOL in 44% (8 years) and 39% (12 years) of the children. The DUX-25 concluded impaired HRQOL for 11% (8 years) and 14% (12 years). Differences were found when the competence questionnaire and the PedsQL were compared at 8 years ($p<0.001$) and 12 years ($p<0.01$).

Conclusions

Based on the definitions of the concepts of HS (the ability to function normally) and HRQOL (the impact of a certain health on quality of life), the PedsQL seems a questionnaire that assesses HS instead of HRQOL. Due to less mortality and more morbidity there is a necessity for good HRQOL measures. Professionals should therefore carefully decide what they want to measure: HS or HRQOL; and need to choose their questionnaire accordingly.

INTRODUCTION

Nowadays, there has been a shift in childhood diseases from incurable to curable with a chronic aspect[1]. For example, long-term physical and neurodevelopmental morbidity are found in children treated with Extra Corporeal Membrane Oxygenation (ECMO)[2-3]. Because the medical and surgical treatment of children with anatomical congenital anomalies has advanced, some children are at risk for morbidity after their hospitalization[4-5]. To evaluate the long-term effects of advanced treatment modalities, many physicians are becoming more interested in their patient's quality of life (QOL)[6] and can choose from a variety of questionnaires. These questionnaires measure health status (HS), QOL or health-related quality of life (HRQOL) and these concepts are often used as equivalent terms[7]. However, these concepts are not interchangeable. The concept of HS measures the ability to function normally. When the patients rate the effects of their functioning on their wellbeing, QOL is assessed[8]. QOL assesses the subjective appraisal of wellbeing and may be influenced by many factors unrelated to health or to changes over time[8]. HRQOL measures the impact of a certain health on QOL and only assesses the influence of those factors that are directly related to health[9]. HS and HRQOL seem to be at least partly independent: physical impairment for example, does not necessarily imply decreased HRQOL[5]. When a HS questionnaire is compared with a HRQOL questionnaire, it is found that the two questionnaires provide different information[6] and when a HS measure is used as a HRQOL measure, the conclusions can be misleading[6,10]. When a HRQOL questionnaire is compared with the outcome of self-esteem, measured with a competence questionnaire, this would provide the same results because the concept of HRQOL is somewhat the same as the concept of self-esteem[11-12].

We wanted to compare two questionnaires who both claim to assess HRQOL. Based on the definitions of the concepts of HS and HRQOL, we hypothesised that these two questionnaires would not present the same results because one questionnaire does not yield the patients' evaluation. The primary goal was to compare two HRQOL questionnaires in children who join a prospective, longitudinal follow up program: i.e. children with anatomical congenital anomalies and/or treated with ECMO. As secondary outcome parameters we compared the results of the HRQOL questionnaires with those of healthy peers and compared the results of a competence questionnaire with both HRQOL questionnaires.

MATERIALS AND METHODS

Participants

This study was part of a structured multidisciplinary prospective follow-up program initiated in 1999 that provides for regular assessments of growth, physical condition, development, quality of life and wellbeing of children and their families until 18 years of age for children with anatomical congenital anomalies and/or who were treated with ECMO[13-15]. The assessment protocol is the standard of care in our institution. The Medical Ethical Review Board Erasmus Medical Center waived IRB approval. All parents were informed about the study and provided written permission to use the data for research purposes.

Study design

For this cross-sectional study the following medical characteristics were recorded: treatment (ECMO yes/no), underlying diagnosis (anatomical congenital anomalies yes/no), birth weight and premature birth (<37 weeks yes/no).

Before assessment the parents were invited to complete questionnaires concerning parental etnicity, socioeconomic status (SES; based on education of the primary caregiver divided by low, moderate and high)[16] and if, in their opinion, their child had behavioral and/or emotional problems. In addition information on education level was recorded.

At assessment all children completed both HRQOL questionnaires and the competence questionnaires under guidance of a developmental psychologist.

Instruments

The Pediatric Quality of Life Inventory (PedsQL) is an internationally well-known and frequently used questionnaire which encompasses 23 items on four scales: physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items). From the emotional, social and school functioning items, a psychosocial functioning scale can also be derived. All items together provide the total functioning score. Children indicate on a 5-point Likert scale to what extent they experience problems, stated in 23 items. Response categories are never (0), almost never (1), sometimes (2), often (3) and almost always (4). The feasibility, reliability and validity of the PedsQL have

been tested and were good[17]. The Dutch version of the PedsQL has adequate psychometric properties[18].

The DUX-25 is based on the TNO-AZL-Quality-of-Life-Questionnaire (TACQOL)[19] and assesses the evaluation of physical, emotional, social and home functioning in every day life of children aged 6 to 16 years[20-21]. It consists of 25 questions, all related to a happy to sad faces scale. All scores are transformed into a scale of 0-100, with higher scores representing higher HRQOL. A total HRQOL score can be calculated by summing up all questions. A school functioning scale is also available, although not yet tested in the general population. The questionnaire has good reliability and good test-retest correlations and results can be compared to a healthy Dutch reference group per age[20-21].

The Dutch adaptation of the Self Perception Profile for Children (SPPC; 8-to-12-years) and the Dutch version of the Self Perception Profile for Adolescents (SPPA;12-to18-years) measure the self-perceived competence[11-12]. The SPPC and SPPA assess competence in cognitive, social, and physical domains and yield a measure of general selfworth (self-esteem). The children first choose which statement describes them best and then decide whether the description selected was ‘‘totally true’’ or ‘‘sort of true’’ in their case. Each item scores from 1 to 4, with higher scores representing greater self-perceived competence. The internal consistency and test-retest reliability of the SPPC and SPPA were respectively found to be acceptable and good[11,22].

Data analysis

The bivariate relationship between the PedsQL and the DUX-25 was calculated with Pearson’s correlation coefficient. A correlation coefficient of 0.10 to 0.29 was considered small, 0.30 to 0.49 as medium and ≥0.50 as large[23].

The scoring on both HRQOL questionnaires was compared with the use of the percentage children scoring below 1 standard deviation (SD) (an impaired HRQOL) in comparison with the healthy reference group. χ^2 tests evaluated differences in percentages. Questionnaire scores were compared with the healthy reference population using unpaired t-tests.

For the competence questionnaires, percentile scores were used to describe the percentage of children scoring below-average (percentile score <15) or average (percentile score 15-85) to above average (percentile score >85). χ^2 tests evaluated differences in percentages between the competence questionnaire and the two HRQOL questionnaires, and also when comparing with competence scores of healthy reference peers.

RESULTS

For a total of 115 children (born between January 1998 and April 2004) two HRQOL questionnaires were parallel assessed from January 2010 till June 2012. At follow-up 71 children were 8 years old and 44 children were 12 years old. An overview of medical and sociodemographic characteristics is shown in Table 1.

Comparison of two HRQOL questionnaires

At 8 years of age overall bivariate correlations were small to medium (Table 2). The highest correlation was found for the (paired) school scales of the PedsQL and the DUX-25, representing 20% common variance (Table 2).

When the PedsQL was used as HRQOL measure, 44% of the children indicated an impaired HRQOL (≥ -1 SD). When the DUX-25 was used, 11% of the children indicated to have an impaired HRQOL (Table 3) (χ^2=77.368, p<0.001).

Compared with a reference group, we found significant *lower* scoring on almost all scales of the PedsQL for the 8 years old children in the follow-up, except for the emotional functioning. For the scales of the DUX-25 we found a significant *higher* score for our cohort on the physical scale. The other scales showed no significant differences between our cohort and the healthy reference group (Table 3).

TABLE 1 Medical and sociodemographic characteristics

Number of patients		n=115
Diagnosis	CA	78 (69%)
	Colorectal malformations	24 (30%)
	CDH (n=8 ECMO)	22 (28%)
	Esophageal atresia	18 (23%)
	CCAML (with lung resection)	4 (5%)
	Cardiac failure[a]	4 (5%)
	Omphalocele	2 (3%)
	Sacrococcygeal teratoma	2 (3%)
	Short bowel	2 (3%)
	Pulmonal atresia (n=1 ECMO)	1 (1%)
	ECMO without CA	36 (31%)
	MAS	22 (61%)
	PPHN	8 (22%)
	Lower airway infection	4 (11%)
	Sepsis	2 (6%)
Birth weight (grams)		3300 (1790-4985)
Gestational age		
	Prematurely born	21 (18%)
	Term born	92 (80%)
	Missing	2 (2%)
Emotional/behavioural problems		
	Yes	39 (34%)
	No	76 (66%)
Education		
	Regular education	108 (94%)
	Special education[b]	7 (6%)
Gender	Male	67 (58%)
Ethnicity		
	Dutch	90 (78%)
	Non-Dutch	24 (21%)
	Missing	1 (1%)
SES		
	Low SES	33 (29%)
	Moderate SES	37 (32%)
	High SES	35 (30%)
	Missing	10 (9%)

Data presented as median (IQR) and n (%). CA=congenital anomalies; ECMO=extra corporeal membrane oxygenation; CDH=congenital diaphragmatic hernia; CCAML= cystic adenomatoid malformations of the lung; MAS=meconium aspiration syndrome; PPHN=persistent pulmonary hypertension of the newborn; SES=socioeconomic status. [a]Pediatric ECMO (ECMO treatment after day 28 of birth): for cardiac failure one child was 2 years and 6 months old and one child was 4 months old; for lower airway infection the child was 2 years and 4 months old. Emotional/behavioral problems were based on the opinion of the parents. [b]Special education for different reasons: hearing problems (n=1); concentration problems (n=1); motor function problems (n=1) and behavioural problems (n=1).

TABLE 2 Correlation coefficients between paired scales of the two questionnaires

	Physical scales	Emotional scales	Social scales	School scales	Total scales
At 8 years	0.24*	0.21	0.37**	0.44**	0.39**
At 12 years	0.43**	0.68***	0.54***	0.59***	0.66***

* Significant at 0.05 level. ** Significant at 0.01 level. ***Significant at 0.001 level.
The two health-related quality of life questionnaires are: the Pediatric Quality of Life Inventory (PedsQL) and the DUX-25 with n=71 at 8 years and n=44 at 12 years.

At 12 years of age overall bivariate correlations ranged from medium to large (Table 2). The highest correlation for the paired scales was found for the emotional scales of the two questionnaires, representing 46% common variance (Table 2).

When the PedsQL was used as HRQOL measure, 39% of the 12 year old children indicated to have an impaired HRQOL. When the DUX-25 was used, 14% of the children indicated to have an impaired HRQOL (Table 2) (χ^2=22.181, p<0.001).

T-test analyses revealed significant *lower* scores on almost all scales of the PedsQL for the 12 year old children in the follow-up when these scores were compared with a healthy reference norm. For the emotional scale of the PedsQL, no significant difference was found. For the scales of the DUX-25, we found no significant differences between the scores indicated by the children in the follow-up and the scores indicated by the healthy reference group (Table 3).

