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 Extracorporeal Membrane Oxygenation (ECMO) between January 1999 and December 2003.

Design Cohort study with 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 ($p=0.015$) 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, 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, 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 Extracorporeal Membrane Oxygenation (ECMO), the use of which is decreasing nowadays [6]. Some studies report an improved survival rate with the use of ECMO [7], others a relatively unchanged rate [8-10]. Of all ECMO-treated neonates, CDH patients 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 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. We present neurodevelopmental outcomes of 8-year-old CDH children 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. 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 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 providing for regular assessments of lung function, exercise capacity and development until age 18 years [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 groups (ECMO/ non-ECMO) (Table 1).

Primary outcome parameters

Intelligence

A short version of the Revised Amsterdam Intelligence Test (RAKIT) was administered [24]. Except for patients born after 2001; the short version of the Wechsler Intelligence Scale for children (WISC-III-NL) [25] was administered to them. Both tests have good reliability and validity [24-25]. 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 [26]. Percentile scores were calculated for the total impairment score, which is the sum of the item scores, and for 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 [27].

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 [28]. 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 [29]. Fifteen percent of the healthy reference group scores below the normal range; this percentage was set as cut-off point [29].

Health status was assessed with the Pediatric Quality of Life Inventory (PedsQL) as described previously [30]. A scale score of 1 SD below healthy reference norm was taken to indicate impaired health status [31].

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 [32]. A subclinical to clinical score in 16% of the children was used as cut-off point for comparison with reference norms [32].

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, prevalence of chronic lung disease (CLD) [22], 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 applicability of the model and assumptions for regression analysis. Multicollinearity was tested using the criterion that variance inflation factors should not exceed 2.5 [33]. 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 (91.7 (19.5)) and non-ECMO group (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 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; 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 treatment groups (χ^2=7.271, p=0.057) (Figure 4).

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 of 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, 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 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 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 (χ^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), prolonged use of morphinomimetics/sedatives (R^2=0.206, p=0.015) and use of methadone (R^2=0.350, p=0.002) negatively influenced intelligence. Having associated anomalies (R^2=0.175, p=0.019), CLD (R^2=0.207, p=0.010), prolonged use of morphinomimetics/sedatives (R^2=0.347, p=0.005) and use of methadone (R^2=0.237, p=0.012) 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 intelligence 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 CDH children 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 [34]. The children in the present study had normal intelligence, in line with other studies in CDH patients without ECMO treatment [5, 35]. 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, 36-37] and support the findings that CDH-survivors – even those without ECMO treatment – are at risk for attention and concentration deficits [5, 35]. The fact that 42% of our cohort needs extra support in regular education vs. 21% in the Dutch reference population [38] also points at subtle cognitive problems.

Motor problems have been reported in 60% of one-year-old and in 73% of 3-year-old CDH children 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 be the ECMO treatment itself that results 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 [39].

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 importance of long-term follow-up of CDH children (supplement Table 2 presents long-term outcome); as more of them survive the neonatal period incidence 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 ECMO-treated children. 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 [40] will facilitate collaborative efforts to evaluate the efficacy of clinical care practices and to decrease morbidity.

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CONTRIBUTORS

Marlous J. Madderom conceptualized and designed the study, analysed and interpretated the data, drafted the initial manuscript, and approved the final manuscript as submitted. Leontien Toussaint interpretated the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Monique H.M. van der Cammen-van Zijp interpretated the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Saskia J. Gischler interpretated the data, critically reviewed the manuscript, and approved the final manuscript as submitted. René M.H. Wijnen interpretated the data, critically reviewed the manuscript, and approved the final manuscript as submitted. D. Tibboel conceptualized and designed the study, analysed and interpretated the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Hanneke IJsselstijn conceptualized and designed the study, analysed and interpretated the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

COMPETING INTERESTS

Not applicable.

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WHAT IS ALREADY KNOWN ON THIS TOPIC?

Congenital diaphragmatic hernia survivors are at high risk for long-term morbidity.

Congenital diaphragmatic hernia patients treated with neonatal ECMO are at risk for neurodevelopmental delay.

WHAT THIS STUDY ADDS

Congenital diaphragmatic hernia patients treated with or without ECMO, are at increased risk for problems with motor function, concentration and health status.

Despite their impairment, congenital diaphragmatic hernia patients have a well developed feeling of self-competence.

