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Psychological outcome and quality of life in children born with congenital diaphragmatic hernia

M G Peetsold,1 J Huisman,2 V E Hofman,2 H A Heij,3 H Raat,4 R J Gemke1

ABSTRACT
Objective: To assess psychological and social functioning and health related quality of life and its early determinants in children born with congenital diaphragmatic hernia (CDH).

Design: Cross-sectional follow-up study.

Setting: Outpatient clinic of a tertiary care hospital.

Participants: 33 CDH survivors aged 6–16 years.

Main exposure: Patients who developed CDH associated respiratory distress within 24 h after birth.

Main outcome measure: Psychological and social functioning assessed with the Wechsler Intelligence Scale for Children (WISC-R), Bourdon-Vos test, Beery Developmental Test of Visual Motor Integration, Child Behavior Checklist (CBCL) and Teacher Report Form (TRF), and health related quality of life assessed with the Child Health Questionnaire (CHQ) and Health Utilities Index (HUI).

Results: Normal mean (SD) total IQ (100.0 (13.2)) and normal visual-motor integration, but significantly lower results for sustained attention (Bourdon-Vos test, 38.8 (11.2) points) were found. Learning difficulties were reported by 30% of parents. Eight children had scores in the clinical range on the CBCL and/or TRF, indicating clinically significant behavioural problems. Except for the CHQ scale General Health, health status was not different from the reference population. No significant correlations between test results and severity of CDH were found, except for an association of general health and physical functioning with length of hospital stay.

Conclusion: CDH patients are at risk for subtle cognitive and behavioural problems, probably not related to CDH severity. Perception of general health is reduced compared to the reference population, indicating that CDH survivors and their parents believe their health is poor and likely to get worse.

Congenital diaphragmatic hernia (CDH) is a life threatening anomaly with a mortality rate ranging from 10% to 50%, depending on case selection.5–9 Long term follow-up studies have shown that patients born with high risk CDH (ie, patients who develop CDH associated respiratory distress within the first day of life) experience significant CDH associated complications including respiratory problems, gastroesophageal reflux disease, nutritional problems and growth retardation.6–7

The first days of life of a CDH patient are a critical period in which the child is at risk of developing neurological damage from hypoxia, hypercapnia and acidosis due to the combination of pulmonary hypoplasia and pulmonary hypertension.6 Most follow-up studies are limited to the first 5 years after CDH repair and include a heterogeneous group of CDH patients treated with and without extracorporeal membrane oxygenation (ECMO). Neurological morbidity has been reported in 10–30% of these patients.9–14 CDH patients are predisposed to several factors, such as perinatal and postnatal hypoxia, hypercapnia and acidosis, that can interfere with central nervous system development15 and serious problems in long-term psychosocial functioning and behaviour can be expected.9–14

Due to high co-morbidity, health related quality of life in a significant proportion of CDH patients may be compromised. However, little is known about the impact of long term health problems on the overall health related quality of life of these patients. Only two studies have assessed health related quality of life in CDH survivors, and they suggest a favourable health related quality of life for the majority of patients.19–20

The primary objective of this study was therefore to assess cognitive, behavioural and psychological outcome as well as the health related quality of life of children not treated with ECMO 6–16 years after surgical repair of high risk CDH. The secondary objective was to investigate whether the
neonatal characteristics of CDH were related to severity of cognitive deficits and health related quality of life.

METHODS

Patients
All patients born with high risk CDH (CDH associated respiratory distress within the first day of life) referred to the Pediatric Surgical Centre of Amsterdam between 1987 and 1999 were considered eligible. The patient’s history was reviewed, in particular several perinatal and postnatal variables, through the use of standardised forms. Ethics permission for the study was granted by the local ethics committee. Written informed consent was obtained from all patients and their parents or guardians prior to participation.