TABLE 3 Health related quality of life scores

		8 years		**12 years**
	N	Mean (SD)	N	Mean (SD)
PedsQL				
Total	71	75.0 (13.1)***	44	78.5 (14.1)*
Physical	71	77.1 (14.6)***	44	80.6 (14.4)**
Emotional	71	71.8 (16.6)	44	75.1 (20.0)
Social	71	77.1 (17.5)***	44	82.1 (15.0)*
Psychosocial	71	74.1 (13.4)***	44	76.3 (14.6)*
School	71	73.5 (15.5)**	44	71.7 (15.4)*
DUX-25				
Total	71	80.6 (11.0)	44	78.1 (12.3)
Physical	71	83.5 (14.9)***	44	75.3 (18.1)
Emotional	71	75.5 (13.5)	44	75.6 (14.3)
Social	71	78.6 (14.3)	44	78.6 (12.5)
Home	71	87.2 (11.6)	44	84.5 (14.5)
School	71	77.5 (21.1)	44	76.3 (17.2)

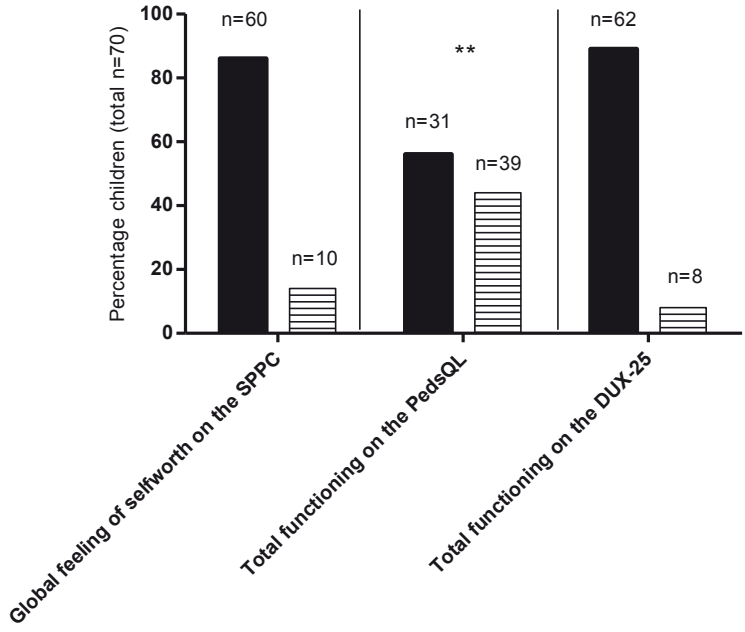
* Significant at 0.05 level. ** Significant at 0.01 level. *** Significant at 0.001 level.
PedsQL=Pediatric Quality of life inventory.

Comparison HRQOL questionnaires with competence feelings

At 8 years of age, 70 children also filled in the SPPC (1 missing due to organisational reasons). The percentage of children scoring a below-average (14%; n=10) and an average-to-above-average (86%; n=60) sense of self-esteem ('global feeling of selfworth' domain of the SPPC) in our cohort of 8-year-olds was compared with the total functioning scores of the PedsQL and the DUX-25 (Figure 1a). Significant differences were found when the SPPC scores were compared with the scores on the total functioning scale of the PedsQL (χ^2=27.071, p<0.001). No significant differences were found when the sense of self-esteem percentages were compared with the total functioning scores of the DUX-25 (χ^2=1.429, p=0.317) (Figure 1a).
No significant differences were found between the SPPC scores and scores of healthy reference peers.

At 12 years of age 42 children also filled in the SPPA (2 missing due to organisational reasons). The percentage of children with a below-average (10%; n=4) and an average-to-above-average (90%; n=38) sense of self-esteem ('global feeling of selfworth' domain of the SPPA) was compared with the percentages of total functioning scores on the PedsQL and the DUX-25 (Figure 1b). Significant differences were found between the SPPA score and the total functioning score of the PedsQL (χ^2=9.751, p<0.01). No significant differences were found when the sense of self-esteem percentages were compared with the total functioning score of the DUX-25 (χ^2=0.093, p=0.816) (Figure 1b). No significant differences were found between the SPPA scores and the scores of healthy reference peers.

A



B

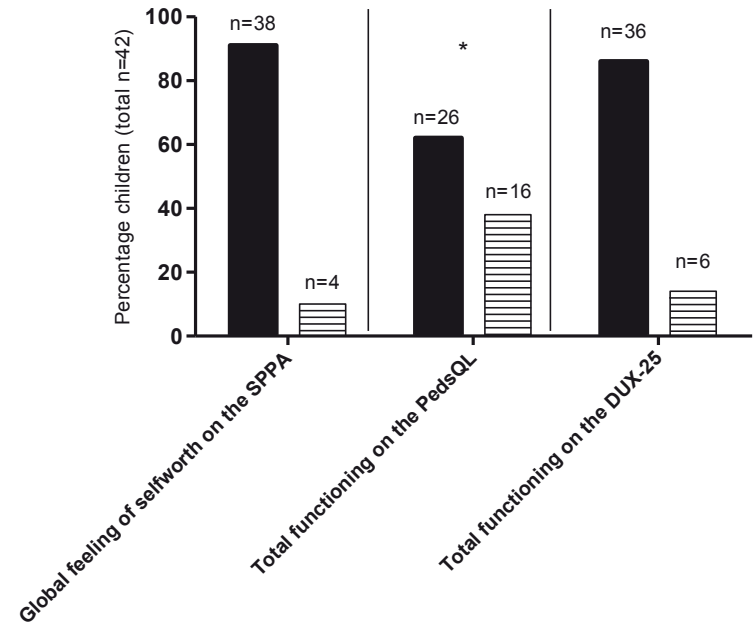


FIGURE 1 Sense of self-esteem compared with health-related quality of life at 8 (1A) and 12 years (1B) of age

In black = average-to-above-average scores. In stripes = below-average scores. SPPC = Self Perception Profile for Children. SPPA = Self Perception Profile for Adolescents. PedsQL = Pediatric Quality of Life Inventory.
*Significant difference with global feeling of selfworth: $p<0.01$. ** Significant difference with global feeling of selfworth: $p<0.001$

DISCUSSION

We compared two HRQOL questionnaires (PedsQL and DUX-25) in a cohort of children with anatomical congenital anomalies and/or ECMO treatment. We hypothesized that both well-known and frequently used questionnaires would not present the same results because the PedsQL does not yield the patients' perception of functional impairment and therefore should be defined as an HS questionnaire.

We found differences in scoring between the PedsQL and DUX-25 questionnaires at 8 and 12 years of age. First of all, we found small to medium correlations at 8 years of age and medium to high correlations at 12 years of age between the scales of the PedsQL and DUX-25. The highest correlation between paired scales (scales that should measure the same concept) had 46% common variance. This means that for the highest correlated scales, still more than half of the variance is explained by other variables.

Next, we found a significant difference in percentages of children with an impaired HRQOL measured with the PedsQL and the DUX-25 at both 8 and 12 years of age. With regard to reports on HRQOL in our study population, different studies have been done and also different outcomes were reported. For patients with anorectal malformations, Hirschsprung's disease, esophageal atresia and congenital diaphragmatic hernia (without ECMO treatment), low quality of life is found[24-26]. Impaired HRQOL for physical and psychosocial domains is reported for children with pulmonary and cardiac failure who were treated with neonatal and pediatric ECMO[27]. However, according to Van der Steeg and coworkers we should be careful to draw firm conclusions based on QOL results[7]. Their evaluation of QOL studies showed that most of these studies assessed HS instead of QOL. Where QOL also reflects to what extent a patient is really bothered by limitations of functional ability, HS indicates only the limitations[7]. We can support this finding with the results of the present study: when the PedsQL was used as outcome, the conclusion of our study would be that the children in our cohort have an impaired HRQOL, expect for their emotional functioning. Based on the DUX-25 the children in our cohort have a normal to high HRQOL at 8 and 12 years of age.

The fact that we found no difference for emotional functioning compared with reference norms, when the PedsQL was used, is not an unusual finding. Engelen and coworkers also did not find any significant difference for the emotional functioning scale of the PedsQL between the healthy sample and the chronic health condition sample (age groups 5-7 and 13-18)[18]. This result might indicate that, even though the children in our cohort experience morbidity and have an impaired HS; their emotional functioning (which is a subjective evaluation) is not affected. For children with anatomical congenital anomalies impaired HS is reported[14,28]. Also, children treated with ECMO experience morbidity[13,29]. We believe that in children with chronic disease the PedsQL is a reliable questionnaire to assess functional disability and should therefore be defined as an HS questionnaire instead of an HRQOL questionnaire.

To strengthen our conclusion that the PedsQL is not a measure of HRQOL, we also found significant differences between sense of self-esteem on the competence questionnaires at 8 and 12 years of age compared with the total functioning score of the PedsQL. A HRQOL questionnaire is based on almost the same construct as is a self-concept measurement and is positively associated with different domains of QOL[11-12]. In the present study the 8-and-12-year-old children indicate normal competence scores compared with healthy peers. Having a (chronic) illness might shift the importance of competence due to changing aspirations for success in different domains of the children's lives[11-12]. Because we found no differences between the sense of self-esteem outcome on the competence questionnaires and the outcome of the DUX-25, we believe that the DUX-25 is a more appropriate questionnaire for assessing HRQOL than the PedsQL is in our cohort of children with congenital anomalies.

A limitation of this study is that our cohort of patients has specific medical conditions and therefore generalization of our results to broader patient populations is not yet plausible. Still, the difference in outcome between both questionnaires raises concern and we therefore recommend professionals to carefully evaluate if the questionnaires used in their study measure HS or HRQOL.

CONCLUSIONS

We found different results between two reliable questionnaires who both claim to assess HRQOL in a cohort of children with anatomical congenital anomalies and/or ECMO treatment. In an era with more children surviving, good HRQOL measures are needed. Based on the differences in HRQOL results in our cohort of patients we strongly recommend professionals to determine whether they are mainly interested in the (medical) functional status of their patients, or if they want to assess HRQOL. Professionals should choose their questionnaires carefully in adjustment to what they wish to measure because the outcome of a HS questionnaire is not able to answer questions concerning HRQOL.

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CHAPTER 9

General discussion

GENERAL DISCUSSION

Since the introduction of neonatal extracorporeal membrane oxygenation over 26,571 children have internationally been treated for severe respiratory failure in registered ECMO centers[1]. The two ECMO centers in the Netherlands, Rotterdam and Nijmegen, have been treating more than 700 neonates since around 1990. Because survival rates have improved markedly, morbidity rather than mortality is now the main outcome of interest; except when discussing outcome of patients with congenital diaphragmatic hernia (CDH). Debates on the usefulness of neonatal ECMO treatment should take into account long-term outcomes in different areas of development, as well as the balance between healthcare costs and long-term outcomes. Quite a few international follow-up studies, including studies from the two Dutch centers, have reported neurodevelopmental follow-up outcome for children treated with neonatal ECMO. However, follow up so far was restricted to school age, most studies include small – single centre – cohorts and selection bias is likely due to high lost to follow-up percentages. We therefore need to longitudinally evaluate in a structured manner whether the scale of mortality and morbidity is not shifting towards higher rates of (severe) morbidity.

This thesis focuses on neurodevelopmental outcome after neonatal ECMO treatment and its impact on health status and wellbeing. Because underlying pathophysiological mechanisms that occur before, during and after ECMO treatment may contribute to the longitudinal outcome, these risk factors will be discussed briefly in the first part of this chapter. The main purpose of this general discussion is to present an overview of longitudinal outcome from preschool age into adolescence and to provide directions for future follow-up of these vulnerable children. Since health status and health-related quality of life (HRQOL) are not directly related to neurodevelopmental outcome but merely reflect the impact of long-term outcome on wellbeing, we will discuss these aspects separately.

Risk factors

Over the years different studies have reported risk factors for delayed neurodevelopmental outcome, categorized in ‘pre-ECMO’, ‘treatment-related’ and

'post-ECMO' factors. The first and latter are both considered 'patient-related' factors – that last even in the post-ECMO phase.