Neurodevelopmental problems in congenital diaphragmatic hernia patients persist beyond pre-school age.

REFERENCES

1 Lally KP. Congenital diaphragmatic hernia. Curr Opin Pediatr 2002;**14**(4):486-90.

2 van den Hout L, Schaible T, Cohen-Overbeek TE, et al. Actual Outcome in Infants with Congenital Diaphragmatic Hernia: The Role of a Standardized Postnatal Treatment Protocol. Fetal Diagn Ther 2011;**29**(1):55-63.

3 Danzer E, Gerdes M, Bernbaum J, et al. Neurodevelopmental outcome of infants with congenital diaphragmatic hernia prospectively enrolled in an interdisciplinary follow-up program. J Pediat Surg 2010;**45**(9):1759-66.

4 Friedman S, Chen C, Chapman JS, et al. Neurodevelopmental outcomes of congenital diaphragmatic hernia survivors followed in a multidisciplinary clinic at ages 1 and 3. J Pediatr Surg 2008;**43**(6):1035-43.

5 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**(11):834-40.

6 Karimova A, Brown K, Ridout D, et al. Neonatal extracorporeal membrane oxygenation: practice patterns and predictors of outcome in the UK. Arch Dis Child Fetal Neonatal Ed 2009;**94**(2):F129-32.

7 Kattan J, Godoy L, Zavala A, et al. Improvement of survival in infants with congenital diaphragmatic hernia in recent years: effect of ECMO availability and associated factors. Pediatr Surg Int 2010;**26**(7):671-76.

8 Azarow K, Messineo A, Pearl R, et al. Congenital diaphragmatic hernia—A tale of two cities: The Toronto experience. J Pediatr Surg 1997;**32**(3):395-400.

9 Keshen TH, Gursoy M, Shew SB, et al. Does extracorporeal membrane oxygenation benefit neonates with congenital diaphragmatic hernia? Application of a predictive equation. J Pediatr Surg 1997;**32**(6):818-22.

10 Wilson JM, Lund DP, Lillehei CW, et al. Congenital diaphragmatic hernia—A tale of two

cities: The Boston experience. J Pediatr Surg 1997;**32**(3):401-05.

11 McGahren ED, Mallik K, Rodgers BM. Neurological outcome is diminished in survivors of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation. J Pediatr Surg 1997;**32**(8):1216-20.

12 Nijhuis-van der Sanden MW, van der Cammen-van Zijp MH, Janssen AJ, et al. Motor performance in five-year-old extracorporeal membrane oxygenation survivors: a population-based study. Crit Care 2009;**13**(2):R47.

13 Spoel M, van den Hout L, Gischler SJ, et al. Prospective longitudinal evaluation of lung function during the first year of life after repair of congenital diaphragmatic hernia. Pediatr Crit Care Med 2011;**13**(3):e133-9.

14 Stolar CJH, Crisafi MA, Driscoll YT. Neurocognitive outcome for neonates treated with extracorporeal membrane oxygenation: Are infants with congenital diaphragmatic hernia different? J Pediatr Surg 1995;**30**(2):366-72.

15 McNally H, Bennett CC, Elbourne D, et al. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. Pediatrics 2006;**117**(5):e845-54.

16 Stolar CJ, Snedecor SM, Bartlett RH. Extracorporeal membrane oxygenation and neonatal respiratory failure: experience from the extracorporeal life support organization. J Pediatr Surg 1991;**26**(5):563-71.

17 Gischler SJ, Mazer P, Duivenvoorden HJ, et al. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. J Pediatr Surg 2009;**44**(7):1382-89.

18 Spoel M, Laas R, Gischler SJ, et al. Diagnosis-related deterioration of lung function after extracorporeal membrane oxygenation. Eur Respir J Published Online First: 10 April 2012. doi:10.1183/09031936.00189911.

19 van der Cammen-van Zijp MHM, Gischler SJ, Hop WCJ, et al. Deterioration of exercise

capacity after neonatal extracorporeal membrane oxygenation. Eur Respir J 2011;**38**(5):1098-104.

20 van der Cammen-van Zijp MHM, Gischler SJ, Mazer P, et al. Motor-function and exercise capacity in children with major anatomical congenital anomalies: An evaluation at 5 years of age. Early Hum Dev 2010;**86**(8):523-28.