Eighty five children born with CDH were referred to the Pediatric Surgical Centre of Amsterdam. Thirty three patients died. Eleven patients were excluded because of late CDH. To prevent confounding, CDH patients treated with ECMO were excluded (n = 1).

Of the remaining 40 high risk CDH patients, 33 (83%) agreed to participate (fig 1), while four refused to participate because of lack of time.

There were no significant differences between the basic characteristics of participants and non-participants (table 1).

Study design
Patients who gave informed consent visited the outpatient clinic, where a detailed medical history and information concerning school and school performance were obtained. Neurocognitive functioning was assessed with the Wechsler Intelligence Scale for Children Revised for the Netherlands (WISC-R), the Bourdon-Vos test and the Beery Developmental Test of Visual Motor Integration (Beery VMI). Behaviour was assessed with the Child Behavior Checklist (CBCL).

Neurocognitive functioning

WISC-R
The WISC-R is the Dutch version of the Wechsler Intelligence Scale for Children-Revised and yields three IQs: full scale, verbal and performance IQ. The test has Dutch norms, standardised with a mean (SD) of 100 (15) for all three IQ scores and is validated for the Dutch population.

Bourdon-Vos test
Selective attention was assessed with the Bourdon-Vos test. This paper-and-pencil test measures sustained selective attention and concentration in terms of speed and accuracy. The validity, sensitivity and reliability of the Bourdon-Vos test appear to be highly acceptable.

Beery VMI test
The Beery VMI test is a paper-and-pencil test for children aged 3–18 years and measures integration of visual perceptual and motor abilities. The test has proven to be valid and reliable. The computed raw item scores are transformed into standard scores (T scores).

Behaviour

CBCL
The CBCL comprises a parent form and a teacher report form (TRF) and contains 120 items which are scored on a three-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very or often true) and was completed by the mother. A total problem score and two broad-band groupings were scored: an internalising grouping containing items such as withdrawn behaviour, somatic complaints without physical cause, and anxious-depressed feelings and an externalising grouping containing items such as aggressive and delinquent behaviour. All scores were converted into T scores. The CBCL has a Dutch version with Dutch norms with good reliability and validity. Teachers completed the teacher’s report form (TRF) which is a teacher version of the CBCL. For the CBCL and the TRF, proportions of children with scores in the normal and the clinical range are given. Total T scores >63 classify children in the clinically significant range (upper 10% of population norm groups).

Health related quality of life and health status

CHQ
Health related quality of life was assessed using the CHQ-PF50 (for parents) and the CHQ-CF87 (for children >10 years of age). Results of the CHQ-PF50 and the CHQ-CF87 were compared with norm scores based on a representative sample of 353 Dutch schoolchildren aged 5–13 years and norm scores based on a sample of 475 Dutch adolescents, respectively, using the unpaired t test (see online supplementary data for more information about the CHQ).

In order to indicate clinical relevance of statistically significant differences, Cohen’s effect sizes were calculated. Effect sizes (d) were calculated as follows: (mean (a)−mean (b))/largest standard deviation. According to Cohen, effect sizes...
between 0.2 and 0.5 indicate a small effect, an effect size between 0.5 and 0.8 indicates a moderate effect, and effect sizes of 0.8 or larger are considered to be a large effect.31

HUI-3
The HUI-3 is a generic multi-attribute health status classification system, consisting of eight attributes. Each attribute consists of five to six levels representing the range of functioning from normal (one) to severely impaired (five or six) (see online supplementary data for more information about the HUI).

Statistical analysis
The unpaired t test was used for normally distributed continuous data and non-parametric tests for non-normally distributed continuous data. The Fisher exact test or the χ² test was used for comparing categorical data. Test results were compared with population norms using the one sample t test. Bonferroni correction was performed in order to correct for multiple testing.