Pre-ECMO factors

Although severe birth asphyxia is rare in neonatal ECMO patients, except for patients with meconium aspiration syndrome (MAS), prolonged hypoxia is a well-known risk factor for cerebral injury. Disruption of cerebral autoregulation due to severe hypoxia makes the cerebral microcirculation vulnerable to alterations in systemic blood pressure, which is common in the critically ill neonate. Loss of cerebral autoregulation may result in ischemic cerebral damage during hypotension, whereas hypertension may cause cerebral hemorrhage[2]. Animal models of ECMO treatment showed impaired cerebral autoregulation after prolonged hypoxia combined with carotid artery and jugular vein ligation. Furthermore, when cerebral perfusion pressure decreased, uneven distribution of blood flow was noted[3]. Underlying diagnoses such as CDH with lung hypoplasia and severe pulmonary hypertension form another risk factor: not only because of hypoxic episodes but also as a result of the ventilatory management applied in these patients. Previously used management of hyperventilation led to vasodilation in the pulmonary vascular bed and resulted in vasoconstriction in the cerebral circulation. Outcome studies have demonstrated that hyperventilation may negatively affect neurodevelopmental outcome[4,5]. On the other hand, gentle ventilation with permissive hypercarbia which has been advocated from the mid 1990s onwards[6], has also a negative effect on cerebral autoregulation[2].

Treatment-related factors

Most ECMO deaths are not secondary to respiratory causes, but to intracranial hemorrhage, except in selected patients with CDH. Several pathophysiological factors, which depend on the technique and equipment used for the ECMO procedure, may contribute to the increased risk for cerebral bleeding problems. However, extensive discussion of the pathophysiology is beyond the scope of this thesis. Moreover, heparinization during ECMO may cause cerebral hemorrhage in the pre-ECMO injured brain that suffers from inadequate autoregulation[2].

A study from the Dutch ECMO centers reported brain injury on cerebral ultrasound in 17% of children treated with neonatal ECMO, with primary hemorrhage most frequently occurring[7]. Others have reported a profile of language vulnerability

following mild brain injury and greater deficits in visual/spatial and visual/motor skills following moderate/severe brain injury[8].

Post-ECMO factors

Factors that may contribute to adverse neurodevelopmental outcome in all ECMO-treated neonates are chronic lung disease (CLD)[9-12], prolonged neonatal hospitalization[13,14] and sensorineural hearing loss (SNHL)[15-17]. ECMO-treated CDH patients – on account of the nature of the birth defect – are most disposed to ECMO-related clinical complications and morbidity[18-21] such as respiratory and gastrointestinal morbidity[14], nutritional morbidity and failure to thrive[22]. This is due both to the nature of the birth defect and the comorbidity of ECMO treatment.

All types of risk factors mentioned above are reported to be associated with delayed neurodevelopmental outcome at least till school age. However, the causes of developmental problems for children treated with neonatal ECMO have not been systematically unravelled yet.

Two groups of survivors

This question then comes to mind: Is ECMO treatment (with its inherent risks) in itself a cause of morbidity or is ECMO treatment related to severity of disease (thus reflected by patient-related factors both pre- and post-ECMO) and as such indirectly the cause of morbidity?

Based on our experience we can distinguish two types of neonatal ECMO survivors. The one type shows severe neurological morbidity as a result of pre-ECMO and treatment-related factors (e.g. intracerebral hemorrhage or ischemia) and presents with developmental problems in infancy which may have major influence on long-term neurodevelopmental outcome. Due to severe disability at preschool age and later these children can usually not be tested with standardized assessments. Some show lifelong morbidity related to cerebral damage (due to – for example – seizures) and profound mental and motor disability. In those children abnormal outcome seems mostly determined by the biological basis (e.g. medical history)[13]. The more severe the eventual outcome, the better the predictability from young age[23]. Therefore,

follow-up of these patients should focus on providing optimal management of their disabilities and preventing further complications. In addition, honest evaluation of the costs and benefits of ECMO treatment for this group of children is desirable, as insight into this matter is largely lacking.

The second type concerns children described in this thesis. These children do not seem to suffer from severe (neurological) morbidity in the neonatal period and in infancy, but are at risk for (slight) academic and behavioural problems for which they need to be monitored. For this group, more subtle insults to the brain might have led to minor lesions which may interfere with normal brain maturation. Their long-term follow-up should focus on *the impact* of the patient-related and treatment-related factors on neurodevelopment.

Neurodevelopmental outcome from preschool into adolescence

Preschool age

Previous studies reported normal mental, speech, language and motor outcome in most of the children at preschool age[13,24-28]. We found normal mental development in 82% and normal motor development in 64% of children at two years of age. These results suggest that many children treated with neonatal ECMO survive without (severe) overall deficits. The others, however, should be closely monitored in a follow-up program that provides for assessment at crucial time points. This is why we designed two prediction models to identify those children at risk for delayed mental and/or motor outcome. Outcome at school age proved to be best predicted by background characteristics and neurodevelopmental outcome at two years of age. This is also true for a cohort of children with non-cardiac congenital anomalies without ECMO treatment[29].

School age

Five-year-old children treated with neonatal ECMO are reported to experience mental and motor problems[11,19,25,30]. Overall intelligence has been found to be in the normal range[19,30,31], with language development reported even above population norms[30]. Other problems reported are social, attention, and visuo-spatial problems, often co-occurring with other cognitive and behavioural problems[19,25,31,32]. These (sometimes

subtle) cognitive deficits can put a child at higher risk for school failure when compared to healthy children[31,32].

Furthermore, it seems important to detect hearing loss at an early stage because even mild bilateral hearing loss may compromise the development of language, communication skills and behaviour at school age[33,34]. We therefore recommend language and developmental assessment at least till school age, with referral to an ENT-department on suspicion of hearing problems. In the Netherlands all children attend well-established social health care services that provide neonatal hearing screening and regular evaluation of development within the first year(s) of life. Primary healthcare workers should be aware of the child's medical history and specific risk factors for impaired development.

Few studies have reported on outcome after the age of five years for children treated with neonatal ECMO. Normal range IQ scores at school age are not an unusual finding[27,35-37]. However, studies also revealed a high need for extra support at regular education, problems with both visual and spatial information-processing as well as hyperactivity/ attention problems[37]. These results suggest that children treated with neonatal ECMO – even without significant overall cognitive deficits – remain at risk for (subtle) cognitive deficits at school age.

As to the influence of the underlying disease, neurodevelopmental outcome is worst in children with CDH (with or without ECMO treatment)[19]. They may experience severe neurodevelopmental delay[14] with concentration and attention problems[38,39], as well as motor problems[9,19,40,41]. It would seem essential, therefore, to devise a tailor made – diagnosis specific – follow-up program for all CDH survivors, even those presenting without severe disability in the neonatal period.

Adolescence

We reported findings from a pilot study in 18-year-old adolescents treated with neonatal ECMO shortly after its introduction in the Netherlands (1991-1995). To our knowledge, we were the first to report outcome at adolescent age. In 2012, we started with a structured follow-up assessment modeled on our findings at school age. Problems were found in the areas of concentration, attention, and memory when

daily activities were disrupted. These problems might be explained by poor executive functioning. Good executive functioning skills are needed for goal-oriented, efficient and socially adaptive behaviour[42,43]; when these are lacking, problems may arise with functioning in a complex and demanding environment[44]. The results of this pilot study might indicate that these children's academic and behavioural problems are due to memory problems and slower working-speed/ information-processing speed. Jensen and coworkers have suggested that individual differences in short-term or working-memory underlie the correlation between working speed/ information-processing speed and intelligence[45]. The ability to reason and solve problems relies on the information held in the working-memory and is thus subject to loss due to either decay or interference[45] (as is true for the adolescents treated with neonatal ECMO). Consequently, when persons process information faster, they are more likely to permit reasoning to reach completion before the information is lost[45,46]. Also, the amount of information held in memory determines the capacity to reason, and therefore better reasoning is permitted when a larger working-memory is present[47]. It might be that the children/adolescents treated with neonatal ECMO process information across the brain at lower speed. When a task gets more demanding more information must be stored in the working-memory and information must be processed faster. This might explain the increasing (subtle) academic problems seen as they get older.

On the other hand, there might be a role for brain injury. As children grow older, they become more capable of executing tasks that require complex cognitive functioning[48]. Because the children treated with neonatal ECMO seem to experience overall normal intelligence but begin to experience more academic and behavioural difficulties at older ages, they may then have trouble with executing more demanding tasks. Capabilities such as working memory, inhibition and attention contribute to overall cognitive development and these capabilities improve with age, partially due to the development of the prefrontal cortex[48]. The increasing synaptic connections and the pruning of synapses, as well as ongoing myelination, are important mechanisms in the development of cognitive skills[48]. The prefrontal cortex is presumed to function as a 'master' regulator of processes mediated by other brain regions[49]. Situation-specific problems with working-memory function may arise if the functioning of the prefrontal cortex is compromised through direct prefrontal damage, damage to one of the areas (such as the hippocampus or caudate nucleus) with

which it is interconnected, or to pathways connecting these brain areas[49]. Beyond the processes that occur in the prefrontal cortex, cognitive improvement with age may be due to more coherent, or more myelinated, non-cortical white matter circuitry in the prefrontal parts of the brain[48]. A study in preterm born children found that not the effects of prematurity alone (the medical background) predicted impairment at older age; all of the children with executive impairment had white matter abnormalities on brain scans[50]. White matter abnormalities are likely to result in compromised axonal networks, with particular relevance for executive functioning in the fronto-striatal and cortical-thalamic systems (prefrontal cortex)[51]. These brain abnormalities might also provide an explanation for the problems in neonatal ECMO survivors. Further research (discussed in the final section of this chapter) could provide evidence for this assumption.

Psychological outcome in terms of quality of life

Due to the shift in many childhood diseases from incurable to curable with chronic morbidity, many physicians are becoming concerned about their patients' quality of life (QOL)[52]. For patients with chronic disabilities, validated – disease specific – questionnaires are available to measure health status, QOL or health-related quality of life (HRQOL). These questionnaires measure different concepts. The World Health Organisation defines health status as the ability to function normally in everyday live; QOL is defined as the subjective appraisal of wellbeing influenced by many factors unrelated to health; HRQOL is defined as the impact of health status on QOL[53].

Health-related quality of life

We were the first to analyse HRQOL in children treated with neonatal ECMO with the use of both proxy-reports as well as child self-reports at the age of five years. However, the internal consistency of the children's self-reports was low, confirming our observation that they found it difficult to put questions in perspective. They tended to compare themselves with their parents and some questions were not applicable to the children's situations (e.g. doing homework). We therefore concluded that the PedsQL is not quite feasible in this young population. Moreover, they might just be too young to evaluate their own HRQOL overall. At older age they will have better verbal skills[54], facilitating communication at psychological assessment. We

therefore encourage the use of proxy-reports at the age of five years to evaluate HRQOL.

Health status

Health status and HRQOL seem to be at least partly independent. It is quite imaginable, and also reported by others, that a person's perception of well-being can be discordant with their objective health status and disability[55-57]. Still, we found that the children's health status was of significant influence on the outcome of the PedsQL. For example, functioning on the cognitive domain of health status significantly influenced the school functioning and psychosocial functioning domains of the HRQOL. Fayed and coworkers concluded that the PedsQL is a measure of functioning, disability and health[58]. They stated that the definition of HRQOL was not applicable to this questionnaire and we agree with this conclusion. We believe that for children with chronic diseases the PedsQL is a reliable measure of health status but not of HRQOL.

Health-related quality of life or health status?