21 Duncan O. A socioeconomic index for all occupations. In: Reiss Jr. AJ, Hatt PK, Nort CC, eds. Occupations and Social Status. New-York: Free Press 1961:109-38.

22 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;**163**(7):1723-9.

23 Tesselaar, CD, Postema, RR, van Dooren, MF, et al. Congenital Diaphragmatic Hernia and Situs Inversus Totalis. Pediatrics 2004;**113**(3 Pt 1):e256-8.

24 Bleichrodt N, Drenth PJD, Zaal JM, et al. Revisie Amsterdamse Kinder Intelligentie Test; Instructies, Normen, Psychometrische gegevens. Lisse: Swets & Zeitlinger, 1984.

25 Kort W, Compaan E.L. WISC-III-NL. Handleiding. Amsterdam: NIP Dienstencentrum; 2002.

26 Smiths- Engelsman B. Dutch Manual Movement Assessment Battery for Children: Lisse: Swets en Zeitlinger, 1998.

27 Vos P. Bourdon-Vos. Handleiding (Manual Bourdon-Vos). Lisse: Swets & Zeitlinger; 1992.

28 Veerman JW, Straathof MAE, Treffers PDA, et al. Competentie Belevingsschaal voor Kinderen (CBSK). Lisse: Swets & Zeitlinger; 1997.

29 Van Dongen-Melman JEWM, Koot HM, Verhulst FC. Cross-Cultural Validation of Harter'S Self-Perception Profile for Children in a Dutch Sample. Educational and Psychological Measurement 1993;**53**(3):739-53.

30 Madderom MJ, Gischler SJ, Duivenvoorden HJ, et al. Neonatal Extra Corporeal

Membrane Oxygenation: Impaired health at five years of age. Pediatr Crit Care Med; accepted.

31 Engelen V, Haentjens MM, Detmar SB, et al. Health related quality of life of Dutch children: psychometric properties of the PedsQL in the Netherlands. Bmc Pediatr 2009;**3**(9):68.

32 Verhulst FC, van der Ende J, Koot HM. Handleiding voor de CBCL/ 4-18. Afdeling Kinder- en Jeugdpsychiatrie, Sophia Kinderziekenhuis/ Academisch Ziekenhuis Rotterdam/ Erasmus Universiteit Rotterdam; 1996.

33 Allison P. Logistic regression using the SAS system: theory and application. New-York: SAS institute; 1999.

34 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**(1):3-7.

35 Frisk V, Jakobson LS, Unger S, et al. Long-term neurodevelopmental outcomes of congenital diaphragmatic hernia survivors not treated with extracorporeal membrane oxygenation. J Pediatr Surg 2011;**46**(7):1309-18.

36 Hofkosh D, Feldman HM, Thompson AE, et al. Ten Years of Extracorporeal Membrane Oxygenation: Neurodevelopmental Outcome. Pediatrics 1991;**87**(4):549-55.

37 Schumacher RE, Palmer TW, Roloff DW, et al. Follow-up of Infants Treated With Extracorporeal Membrane Oxygenation for Newborn Respiratory Failure. Pediatrics 1991;**87**(4):451-57.

38 Inspectie van het onderwijs. De staat van het onderwijs. Onderwijsverslag 2009/2010. Utrecht: Inspectie van het onderwijs; 2011.

39 Poley M, Stolk E, Tibboel D, et al. Short term and long term health related quality of life after congenital anorectal malformations and congenital diaphragmatic hernia. Arch Dis Child

2004;**89**(9):836-41.

40 Tsao K, Lally KP. The Congenital Diaphragmatic Hernia Study Group: a voluntary international registry. Seminars in Pediatric Surgery 2008;**17**(2):90-97.

FIGURE LEGENDS

Figure 1

Flowchart

CDH = Congenital diaphragmatic hernia

ECMO = Extra Corporeal 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

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

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

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			0.017*
< 1 week	1 (6)	9 (47)	
1 week- 1 month	3 (19)	4 (21)	
>1 month	6 (38)	1 (5)	
Missing	6 (38)	5 (26)	
Use of methadone			0.005*
Yes	8 (50)	1 (5)	
Missing	3 (19)	3 (16)	
Use of muscle relaxants			0.010*
Preoperative only	5 (32)	14 (74)	
ICU 1 day- 1 week	0 (0)	1 (5)	
Missing	11 (69)	4 (21)	
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 [22]; 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 (VSD n=1 and ASD n=1) and situs inversus totalis (n=1) [23].Intracranial abnormalities were diagnosed with ultrasound during the initial admission and represent: corpus callosum agenesis j(n=1) and stroke (n=1).