We used the following independent variables, estimating the severity of the CDH, that could predict psychological test results and health related quality of life (dependent variables): length of stay in the hospital (LOS), Apgar score after 5 min (ASS), duration of ventilation and use of a patch. After an univariate regression analysis was carried out, multivariate regression analysis was performed entering all independent variables that had a p value of less than 0.1 on univariate analysis. This was done only for the dependent variables psychological test results and CHQ item scales with significant analysis. This was done only for the dependent variables. Statistical significance was reached when p<0.05. All procedures were performed with SPSS 15.0.

RESULTS
Patients
The mean (SD) gestational age of the participants was 38.9 (2.0) weeks. Three children were born before or at a gestational age of 36 weeks (one at 32 weeks, one at 34 weeks and one at 36 weeks). Twenty one (64%) of the participants were male. CDH repair was performed 1.8 (SD 2.3) days (median 1 day; range 0–12 days) after birth. All patients reported to have neurological abnormalities had a mild (motor) developmental delay in the first 2 years of life.

One patient was discharged with oxygen and needed it for 5 months after discharge due to persistent pulmonary hypertension.
Mean (SD) age at follow-up was 10.2 (3.3) years (table 1).

Neurocognitive and school functioning and behaviour
The majority of the participants (61%) attended primary school and nine children (27%) went to secondary school. Four children (12%) required special educational services. Learning problems were reported by the parents of 10 children (30%).

WISC-R
Thirty of 33 patients completed the WISC-R (table 2). One patient had already performed the test at school, but the results were not complete and could not be used. Two children did not complete the test because of concentration failure and visual incapacity, respectively. Four children had a total IQ that was significantly lower than the Dutch norm score (<−1 SD).

Bourdon-Vos test
The same two children who did not complete the WISC-R did not complete the Bourdon-Vos test either and for the same reasons. The mean (SD) score was significantly lower in CDH patients when compared to population norms (38.8 (11.2) points; 95% CI of the difference: −15.4 to −7.11; p<0.001). The difference remained significant after Bonferroni correction. Twelve children (39%) had a score at or below −1 SD.

Beery VMI test
All patients completed the Beery VMI test. Mean (SD) score was 47.8 (10.9) (95% CI of the difference: −6.00 to 1.70; p = 0.26); no significant difference was found compared to the mean population norm group scores.

CBCL
Twenty eight mothers and 24 teachers of 28 children completed the CBCL and/or TRF. In five children no CBCL or TRF was...
Table 2 Results of the WISC-R

<table>
<thead>
<tr>
<th>WISC-R, n = 31</th>
<th>Score, mean (SD)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total verbal IQ</td>
<td>99.5 (14.0)</td>
<td>94.3</td>
</tr>
<tr>
<td>Total performance IQ</td>
<td>100.6 (14.5)</td>
<td>95.2</td>
</tr>
<tr>
<td>Total IQ</td>
<td>100.0 (13.2)</td>
<td>95.0</td>
</tr>
</tbody>
</table>

WISC-R, Wechsler Intelligence Scale for Children Revised for the Netherlands.

Table 3 Results of the CBCL

<table>
<thead>
<tr>
<th>CBCL score</th>
<th>Mother (CBCL) (n = 28)</th>
<th>95% CI difference (SD)</th>
<th>Teacher (TRF) (n = 24)</th>
<th>95% CI difference (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total problem score</td>
<td>6 (21%)</td>
<td>−3.8 (6.0)</td>
<td>3 (13%)</td>
<td>−2.4 (8.6)</td>
</tr>
<tr>
<td>Internalising problem score</td>
<td>6 (21%)</td>
<td>−3.1 (6.5)</td>
<td>5 (21%)</td>
<td>−2.2 (9.4)</td>
</tr>
<tr>
<td>Externalising problem score</td>
<td>3 (11%)</td>
<td>−5.6 (2.9)</td>
<td>2 (8%)</td>
<td>−3.6 (7.8)</td>
</tr>
</tbody>
</table>

CBCL, Child Behavior Checklist; TRF, Teacher Report Form.