Conclusions about HRQOL drawn from questionnaires that actually assess health status can be misleading[59,60]. Professionals should be aware of the differences in concepts before drawing conclusions on HRQOL outcome of their patients. We compared outcomes of two HRQOL questionnaires in a cohort of children with anatomical congenital anomalies and/or ECMO treatment. Other studies have indicated low QOL in all these children[39,61,62]. We found significant differences in outcome between the two questionnaires. Furthermore, we found significant differences between the PedsQL and the sense of self-esteem score. Sense of self-esteem is based on almost the same construct as HRQOL and is positively associated with different domains of HRQOL[63,64]. The question then comes to mind: for the purpose of evaluating long-term outcome should we attempt to measure HRQOL anyway? We feel that it might be enough to objectively measure health status and subjectively measure psychological/emotional functioning (such as self-esteem) with structured assessments.

Limitations and strengths

Throughout the chapters of this thesis we reported that structured assessment was not possible in all eligible children due to severe disability. This has certainly caused a biased outcome. We should be aware of the differences between these two groups of survivors. For the first group (experiencing neurological impairments in the neonatal period) we might need to re-evaluate whether the severe morbidity that can be expected is 'balanced' against the lower mortality. And for the second group (with absent or minor neurological impairments present) we need to identify specific risk factors for delayed neurodevelopmental outcome and the best way to curb hazards. This group of children should be followed carefully because they are prone to miss-out on support that they really need. An overview of all topics discussed in the present chapter, with recommendations for prospective research, is provided in Figure 1.

As another limitation, we used Dutch neuropsychological tests, which limit international comparison. A strength is that we could compare our data to Dutch normative data. For future studies, we would recommend tests that are used internationally (with also Dutch normative data available), to be decided on within the framework of international organizations such as the Extracorporeal Life Support Organization. Furthermore, in some studies we needed to combine outcomes of an older version of a neuropsychological test with those of a newer version. This can be seen as a limitation even though the versions differed only slightly.
Most of the research described in this thesis is unique because we reported outcome in large sample sized cohorts, sometimes even in a nationwide cohort (chapters 2 and 4). However, the cohorts described in chapters 5 and 6 were relatively small. Concerning chapter 6; this is the first report on outcome of 18-year-old-adolescents and as such valuable because it can be seen as a 'start' for new research in this area.

Finally, the children in these studies were treated with ECMO between 1991 and 2006. The marked changes in ECMO-technique over this period may have impacted neurodevelopmental outcomes. Nowadays, ECMO is a well-established therapeutic modality and earlier transfer to designated ECMO centers will certainly have an effect

on long-term outcome. In addition, the increased use of veno-venous ECMO will be of influence as well. It may be questioned therefore whether the findings can be extrapolated to all newborns treated with neonatal ECMO. Still, the findings testify to problems in different areas of development that are likely to be present in all neonatal ECMO populations. As such, close monitoring of longitudinal outcome remains warranted in all ECMO survivors.

Partly counteracting these limitations, a strength of our studies is that we report findings on a multicenter – nationwide – cohort with small lost to follow-up percentages (low selection bias) and as a consequence large sample sizes when compared to the studies published so far.

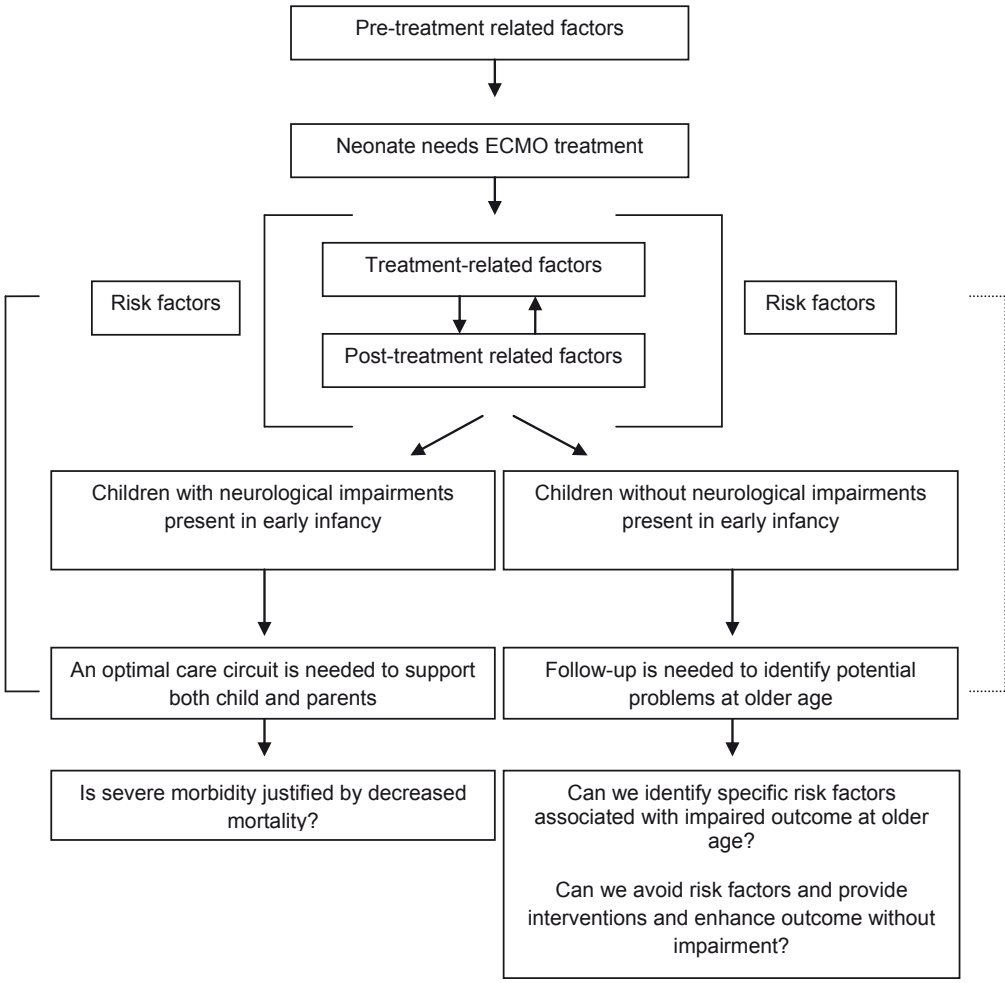

FIGURE 1 Overview

The dotted line represents an uncertain association

FUTURE

Follow-up

Based on the results presented in this thesis, we propose a flowchart for follow-up assessments (Figure 2).

We suggest assessment of all children treated with neonatal ECMO at the age of two years to define the individual 'starting point' of development. Clinical assessment at five years of age can be restricted to children who seem at risk – as supported by the prediction models – for delayed development. However, the parents of the others should be invited to complete questionnaires online on school progress, motor development and executive functioning skills. This will enable to evaluate whether problems have occurred since the age of two years. In addition, the parents and child can be invited to undergo a short screening assessment when needed.

Next, we believe that all parents are entitled to receive detailed information at the two years assessment about the long-term outcome (specifically concerning executive functioning skills) of children treated with neonatal ECMO. Parents should be alert to any developmental problems their child might be at risk for; so they can seek help at an early stage. The question remains whether they should be informed of possible long-term consequences in the neonatal period, when they are burdened with the decision to consent with ECMO treatment. They are not likely to be sensitive to information on long-term outcome right then – being in a short-term mind set and "just" wanting their newborn child to survive. Still, information on short-term outcome of children who experience delays already in the neonatal period might be of value at that moment. Research should focus on identifying risk factors associated with both short-term and long-term delayed outcome. Only then will we be able to provide valuable knowledge to parents/caregivers at the moment they need to make very important – and well-considered – decisions.

Exclusive assessment of intelligence does not capture the full range of executive skills that underlie academic and behavioural problems. Considering the concentration and attention problems found at eight years and the memory and information-processing speed problems found at adolescent age, structured

assessment of specific domains of cognitive and executive functioning skills at these ages seems essential.

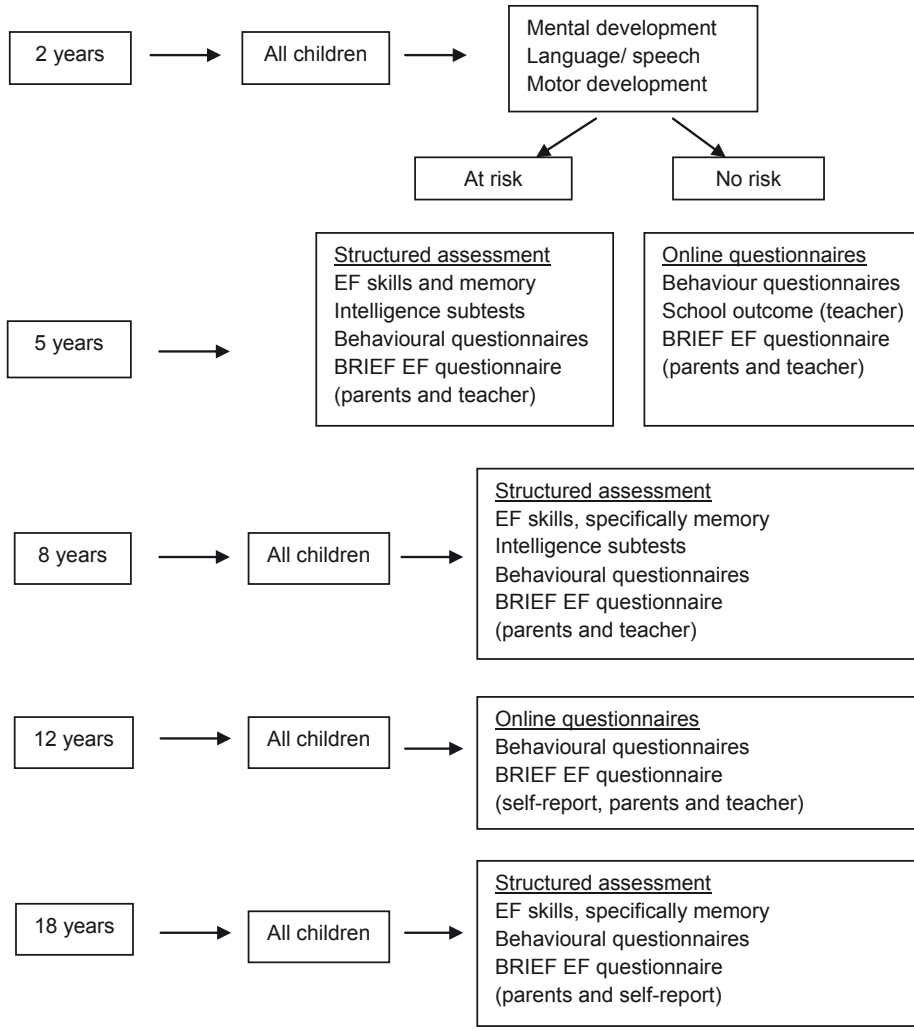

FIGURE 2 Flowchart follow-up assessments

Suggestions for neuropsychological tests at 5/8-18 years: EF skills=adaption of the original Go/noGo trial, the Shape School, Day-night task, Behavior Rating Inventory of Executive Functioning (BRIEF)/ STROOP, Trail Making Test, Tower Test, subtests of the Cambridge Neuropsychological Testing Automated Battery, BRIEF and BRIEF-SR (self-report for 11-18 years); memory = subtests of the Working Memory Test Battery for Children/ digit-span, spatial span, subtests of the Kaufman Intelligence test for adolescents and adults; IQ = subtests of the Wechsler intelligence tests for (primary and preschool) children and adolescence/adults.

Research

A solid research infrastructure combined with patient care is still needed to elucidate the underlying causes of the academic and behavioural problems seen in neonatal ECMO survivors. But we also need to evaluate the impact of (preventive) interventions on short- and long-term outcome. Furthermore, it is important to identify not only those risk factors in the neonatal period that best predict long-term outcome but also those that negatively impact brain development in the long term, ideally with the use of imaging studies of the central nervous system. Because studies currently are difficult to compare, it is not easy to get a full picture of the risk factors that are of essential influence. It is therefore crucial that we investigate in comprehensive data-management of patient-related and treatment-related factors, preferably harmonized between all ECMO centers. Only then will we be able to put together all pieces of the puzzle provided by the different centres and obtain a more complete picture of what children treated with neonatal ECMO and their parents may expect.