Figure 1 Flowchart

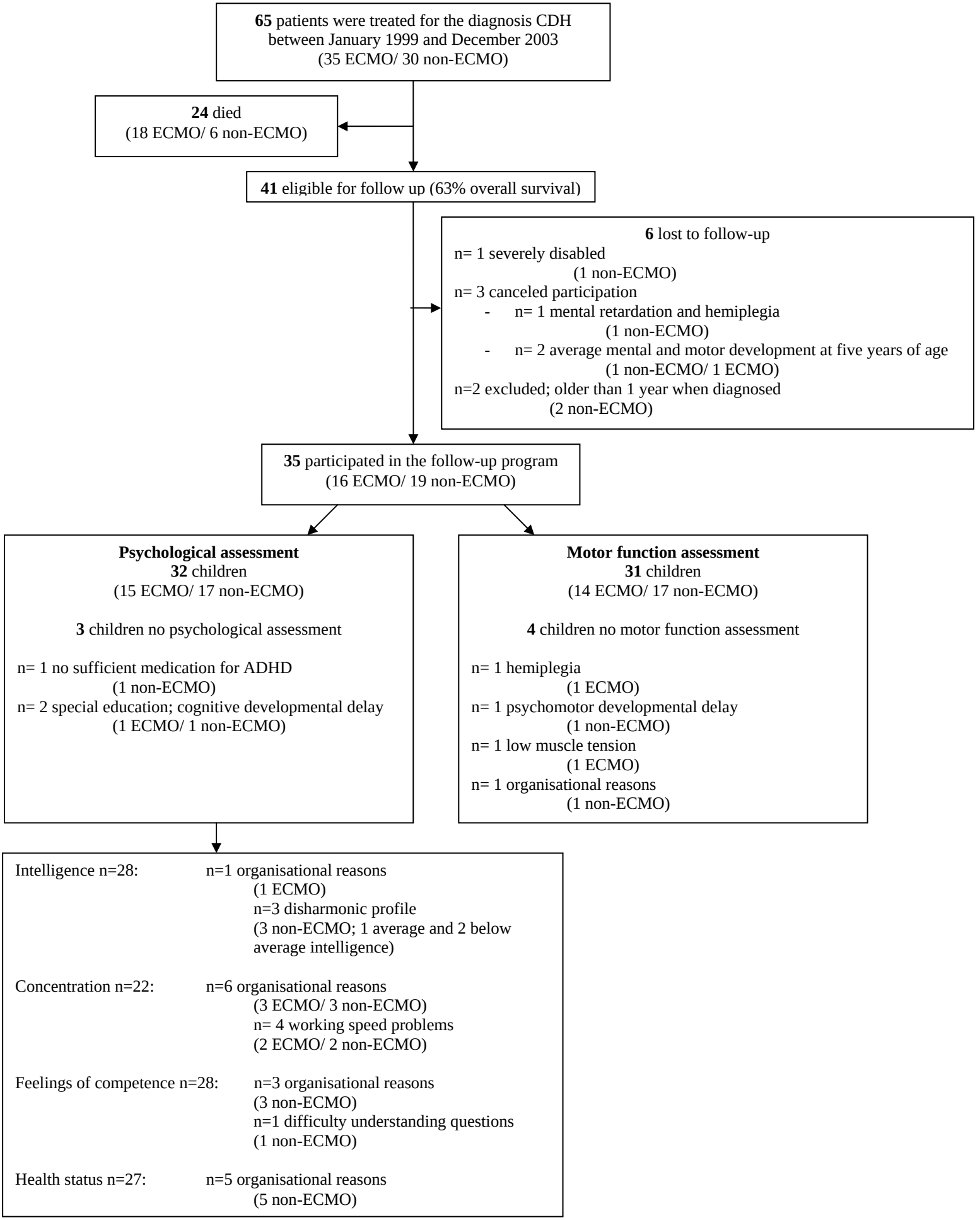

Figure 2 Intelligence in eight-year-old CDH-patients

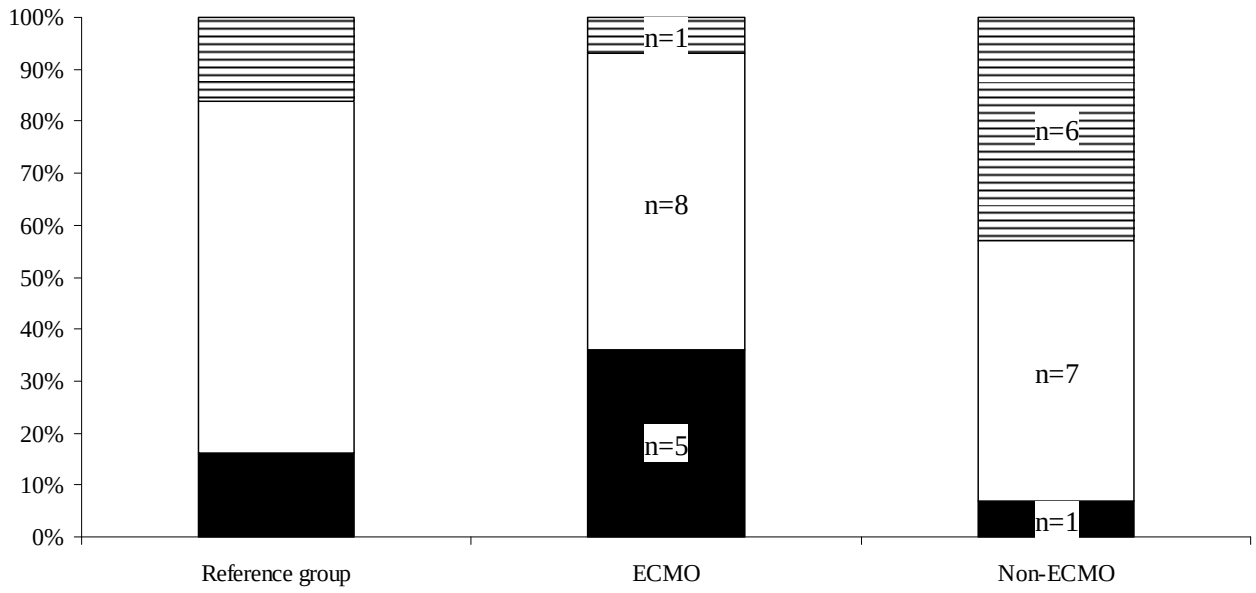

Figure 3 Motor function in eight-year-old CDH patients

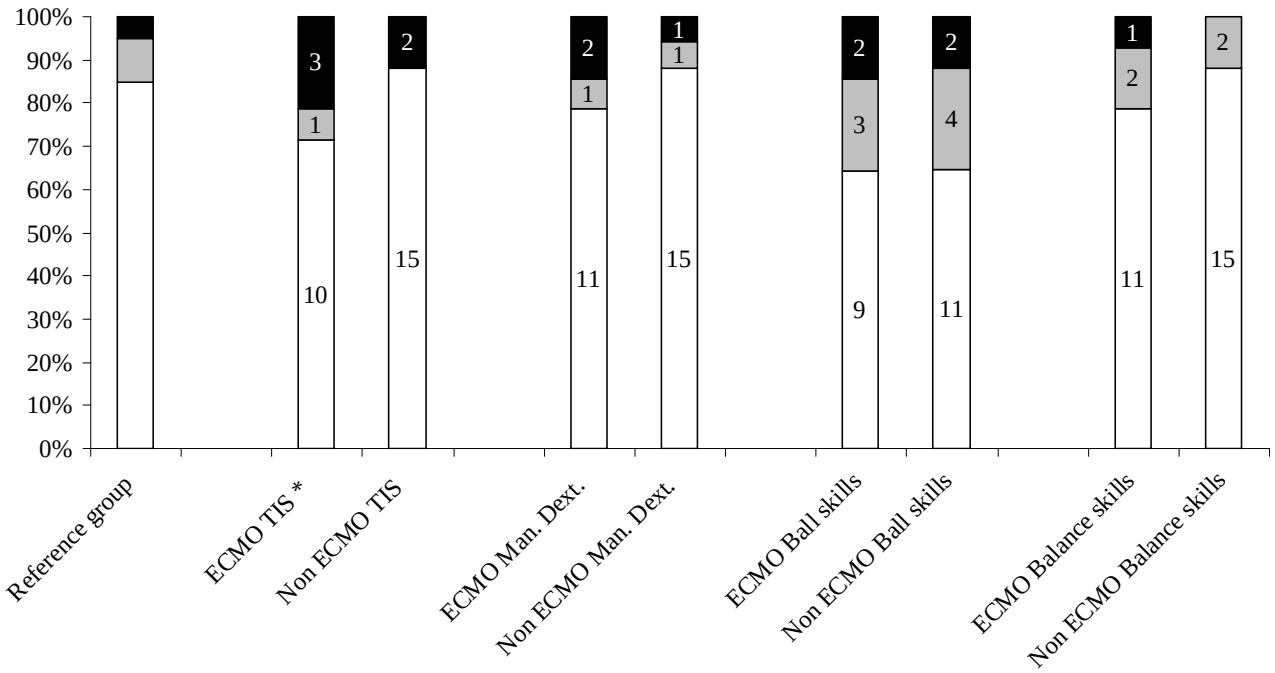