95% Confidence intervals (CI) of the difference with norm scores of the mother and teacher (both 50 (SD 10)) were calculated. No significant differences were found when compared to the norm score.
Table 4  Results of the CHQ-PF50 and the CHQ-CF87 compared to reference populations

<table>
<thead>
<tr>
<th>CHQ-PF50</th>
<th>CDH patients (n = 33)</th>
<th>Reference population* (n = 353)</th>
<th>p Value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>93.4 (15.3)</td>
<td>99.1 (4.3)</td>
<td>&lt;0.001</td>
<td>0.37</td>
</tr>
<tr>
<td>Role functioning: emotional/behaviour</td>
<td>98.6 (4.7)</td>
<td>97.9 (7.2)</td>
<td>0.58</td>
<td>0.10</td>
</tr>
<tr>
<td>Role functioning: physical</td>
<td>99.5 (3.0)</td>
<td>95.8 (15.6)</td>
<td>0.18</td>
<td>0.24</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>90.6 (14.4)</td>
<td>85.7 (17.2)</td>
<td>0.11</td>
<td>0.29</td>
</tr>
<tr>
<td>General behavior</td>
<td>80.7 (12.6)</td>
<td>78.5 (13.1)</td>
<td>0.35</td>
<td>0.17</td>
</tr>
<tr>
<td>Mental health</td>
<td>79.5 (15.4)</td>
<td>81.4 (12.1)</td>
<td>0.41</td>
<td>0.12</td>
</tr>
<tr>
<td>Self esteem</td>
<td>77.7 (11.4)</td>
<td>79.2 (11.0)</td>
<td>0.47</td>
<td>0.13</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>66.4 (19.0)</td>
<td>82.9 (13.4)</td>
<td>&lt;0.001</td>
<td>0.87</td>
</tr>
<tr>
<td>Parental impact: emotional</td>
<td>77.3 (24.1)</td>
<td>86.3 (15.2)</td>
<td>0.002</td>
<td>0.37</td>
</tr>
<tr>
<td>Parental impact: time</td>
<td>93.1 (18.5)</td>
<td>94.0 (13.0)</td>
<td>0.70</td>
<td>0.05</td>
</tr>
<tr>
<td>Family activities</td>
<td>89.1 (17.1)</td>
<td>91.5 (11.9)</td>
<td>0.28</td>
<td>0.14</td>
</tr>
<tr>
<td>Family cohesion</td>
<td>72.5 (19.6)</td>
<td>72.2 (19.4)</td>
<td>0.93</td>
<td>0.02</td>
</tr>
<tr>
<td>Physical summary score</td>
<td>53.3 (6.7)</td>
<td>56.4 (5.7)</td>
<td>0.003</td>
<td>0.46</td>
</tr>
<tr>
<td>Psychosocial summary score</td>
<td>52.8 (7.2)</td>
<td>53.2 (6.4)</td>
<td>0.73</td>
<td>0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHQ-CF87</th>
<th>CDH patients (n = 16)</th>
<th>Reference population† (n = 475)</th>
<th>p Value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>92.8 (8.6)</td>
<td>96.0 (6.9)</td>
<td>0.07</td>
<td>0.37</td>
</tr>
<tr>
<td>Role social limitations: emotional/behavior</td>
<td>91.3 (15.0)</td>
<td>89.4 (17.2)</td>
<td>0.66</td>
<td>0.11</td>
</tr>
<tr>
<td>Role functioning: physical</td>
<td>91.7 (14.9)</td>
<td>95.0 (12.9)</td>
<td>0.31</td>
<td>0.22</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>80.0 (16.7)</td>
<td>73.5 (22.7)</td>
<td>0.06</td>
<td>0.29</td>
</tr>
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<td>General behavior</td>
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<td>0.11</td>
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<td>0.42</td>
</tr>
<tr>
<td>Family cohesion</td>
<td>78.4 (21.0)</td>
<td>70.6 (23.5)</td>
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CDH, congenital diaphragmatic hernia; CHQ, Child Health Questionnaire.
Values are mean (SD). Effect sizes (d) were calculated as follows: \[ \text{mean (a) - mean (b)} / \text{largest standard deviation}. \] According to Cohen, effect sizes between 0.2 and 0.5 indicate a small effect, an effect size between 0.5 and 0.8 indicates a moderate effect, and effect sizes of 0.8 or larger are considered to be a large effect.31

Table 4 Results of the CHQ-PF50 and the CHQ-CF87 compared to reference populations.