Because we found low working-speed/ information-processing speed combined with memory problems in the 18-year-olds, we feel that research (perhaps interwoven with the follow-up assessments) should focus on cognitive skills such as executive functioning at ages five, eight or twelve years, and eighteen years. Specific intelligence subtests should be administered to complete the picture of cognitive functioning in addition to executive functioning. Furthermore, the children, parents and teachers should report on executive functioning skills at home and at school. Behaviour should be reported with proxy-reports as well as with self-reports.

There is a role for brain imaging techniques at the ages eight or twelve years and eighteen years; i.e. DTI (neural tract images) and functional MRI (fMRI) scans. In our institution, Van den Bosch and coworkers are currently using fMRI and DTI scans to examine long-term effects of neonatal ECMO on pain processing later in life. They are focusing on pain-related brain activation patterns and white matter development in – among others – a cohort of neonatal ECMO survivors aged 5-15 years (Van den Bosch, personal communication). fMRI and DTI scanning could also be useful to identify typical alterations in the developmental trajectory of the brain in those children, treated with neonatal ECMO, who experience problems with development, cognition and behaviour.

Another possibly interesting research-track is applying and evaluating cognitive rehabilitation. Cognitive rehabilitation is a concept that refers to systematic therapeutic efforts designed to improve information-processing[65-67]. Cognitive rehabilitation has been proven effective for adults after stroke or traumatic brain injury and the European Federation of Neurological Societies developed in 2003 a set of practical guidelines for adults[68,69]. Patients with acquired brain injury are reported to experience problems with attention and memory, and to process information at lower speed[70,71]. Examples of cognitive rehabilitation programmes for children are the computerized COGMED^{RM} training[72] and the Amsterdam Memory and Attention Training for children (AMAT-c)[73]. These programmes can be used to improve memory and attention dysfunctions. It would perhaps be interesting to set up a randomized controlled trial: one group would then receive cognitive rehabilitation training while the second group functions as a control group. If cognitive rehabilitation training would show to be successful in the neonatal ECMO population, we might implement it as a (preventive) intervention in all neonatal ECMO survivors and as a result reduce the academic and attention problems they experience.

New treatment

ECMO treatment has greatly advanced since its introduction almost 40 years ago with the development of new techniques – the most important neonatal veno-venous ECMO. Nowadays, also other intensive care treatment modalities are being used to improve oxygenation, such as surfactant, inhaled nitric oxide and high-frequency oscillatory ventilation. These could circumvent the need of neonatal ECMO treatment in many cases and ECMO will therefore be reserved for the most critically ill patients. This negative case selection might have negative effects on outcome because they are expected to be worse. Moreover, the incidence of severe respiratory insufficiency in MAS patients has decreased dramatically after changes in obstetric management. All in all, in the future we have to deal with neonatal ECMO survivors with different characteristics than the ones described in this thesis. It is therefore imperative that these “new” ECMO survivors and those who are being treated with other intensive care techniques are also followed in structured follow-up assessments. Only then can we decide on the best treatment for (cardio)respiratory disease in neonates. With the long-term outcome of the new treatment modalities incorporated, the balance between mortality and morbidity can be re-defined.

GENERAL CONCLUSION

Overall, this thesis reports neurodevelopmental and psychological outcome at ages 2-18 years for a unique nationwide cohort of children treated with neonatal ECMO. At preschool age, most children experience normal mental and motor development. At school age, neurodevelopment is mostly affected in the areas of concentration, behaviour (notably attention problems), motor function and health status. The children seem to experience sometimes subtle, cognitive deficits without apparent cognitive delay. In adolescents we found a trend in memory and working-speed/ information-processing speed problems. Psychological outcome in terms of emotional functioning, HRQOL and feelings of competence seems unaffected at all ages.

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CHAPTER 10

Summary of the findings

This thesis aimed to describe the long-term neuropsychological outcome till the age of 18 years of children treated with neonatal extracorporeal membrane oxygenation (ECMO). In this chapter, findings of the studies addressing this aim are summarized with Figure 1 providing an overview.

Chapters 2 to 6 described neurodevelopmental outcome.

In **chapter 2** we described two prediction models based on mental development (MDI) and motor development (PDI) at two years of age and intelligence (intelligence quotient (IQ)) and motor function at the age of five years. Of all children treated with neonatal ECMO between January 1996 and December 2005; 177 children (69%) joined the follow-up program both at two and at five years. At two years of age, overall MDI scores fell within the normal range with 82% of the children experiencing normal mental outcome. Overall PDI scores fell below the normal range with 64% of the children experiencing normal psychomotor outcome. At five years, overall intelligence of these children was comparable to normative data with 84% of the children experiencing intelligence within the normal range. Motor outcome was significantly worse compared to normative proportions, with 73% of the children experiencing normal motor development.
Delayed mental outcome at five years of age was predicted by non-Dutch ethnicity, low socio-economic status (SES) of the parents, and MDI <85 at two years. Normal mental outcome was predicted by a diagnosis of meconium aspiration syndrome. We would have invited 91 of the 155 children, improving the efficiency of the follow-up by 41%. However, we would have wrongly predicted a normal intelligence outcome for two children (9% of the 23 children with delayed mental outcome at five years). The predictive variables for delayed motor outcome at five years of age were: low SES of the parents and PDI <85 at two years of age. We would have invited 85 of the 163 children, improving the efficiency of the follow-up by 48%. However, we would have wrongly predicted a normal motor outcome at five years of age for ten children (23% of the 44 children with delayed motor outcome at five years of age). Therefore, we feel that the children who are not invited for an assessment at five year of age should be assessed with (online) questionnaires and follow-up should be scheduled for all children at older school age/adolescent age.

Chapter 3 described the incidence of sensorineural hearing loss (SNHL) at five years of age of children treated with neonatal ECMO between January 1992 and February 2005. Also, the influence of hearing loss on verbal and non-verbal mental development at two years of age, and on intelligence and language at five years of age was analysed. Tone audiometry was done in 136 children. Normal hearing was found in 76% of the 136 children aged five years. Bilateral SNHL was found in 4% (n=5) of the children; three of them wore hearing aids and/or received special audiological care. At five years of age intelligence and language development was tested in 101 children; language development at two years of age was tested in 62 of those. At two years of age, the overall mental development (median; range) was normal for verbal (98; 50-136) and non-verbal (106; 48-133) development. At five years, the children's intelligence (IQ: 104; 68-132) and language development (receptive language: 95; 56-138/ syntactical expression: 101; 50-141/ lexical expression: 104; 55-133) were normal and no differences in outcome were found for children with or without hearing loss. It would seem that structured follow-up assessments detect hearing loss at an early stage so that interventions such as hearing aids can be provided at an early age. Taking into account that previous studies have reported late occurrence and a progressive track of SNHL; we concluded that referral to an ENT-department, with expertise in profound audiological evaluation in children, should be considered even at minor signals of hearing impairment.

In **chapter 4** we evaluated neurodevelopmental, educational and behavioural outcome at eight years of age of children treated with neonatal ECMO from January 1996 till December 2001. Structural assessment of intelligence, concentration, eye-hand coordination and behaviour was performed in 135 eight-year-olds. Intelligence (mean IQ: 99.9, SD: 17.7; n=125) fell in the normal range when compared to the Dutch population. However, significantly more children needed special education (9%) or extra support in regular education (39%). The children's working-speed was slow and they showed low accuracy on a concentration test (n=123). Their eye-hand coordination fell in the normal range (mean: 97.6, SD: 14.3; n=126); children with congenital diaphragmatic hernia (CDH) scored lowest but still normal (mean: 91.0, SD: 16.4; n=28). The mothers of the eight-year-old children indicated more somatic and attention behaviour problems for their children; the teachers indicated more

somatic, social, thought, aggression and total problems, compared with normative data. The mothers indicated more somatic problems than the teachers; the teachers reported more attention problems than the mothers. A significant negative predictor of intelligence was a diagnosis of CDH (β= -0.350, p=0.008). We concluded that long-term follow-up for children treated with neonatal ECMO should focus on early detection of subtle learning deficits and providing adequate support.

Chapter 5 compared intelligence and motor function outcome at eight years of age of 35 children with CDH treated with (n=16) or without (n=19) neonatal ECMO between January 1999 and December 2003. Mean (SD) intelligence was normal for both treatment groups (IQ: 101.6 (22.3)), however, with significant lower scores for the ECMO-treated children (IQ: 91.7 (19.5)). Motor problems were significantly more apparent compared to normative data and found in 16% of all children with CDH (specifically ball skills were affected), with no differences between treatment groups. Problems with concentration (low working-speed) and behaviour (attention problems; reported by the mothers) were significantly more apparent for all the children with CDH compared to normative data. Health status was significantly lower than Dutch normative data, except for emotional functioning; school performance and feelings of competence were not affected. We concluded that children with CDH, whether or not treated with neonatal ECMO, are at risk for long-term morbidity especially in the areas of motor function, concentration and attention. But, despite their impairment, these children have a well developed feeling of self-competence.

In **chapter 6** we evaluated neurodevelopmental outcome at 18 years of age of 19 adolescents treated with neonatal ECMO between February 1991 and December 1995. Memory was assessed with two subtests of the Kaufman Adolescent and Adult Intelligence Test (n=14); one subtest of the Wechsler Adult Intelligence Scale (n=7); and the Rey's Auditory-Verbal Learning Test (AVLT) (n=13). Executive function (EF) was assessed with the Tower Test (n=15); Stroop test (n=7); Trail Making Test (TMT) (n=7); and the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire (n=12). In addition: self-esteem was assessed with the Self Perception Profile for Adolescents (n=19); behaviour was assessed with the Youth Self Report (n=18); and HS was assessed with the Pediatric Quality of Life Inventory (PedsQL) (n=17). The aim of the study was two-fold. First, we wanted to cross-sectionally

evaluate the functioning of the entire adolescent cohort (n=19). Second, we wanted to longitudinally evaluate outcome of a subgroup of six adolescents whose intelligence and concentration had also been assessed at ages eight and twelve years.

The cross-sectional outcome indicated higher proportions of visual and auditory memory problems (immediate and delayed recall) compared to normative proportions (percentages ranging from 36-57%). The adolescents experienced more problems (e.g. score < -1 SD) compared to normative proportions for working-speed (TMT: 57%). Planning (Tower Test: 20%), inhibition (Stroop: 14%) and cognitive flexibility (TMT: 14%) seemed not affected. Parent-reported EF skills (BRIEF) and self-reported self-esteem, behaviour and health status were within normal range.

The longitudinal outcome of six adolescents indicated that three and four, respectively, had problems with visual and auditory memory skills (immediate and recall). However, recall for auditory memory for words (AVLT) seemed less affected with one adolescent (17%) experiencing a problem score (< -1 SD). Concerning EF skills; planning (Tower Test) seemed unaffected; as did cognitive flexibility (TMT) and working-speed and inhibition (Stroop) with one being assigned a score below -1 SD. Working-speed (TMT) seemed affected in three to four. Parents reported problems with emotional regulation/control for one adolescent. Sense of self-esteem, behaviour and health status seemed unaffected in all six.

Considering the outcome at school age and the preliminary findings at adolescent age it would seem that future studies in neonatal ECMO survivors need to focus on the longitudinal outcome of specific cognitive skills such as memory, working-speed/ information-processing speed and overall EF skills.