Figure 4 Combined intelligence and motor function development

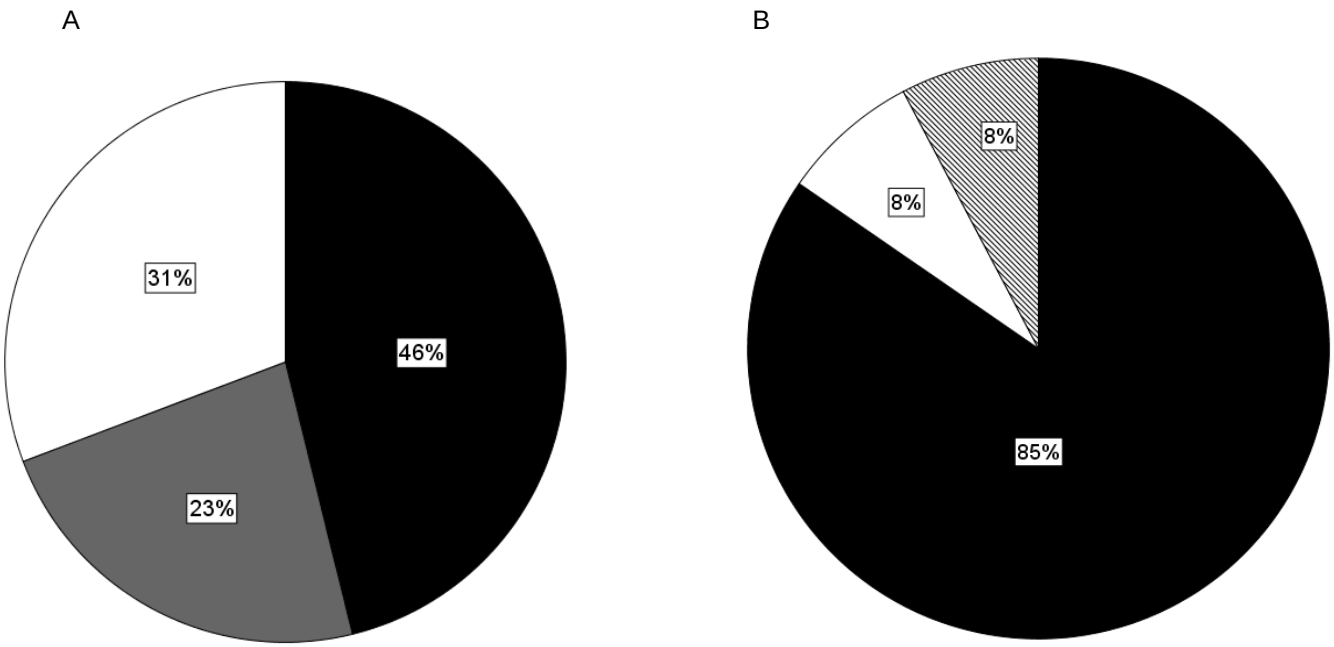

Table in online supplement

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**(1):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**(4):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**(9):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**(11):834-40. NA=not available.

Table in online 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.