Chapters 7 and 8 described psychological outcome in terms of quality of life.

In **chapter 7** we evaluated health related quality of life (HRQOL) at five years of age of children treated with neonatal ECMO between January 1999 and December 2005. We used both PedsQL mother proxy-reports (n=74) and child self-reports (n=78). Next, we evaluated the children's health status (HS) to gain insight into the effect of long-term morbidity on the reported HRQOL. While HS is the ability to function normally and is related to health, HRQOL is the impact of a certain health on quality of life. The children's HS was classified in eight clinical domains: cognitive ability,

behaviour, neuromotor skills, maximum exercise capacity, general health, scoliosis, hearing and vision. Rating of 42% of the mothers and 41% of children was indicative of an impaired HRQOL. However, there was an overall disagreement in responses between mothers and children (for 57 children both mother proxy- and child self-reports were available). Mother proxy-reports showed suitable Cronbach's alpha scores (internal consistency) for all PedsQL domains; the child self-reports, however, were found to have low internal consistency scores for multiple domains of the PedsQL. Children with a disabled HS for neuromotor functioning (19%), maximum exercise capacity (25%), behavior (42%) and cognitive functioning (37%) at five years of age had a higher odds ratio of also having reported a lower HRQOL. HS had no influence on reported emotional functioning. Also, duration of ECMO support (R^2=0.090, p=0.010) and the presence of chronic lung disease (R^2=0.133, p=0.002) were negatively related to HS. Because only emotional HRQOL was not associated with HS; we concluded that the PedsQL might be a measure of HS rather than of HRQOL. In contrast with reports from others, we also concluded that five-year-old children might be too young to rate their own HRQOL.

Chapter 8 compared two HRQOL questionnaires (PedsQL and DUX-25) at the age of eight and twelve years for 115 children with anatomical congenital anomalies and/or neonatal ECMO treatment (born between January 1998 and April 2004). We hypothesised that these two questionnaires would not present the same results because one questionnaire does not yield the children's evaluation and should be defined as a HS questionnaire. Because the concept of self-esteem (measured with a competence questionnaire) is related to the concept of HRQOL, we also assessed competence. The correlation between paired (measuring the same concept) scales of the PedsQL and DUX-25 ranged from small to large at both ages. The PedsQL concluded impaired HRQOL in 44% (eight years) and 39% (twelve years) of children, while the DUX-25 concluded impaired HRQOL for 11% (eight years) and 14% (twelve years). Differences, at both ages, were found when the competence questionnaires and the PedsQL were compared; but not when compared to the DUX-25. We concluded that, based on the definitions of the concepts of HS and HRQOL, the PedsQL seems a questionnaire that assesses HS instead of HRQOL. Due to less mortality and more morbidity there is a necessity for good HRQOL measures.

Professionals should therefore carefully decide what they want to measure: HS or HRQOL; and choose their questionnaire accordingly.
Overall, this thesis reports neurodevelopmental and psychological outcome for children, treated with neonatal ECMO, in the age range of 2-18 years. At preschool age normal mental and motor outcome is found in most children. At school age; neurodevelopment is mostly affected in the area of concentration, behaviour (most notably attention problems), motor function and HS. The children seem to experience, sometimes, subtle cognitive deficits without apparent cognitive delay. At adolescent age; we found a trend in memory and working-speed/ information-processing speed problems. Psychological outcome – in terms of emotional functioning, HRQOL and feelings of competence – seems unaffected.

In **chapter 9** we discuss the findings presented in this thesis and make recommendations for future studies. Our most important recommendations are:

- We need to research which of the risk factors present in the neonatal period have the largest association (prediction value) with long-term outcome. It is therefore crucial that we investigate in comprehensive data-management of patient-related and treatment-related factors, preferably harmonized between all ECMO centers.
- Future research should focus on cognitive skills such as executive functioning.
- The use of brain imaging techniques at the ages eight-or-twelve and eighteen (i.e. diffusion tensor imaging (DTI; neural tract images) and functional MRI (fMRI) scans) could be useful to identify typical alterations in the developmental trajectory of the brain.
- To set up a randomized controlled trial to evaluate if cognitive rehabilitation training would show to be successful in the neonatal ECMO population.

Figure 1 Overview findings

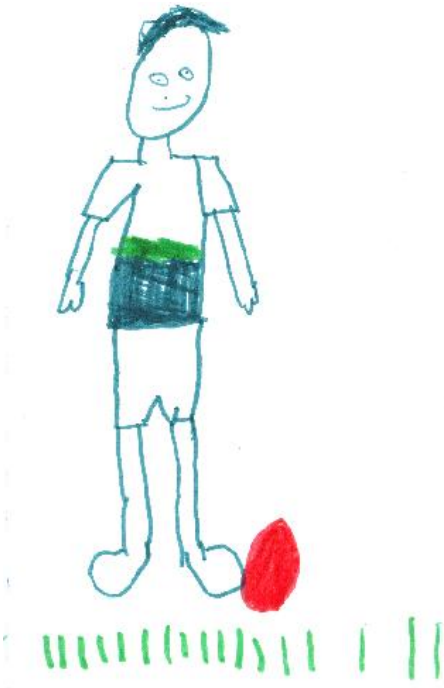
	Mental outcome	Motor outcome	Health status	HRQOL and behaviour
2 years	**Chapter 2** 82% normal mental outcome **Chapter 3** Verbal & non-verbal development within normal range	**Chapter 2** 64% normal motor outcome		
5 years	**Chapter 2** 84% normal mental outcome **Chapter 3** Language and intelligence within normal range **Chapter 7** 37% disabled cognitive function	**Chapter 2** 73% normal motor outcome **Chapter 7** 19% disabled neuromotor function 25% disabled exercise capacity	**Chapter 7** Mothers report low health status: physical/ social/ school/ psychosocial/ total functioning Normal emotional functioning. Children report low health status: physical/ social/ emotional/ school/ psychosocial/ total functioning 76% normal hearing/ no hearing loss	**Chapter 7** 42% disabled behavioural functioning
8 years	**Chapter 4** **<u>All diagnoses</u>** Intelligence within normal range Special education + extra support at regular education more needed Slow working speed + less accuracy in work Normal eye-hand coordination **Chapter 5** **<u>CDH only</u>** Intelligence within normal range; ECMO group lower than non-ECMO group Slow working speed ECMO group: 46% normal intelligence non-ECMO group: 85% normal intelligence	**Chapter 5** **<u>CDH only</u>** 81% normal motor development 84% normal manual dexterity 65% normal ball skills; significantly lower than Dutch children 84% normal balance skills ECMO group: 46% normal motor outcome non-ECMO group: 85% normal motor outcome	**Chapter 4** **<u>All diagnoses</u>** 44% impaired health status **Chapter 5** **<u>CDH only</u>** Children report lower health status for physical/ social/ school/ psychosocial and total functioning Normal emotional functioning ECMO group lower health status than non-ECMO group Except for emotional functioning	**Chapter 4** **<u>All diagnoses</u>** Mothers report more somatic and attention behaviour problems Teachers report more somatic, social, thought, aggression and total behaviour problems **Chapter 5** **<u>CDH only</u>** Normal self-perceived competence Mothers report more attention problems **Chapter 8** 17% impaired HRQOL 11% impaired sense of self-esteem
12 years			**Chapter 8** 39% impaired health status	**Chapter 8** 15% impaired HRQOL 13% impaired sense of self-esteem
18 years	**Chapter 6** 36-57% visual and auditory memory problems (immediate and recall) 43-57% working-speed problems 20% planning problems 14% inhibition problems 14% cognitive flexibility problems		**Chapter 6** 12% impaired health status	**Chapter 6** 25% parent-reported emotional regulation problems Normal self-perceived competence 6% self-reported externalising behaviour problems

“THIS IS ME”

Boy, 8 years old

This is me at the hospital

This is me now



This is me when I am grown up

CHAPTER 11

Appendices

LIST OF ABBREVIATIONS

ADHD = attention deficit hyperactivity disorder

AMAT-c = Amsterdam Memory and Attention Training for Children

ANOVA = analysis of variance

AUC = area under the curve

AVLT = Rey's Auditory-Verbal Learning Test

Beery VMI = developmental test of Visual-Motor Integration

BOS 2-30 = Bayley Developmental Scales

BRIEF = Behaviour Rating Inventory of Executive function

BRIEF-SR = Behaviour Rating Inventory of Executive Function – Self-Report

BSID-II-NL = Bailey Scales of Infant Development – Second edition – Dutch version

CA = congenital anomalies

CBCL = Child Behaviour Checklist

CCAML = cystic adenomatoid malformations of the lung

CDH = congenital diaphragmatic hernia

CI = confidence interval

CLD = chronic lung disease

CUS = cerebral ultrasound

DTI = diffusion tensor imaging

ECMO = extracorporeal membrane oxygenation

EF = executive function

fMRI = functional magnetic resonance imaging

HL = hearing loss

HRQOL = health-related quality of life

HS = health status

ICC = intraclass correlation coefficient

IQ = intelligence quotient
IQR = interquartile range

KAIT = Kaufman Adolescent and Adult Intelligence Test

MABC = Movement Assessment Battery for Children
MAS = meconium aspiration syndrome
MAP = mean airway pressure
MD = mean difference
MDI = mental developmental index

NA = not available

OI = oxygenation index
OR = odds ratio

PDI = motor developmental index
PedsQL = Pediatric Quality of Life Inventory
PPHN = persistent pulmonary hypertension of the newborn

QOL = quality of life

RAKIT = Revised Amsterdam Child Intelligence test
ROC = receiver operating characteristics

SD = standard deviation
SES = socio-economic status
SNHL = sensorineural hearing loss
SPPA = Self Perception Profile for Adolescents
SPPC = Self Perception Profile for Children

TACQOL = TNO-AZL-Quality-of-Life-Questionnaire
TIS = total impairment score
TMT = Trail Making Test

TRF = Teacher Report Form

UK trial = United Kingdom randomized trial

VA = venoarterial
VV = venovenous

WISC-III-NL = Wechsler Intelligence Scale for Children – Third edition – Dutch version

YSR = Youth Self Report

SAMENVATTING VAN DE BEVINDINGEN

Dit proefschrift richt zich de neuro-psychologische uitkomst tot de leeftijd van 18 jaar van kinderen behandeld met neonatale extracorporele membraan oxygenatie (ECMO). In dit hoofdstuk zijn de bevindingen van de verschillende studies samengevat (Figuur 1 geeft een overzicht).

Hoofdstuk 2 tot en met 6 beschrijven de neuro-psychologische uitkomsten.

In **hoofdstuk 2** beschrijven we twee voorspellingsmodellen gebaseerd op de mentale ontwikkeling (MDI) en psychomotorische ontwikkeling (PDI) op de leeftijd van twee jaar, en op intelligentie (intelligentie quotiënt (IQ)) en motorische ontwikkeling op de leeftijd van 5 jaar. Van alle kinderen behandeld met neonatale ECMO tussen januari 1996 en december 2005, hebben 177 kinderen (69%) meegedaan aan het follow-up programma op de leeftijden twee en vijf jaar. Op de leeftijd van twee jaar vonden we voor de hele groep gemiddelde MDI scores met een normale mentale uitkomst in 82% van de kinderen. De PDI scores van de hele groep vielen onder het gemiddelde en 64% van de kinderen hadden een normale psychomotorische uitkomst. Op de leeftijd van vijf jaar vonden we voor de hele groep gemiddelde intelligentie, 84% van de kinderen had een gemiddeld IQ. De motorische ontwikkeling was significant slechter vergeleken met de normgroep, en 73% van de kinderen hadden een normale motorische uitkomst.
Een achterstand in mentale ontwikkeling op de leeftijd van vijf jaar werd voorspeld door niet-Nederlandse etniciteit en een lage sociaal economische status (SES) van de ouders, en een MDI score <85 op de leeftijd van twee jaar. Normale mentale ontwikkeling werd voorspeld door een diagnose van meconium aspiratie syndroom. We zouden 91 van de 155 kinderen hebben uitgenodigd op de follow-up van vijf jaar, en daarmee zouden we de efficiëntie van de follow-up hebben verhoogd met 41%. Echter, we zouden een verkeerde voorspelling (normale uitkomst op de leeftijd van vijf jaar) hebben gemaakt voor twee kinderen (9% van de 23 kinderen met een achterstand in mentale ontwikkeling met vijf jaar). Een achterstand in motorische ontwikkeling op de leeftijd van vijf jaar werd voorspeld door een lage SES van de ouders en een PDI <85 op de leeftijd van twee jaar. We zouden 85 van de 163 kinderen hebben uitgenodigd voor follow-up op de leeftijd van vijf jaar en daarmee

zouden we de efficiëntie van de follow-up hebben verhoogd met 48%. Maar, we zouden een verkeerde voorspelling (normale motorische uitkomst op de leeftijd van vijf jaar) hebben gemaakt voor tien kinderen (23% van de 44 kinderen met een motorische ontwikkelingsachterstand met vijf jaar). Daarom vinden wij dat bij de kinderen die niet uitgenodigd worden voor follow-up op de leeftijd van vijf jaar wel (online) vragenlijsten afgenomen moet worden. Verder moeten op latere leeftijd alle kinderen uitgenodigd worden voor follow-up.

Hoofdstuk 3 beschrijft de incidentie van sensorineurale doofheid/gehoorproblemen (SNHL), ook wel genoemd perceptief gehoorsverlies, op de leeftijd van vijf jaar van kinderen behandeld met neonatale ECMO tussen januari 1992 en februari 2005. Ook is onderzocht wat de invloed is van gehoorproblemen op verbale en non-verbale mentale ontwikkeling op de leeftijd van twee jaar, en op intelligentie en taalontwikkeling op de leeftijd van vijf jaar. Bij 136 kinderen is een toonaudiogram verricht. Normaal gehoor werd gevonden in 76% van de 136 kinderen op de leeftijd van vijf jaar. Bilaterale SNHL werd gevonden in 4% (n=5) van de kinderen; drie van hen droegen gehoorapparaten en/of kregen speciale audiologische zorg. Op de leeftijd van vijf jaar werd intelligentie en taalontwikkeling getest in 101 kinderen en van deze groep kinderen was bij 62 kinderen ook de taalontwikkeling op de leeftijd van twee jaar getest. Op de leeftijd van twee jaar was de mentale ontwikkeling (mediaan; range) voor de hele groep gemiddeld ontwikkeld voor verbale (98; 50-136) en non-verbale (106; 48-133) taalontwikkeling. Op de leeftijd van vijf jaar was, voor de hele groep, intelligentie (IQ: 104; 68-132) en taalontwikkeling (receptieve vaardigheden: 95; 56-138)/ syntactische vaardigheden: 101; 50-141/ lexicale vaardigheden: 104; 55-133) gemiddeld ontwikkeld. Er werden geen verschillen gevonden in mentale uitkomst tussen kinderen met en zonder gehoorproblemen. Door gestructureerde follow-up worden gehoorproblemen vroeg ontdekt en kunnen interventies zoals gehoorapparaten) in een vroeg stadium worden ingezet waardoor er geen achterstand in de ontwikkeling optreedt. Aangezien eerdere studies een late en progressieve ontwikkeling van SNHL hebben gerapporteerd lijkt doorverwijzing naar een KNO-arts aangewezen bij nog maar minimale signalen van gehoorproblemen.

In **hoofdstuk 4** evalueren we neuro-psychologische uitkomsten, onderwijs en gedrag op achtjarige leeftijd van kinderen behandeld met neonatale ECMO van januari 1996 tot en met december 2001. Intelligentie, concentratie, oog-hand coördinatie en gedrag werden structureel getest bij 135 kinderen. Intelligentie (gemiddelde IQ: 99.9, SD: 17.7; n=125) was gemiddeld voor de hele groep vergeleken met de Nederlandse populatie. Echter, significant meer kinderen zaten op speciaal onderwijs (9%) of hadden extra begeleiding bij regulier onderwijs (39%). De kinderen hadden een lage snelheid van werken en werkten ook minder accuraat bij de concentratietest (n=123). Hun oog-hand coördinatie was gemiddeld (gemiddelde: 97.6, SD: 14.3; n=126); kinderen met een congenitale hernia diaphragmatica (CHD) scoorden het laagst ook al scoorde de hele CHD groep nog gemiddeld (gemiddelde: 91.0, SD: 16.4; n=28). De moeders van de achtjarige kinderen gaven meer somatische en aandachtsproblemen aan bij hun kinderen; de leerkrachten gaven meer somatische, sociale, denk, agressie en totale problemen aan vergeleken met de normgroep. De moeders gaven meer somatische problemen aan dan de leerkrachten; de leerkrachten rapporteerden meer aandachtsproblemen dan de moeders. Een significante negatieve voorspeller voor intelligentie was een diagnose van CHD (β= -0.350, p=0.008). We concludeerden dat lange termijn follow-up voor kinderen behandeld met neonatale ECMO gericht moet zijn op vroege detectie van subtiele leerproblemen en het geven van adequate begeleiding.

Hoofdstuk 5 vergelijkt intelligentie en motorische ontwikkeling op de leeftijd van acht jaar van 35 kinderen met CHD behandeld met (n=16) en zonder (n=19) neonatale ECMO tussen januari 1999 en december 2003. Gemiddelde (SD) intelligentie was normaal voor beide behandelgroepen (IQ: 101.6 (22.3)), maar met significant lagere IQ scores voor de kinderen in de ECMO groep (IQ: 91.7 (19.5)). Motorische problemen waren significant vaker aanwezig vergeleken met de normgroep en aanwezig in 16% van alle kinderen met CHD (voornamelijk een achterstand in balvaardigheden), met geen verschil tussen de behandelgroepen. Problemen met concentratie (lage snelheid van werken) en gedrag (aandachtsproblemen; gerapporteerd door moeders) waren significant meer aanwezig in alle kinderen met CHD vergeleken met de normgroep. Gezondheidsstatus was significant lager dan de Nederlandse normgroep, behalve voor emotionele ontwikkeling. Verder was het schoolfunctioneren niet verminderd en hadden de kinderen een gemiddeld

ontwikkeld competentiegevoel. We concludeerden dat kinderen met CHD, wel of niet behandeld met neonatale ECMO, een risico hebben op lange termijn morbiditeit met name wat betreft motorische ontwikkeling, concentratie en aandacht. Maar ondanks deze beperkingen ervaren zij wel een normaal ontwikkeld gevoel van zelfvertrouwen/ gevoel van competentie.

In **hoofdstuk 6** evalueren we neuro-psychologische uitkomst op de leeftijd van 18 jaar van 19 adolescenten behandeld met neonatale ECMO van februari 1991 tot en met december 1995. Geheugen werd getest met twee subtesten van de Kaufman Adolescent en Volwassen Intelligentie Test (n=14); een subtest van de Wechsler Volwassen Intelligentie Test (n=7); en de 15 woordentest (n=13). Executief functioneren (EF) werd getest met de Toren Test (n=15); Stroop test (n=7); Trail Making Test (TMT) (n=7); en de Executieve functies gedragsvragenlijst (BRIEF) (n=12). Verder werd gevoel van zelfvertrouwen (gevoel van competentie) nagevraagd met de Competentie Belevingsschaal voor Adolescenten (n=19); gedrag werd nagevraagd met de Nederlandse versie van de Youth Self Report (n=18); en gezondheidsstatus (GS) met de Nederlandse versie van de Pediatric Quality of Life Inventory (PedsQL) (n=17). Het doel van deze studie was tweevoudig. Ten eerste wilden we – cross-sectioneel – het functioneren van de gehele groep (n=19) beschrijven. Ten tweede wilden we de lange termijn uitkomst beschrijven van een subgroep van zes adolescenten die allemaal ook getest waren op intelligentie en concentratie op de leeftijd van acht en 12 jaar.
De gehele adolescenten groep liet hogere percentages van visuele en auditieve geheugenproblemen (direct en uitgesteld) zien vergeleken met de normale bevolking (percentages varieerden van 36-57%). De adolescenten leken meer problemen (te weten: score < -1 SD) te ervaren, vergeleken met de normgroep, voor snelheid van werken (TMT: 57%). De adolescenten leken minder problemen te ervaren met planning (Toren Test: 20%), inhibitie (Stroop: 14%) en cognitieve flexibiliteit (TMT: 14%). De door ouders gerapporteerde EF vaardigheden en de zelf-gerapporteerde gevoelens van zelfvertrouwen, gedrag en GS waren vergelijkbaar met die van leeftijdgenoten.
Respectievelijk drie en vier van de zes adolescenten leken visuele en auditieve geheugenproblemen (direct en uitgesteld) te ervaren. Uitgesteld auditief geheugen voor woorden (15 woordentest) leek beter ontwikkeld; slechts één adolescent (17%)

had een probleemscore (< -1 SD). Op het gebied van EF leek planning (Toren Test) normaal ontwikkeld, net als cognitieve flexibiliteit (TMT) en snelheid van werken en inhibitie (Stroop) met op elke test slechts één van de adolescenten met een score < -1 SD. Snelheid van werken (TMT) was problematisch in drie tot vier gevallen. Ouders van één adolescent rapporteerden problemen met emotionele regulatie. Een positieve uitkomst was dat gevoelen van zelfvertrouwen, gedrag en GS gemiddeld ontwikkeld waren bij alle zes.
Gezien de uitkomsten op schoolleeftijd en de eerste bevindingen in de adolescentie zouden toekomstige studies zich moeten richten op de lange termijn uitkomst van specifieke cognitieve vaardigheden zoals geheugen, snelheid van werken/ snelheid van informatieverwerking en EF vaardigheden.

Hoofdstuk 7 en 8 beschrijven psychologische uitkomsten termen van kwaliteit van leven.

In **hoofdstuk 7** evalueren we gezondheidsgerelateerde kwaliteit van leven (GKvL) met de PedsQL op de leeftijd van vijf jaar van kinderen behandeld met neonatale ECMO tussen januari 1999 en december 2005. We gebruikten PedsQL moeder-rapportage (n=74) en kind zelf-rapportage (n=78). Daarnaast evalueerden we de GS van de kinderen om een beeld te krijgen van de effecten van lange termijn morbiditeit op de gerapporteerde GKvL. GS is de mogelijkheid om normaal te kunnen functioneren en is gerelateerd aan gezondheid, terwijl GKvL de impact van een bepaalde gezondheid op de kwaliteit van leven aangeeft. De GS van de kinderen werd geclassificeerd in acht klinische domeinen: cognitieve vaardigheden, gedrag, neuro-motorische vaardigheden, uithoudingsvermogen, algemene gezondheid, scoliose, gehoor en zicht. Tweeënveertig procent van de moeders en 41% van de kinderen gaven een score die indicatief was voor een verminderde GKvL. Maar, de moeders en kinderen hadden weinig tot geen overeenkomst in de antwoorden (voor n=57 kinderen hadden moeder en kind een PedsQL ingevuld). De moeder-rapportages hadden goede Cronbach Alpha scores (interne consistentie) voor alle domeinen van de PedsQL; terwijl de zelf-rapportages lage interne consistentie hadden voor meerdere domeinen van de PedsQL. Kinderen met een verminderde GS op de leeftijd van vijf jaar voor neuro-motorisch functioneren (19%), uithoudingsvermogen (25%), gedrag (42%) en cognitief functioneren (37%) hadden

ook een hogere kans (odds-ratio) dat zij een verminderde GKvL hadden gerapporteerd. GS had geen invloed op het domein emotionele functioneren van de PedsQL. Daarnaast was ook de duur van de ECMO-behandeling (R^2=0.090, p=0.010) en de aanwezigheid van een chronische longziekte (R^2=0.133, p=0.002) negatief gerelateerd aan GS. Omdat alleen emotioneel functioneren niet geassocieerd was met GS concludeerden wij dat de PedsQL misschien meer een vragenlijst is die GS navraagt dan GKvL. In tegenstelling tot andere studies concludeerden wij ook dat vijfjarige kinderen misschien te jong zijn om hun eigen GKvL te kunnen rapporteren.

Hoofdstuk 8 vergelijkt twee GKvL vragenlijsten (PedsQL en DUX-25) op de leeftijd van acht en twaalf jaar voor 115 kinderen met anatomische aangeboren afwijkingen en/of neonatale ECMO behandeling (geboren tussen januari 1998 en april 2004). Onze hypothese was dat deze twee vragenlijsten niet dezelfde resultaten zouden geven aangezien één van de vragenlijsten niet de evaluatie van het functioneren navraagt en daarom gedefinieerd zou moeten worden als GS vragenlijst. Omdat het concept van zelfvertrouwen/ gevoel van competentie (gemeten met een competentievragenlijst) gerelateerd is aan het concept van GKvL, hebben we ook het gevoel van zelfvertrouwen nagevraagd. De correlatie tussen gepaarde (die hetzelfde behoren te meten) schalen van de PedsQL en de DUX-25 varieerde van laag tot hoog op beide leeftijden. De PedsQL concludeerde verminderde GKvL in 44% (acht jaar) en 39% (twaalf jaar) van de kinderen; de DUX-25 in 11% (acht jaar) en 14% (twaalf jaar). Ook werden er verschillen gevonden, op beide leeftijden, tussen de competentievragenlijst en de PedsQL; maar niet tussen de competentievragenlijst en de DUX-25. We concludeerden dat, op basis van de definities van de concepten van GS en GKvL, de PedsQL een vragenlijst lijkt te zijn die GS navraagt in plaats van GKvL. Omdat er door de nieuwe medische technieken minder sprake is van mortaliteit maar meer van morbiditeit zijn goede GKvL instrumenten zeer wenselijk. Professionals zouden daarom goed moeten beslissen wat zij willen meten: GS of GKvL. En zij moeten hun vragenlijst/ instrument daar goed op laten aansluiten.

Dit proefschrift beschrijft neuro-psychologische uitkomsten van kinderen behandeld met neonatale ECMO, in de leeftijd van twee tot en met 18 jaar. Voor het vijfde levensjaar ervaren de meeste kinderen een normale mentale en motorische

ontwikkeling. In de schoolleeftijd lijken de kinderen de meeste problemen te ervaren op het gebied van concentratie, gedrag (voornamelijk aandachtsproblemen), motorisch functioneren en GS. De kinderen lijken soms subtiele cognitieve problemen te ervaren zonder algemeen verminderd cognitief functioneren. In de adolescentieperiode lijkt er een trend te zijn van geheugenproblemen en vertraagde snelheid van werken/ snelheid van informatieverwerking. De emotionele ontwikkeling, GKvL en gevoelens van zelfvertrouwen lijken niet verminderd.

In **hoofdstuk 9** bediscussiëren we onze belangrijkste bevindingen en geven we aanbevelingen voor verder onderzoek. De belangrijkste aanbevelingen voor verder onderzoek zijn volgens ons:

- Het onderzoeken van welke risico factoren in the neonatale periode de grootste voorspellende invloed hebben op de lange termijn uitkomst. Het is daarom van groot belang dat we investeren in gedegen datamanagement van patiëntgerelateerde en behandelingsgerelateerde factoren.
- Toekomstig onderzoek zou gericht moeten zijn op specifieke cognitieve vaardigheden zoals executief functioneren.
- Het gebruik van beeldvormende technieken zoals tractografie en functionele MRI (fMRI) kunnen gebruikt worden om veranderingen in de ontwikkeling van het brein weer te geven.
- Het opzetten van een gerandomiseerd onderzoek om te evalueren of cognitieve training succesvol kan zijn in de neonatale ECMO populatie.

Figuur 1 Overzicht bevindingen

	Mentale ontwikkeling	Motorische ontwikkeling	Gezondheidsstatus	GKvL en gedrag
2 jaar	**Hoofdstuk 2** 82% normale mentale ontwikkeling **Hoofdstuk 3** Verbale & non-verbale ontwikkeling in het normale bereik	**Hoofdstuk 2** 64% normale motorische ontwikkeling		
5 jaar	**Hoofdstuk 2** 84% normale mentale ontwikkeling **Hoofdstuk 3** Taalontwikkeling en intelligentie in het normale bereik **Hoofdstuk 7** 37% verminderd cognitief functioneren	**Hoofdstuk 2** 73% normale motorische ontwikkeling **Hoofdstuk 7** 19% verminderd neuro-motorisch functioneren 25% verminderd uithoudingsvermogen	**Hoofdstuk 7** Moeders rapporteren lage gezondheidsstatus: fysiek/ sociaal/ school/ psychosociaal/ totaal functioneren Normaal emotioneel functioneren Kinderen rapporteren lage gezondheidsstatus: fysiek/ sociaal/ emotioneel/ school/ psychosociaal/ totaal functioneren 76% geen gehoorsproblemen	**Hoofdstuk 7** 42% gedragsproblemen
8 jaar	**Hoofdstuk 4** **<u>Alle diagnoses</u>** Intelligentie in het normale bereik Speciaal onderwijs + extra begeleiding op regulier onderwijs meer nodig Lage snelheid van werken + minder accuraat Normale oog-hand coördinatie **Hoofdstuk 5** **<u>Alleen CHD</u>** Intelligentie in het normale bereik; ECMO groep lager dan niet-ECMO groep Lage snelheid van werken ECMO groep: 46% normale intelligentie niet-ECMO groep: 85% normale intelligentie	**Hoofdstuk 5** **<u>Alleen CHD</u>** 81% normale motorische ontwikkeling 84% normale handvaardigheden 65% normale balvaardigheden; significant lager dan Nederlandse kinderen 84% normale balansvaardigheden ECMO groep: 46% normale motorische ontwikkeling niet-ECMO groep: 85% normale motorische ontwikkeling	**Hoofdstuk 4** **<u>Alle diagnoses</u>** 44% verminderde gezondheidsstatus **Hoofdstuk 5** **<u>Alleen CHD</u>** Kinderen rapporteren lage gezondheidsstatus voor fysiek/ sociaal/ school/ psychosociaal en totaal functioneren Normaal emotioneel functioneren ECMO groep lagere gezondheidsstatus dan niet-ECMO groep behalve voor emotioneel functioneren	**Hoofdstuk 4** **<u>Alle diagnoses</u>** Moeders rapporteren meer somatische en aandachtsproblemen Leerkrachten rapporteren meer somatische, sociale, denk, agressieve en totale gedragsproblemen **Hoofdstuk 5** **<u>Alleen CHD</u>** Normaal competentiegevoel Moeders rapporteren aandachtsproblemen **Hoofdstuk 8** 17% verminderde GKvL 11% verminderd gevoel van eigenwaarde
12 jaar			**Hoofdstuk 8** 39% verminderde gezondheidsstatus	**Hoofdstuk 8** 15% verminderde GKvL 13% verminderd gevoel van eigenwaarde
18 jaar	**Hoofdstuk 6** 36-57% visuele en auditieve geheugenproblemen (direct en uitgesteld) 43-57% lage snelheid van werken 20% problemen met planning 14% problemen met inhibitie 14% problemen met cognitieve flexibiliteit		**Hoofdstuk 6** 12% verminderde gezondheidsstatus	**Hoofdstuk 6** 25% emotionele regulatie problemen (gerapporteerd door de ouders) Normaal competentiegevoel 6% externaliserende gedragsproblemen (gerapporteerd door de adolescent zelf)

If the only prayer
you ever say in your entire life is
“thank you”
it will be enough

Meister Eckhart

DANKWOORD

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Collega’s
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Lieve Lisanne, bedankt dat je mijn paranimf wilt zijn. Jouw nuchtere kijk op dingen en vrolijke maar rustige karakter kan ik goed gebruiken als ik daar sta te zweten! ;)

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kijk op dingen kan ik goed gebruiken op dat “zweet-moment”. Bovendien is het altijd handig om een dokter in de zaal te hebben voor het geval dat.. ;)

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PhD PORTFOLIO

Summary of PhD training and teaching activities	126 hours + 17.1 ECTS	
Name of PhD student	Marlous Madderom	
Erasmus MC Department	Intensive Care and Pediatric Surgery	
PhD period	2010-2013	
Promotor	Prof.dr. D. Tibboel	
Co-promotor	Dr. H. IJsselstijn	
	Dr. A.F.J. van Heijst	
	Year	**Workload**
Courses		
Literature search basic and advanced course and EndNote course, Medical library	2010	0.2 ECTS
Mini course methodology	2010	7 hours
Biomedical English Writing and Communication	2011	4 ECTS
Integrity in Medical Research	2011	0.2 ECTS
BROK	2011	2 ECTS
Nihes Course Health status measurement	2011	1 ECTS
Nihes Course Biostatistical Methods I	2011	5.7 ECTS
Nihes Course Statistics and Survival Analysis	2011/2012	0.5 ECTS
Presentation Skills	2012	0.2 ECTS
Workshop on Photoshop and Illustrator CS5	2012	0.3 ECTS
Poster		
“Hearing loss”	2010	1 ECTS
“Health related quality of life”	2011	1 ECTS
“Outcome at eight years of age”	2013	1 ECTS
Conferences		
Mini symposium life ends	2010	3 hours
Symposium neuroimaging	2010	8 hours
Pediatric Psychology Network Netherlands	2011	8 hours
PhD day	2011	8 hours
Presentations		
Research meeting pediatric surgery	2010	8 hours
Referaat psychology	2011	8 hours
Research meeting pediatric surgery	2011	8 hours
Presentation quality of life (Alexandra Quittner)	2011	8 hours
Presentation paediatricians symposium Utrecht	2012	8 hours
Presentation CDH patient-day	2012	8 hours
Meetings		
Research meetings pediatric surgery	2010-2012	1 hour each (15)
Research meetings psychology department	2011/2012	1 hour each (12)
Grand round	2011/2012	1 hour each (4)
Paediatricians symposium Utrecht	2012	8 hours
CDH patient-day	2012	5 hours

CURRICULUM VITAE

Marlous Madderom was born on 27 February 1984 in Sint-Pancras. She obtained the pre-university diploma at Melanchthon College in Rotterdam in 2003 and in the same year enrolled for the psychology programme at the faculty of Social Sciences of the University of Leiden. She finished her master in developmental psychology with an internship at the follow-up team of children treated with ECMO and/or born with congenital anomalies of the Sophia Children's Hospital in Rotterdam under supervision of A. Zirar-Vroegindeweij, MSc and P. Honig-Mazer, PhD. After obtaining her degree as developmental psychologist she started her PhD track at the Sophia Children's Hospital in 2010, studying development of children treated with ECMO, under supervision of Prof. D. Tibboel, PhD; H. IJsselstijn, PhD; and A.F.J. van Heijst, PhD. Findings from this research are presented in this thesis.