Figure 2  Effect sizes of all item scales of the CHQ-CF87 and the CHQ-PF50. BP, bodily pain; FA, family activities; FC, family cohesion; GB, general behavior; GH, general health perceptions; MH, mental health; PF, physical functioning; PhSS, physical summary score; PIE, parental impact: emotional; PIT, parental impact; PsSS, psychosocial summary score; REB, role functioning emotional/behavior; RFP, role functioning physical; SE, self esteem.
problems in the internalising broad-band grouping reported by teachers.

We found that health related quality of life was lower than in other studies.\textsuperscript{19, 20} CDH patients gave themselves a higher CHQ score than their parents. Whereas CDH survivors only rated the domain general health perceptions significantly lower than the general population, parents of CDH patients also documented a lower physical functioning, general health and physical summary score for their child, but with rather small effect sizes. An explanation could be that CDH patients tend to underestimate their physical complaints and might not fully comprehend their limitations. Another possibility may be that the way CDH patients experience themselves reflects a self-defensive adaptation style. Except for two CHQ domains (general health perceptions and physical functioning) and length of hospital stay, we did not find a correlation between test results and estimation of severity of CDH. This could be due to the relative small sample size. Furthermore, we defined a selected group of variables with most relevant clinical information to be included in the univariate and multivariate analysis. We may have missed associations of perinatal variables that could not be established unequivocally, such as using the best oxygenation index on day 1 to represent hypoxaemia rather than Apgar scores.

Our cohort had similar neonatal characteristics compared to those survivors who did not participate. We therefore infer that the results from our cohort are generalisable to the group of CDH patients that present with early respiratory symptoms (ie, high risk CDH patients).

We recognise that, despite comparing our data with norm scores based on a healthy reference population, a control group is preferable. Another limitation is the broad age range of the studied patients and, as stated above, the relatively small sample size (although larger than in most other reports), which is almost inevitable due to the relatively low incidence of CDH and the high mortality. Furthermore, we are aware that assessment of health related quality of life in children can be difficult, especially for the younger children who might have problems with abstract concepts and language.

In summary, our study demonstrated that, 6–16 years after repair, the perception of the general health of CDH survivors is reduced when compared to the reference population, indicating that parents as well as CDH survivors themselves believe their health is poor and likely to get worse. CDH patients may be at risk for behavioural problems, which is not related to estimation of severity of CDH. This may contribute to school failure and the need for special educational services. In contrast with other studies, we did not find evidence of severe cognitive deficits. This underscores the fact that a long-term prospective cross-sectional follow-up study, with a standardised test battery particularly of cognitive functioning, is mandatory in all CDH patients.

**Competing interests:** None.

**Ethics approval:** Ethics approval for the study was granted by the local ethics committee.

**Patient consent:** Obtained.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

**REFERENCES**


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**Table 5 Results of the HUI-3**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>CDH patients, n = 33</th>
<th>Reference population, n = 1435* p Value</th>
</tr>
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<tbody>
<tr>
<td>Vision</td>
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</tr>
<tr>
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</tr>
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</table>

**CDH, congenital diaphragmatic hernia.**

The HUI-3 multi-attribute utility score (u) is calculated according to the following formula: $u = 1.371 + b_1 x_1 + b_2 x_2 + b_3 x_3 + b_4 x_4 + b_5 x_5 + b_6 x_6 + b_7 x_7$ – 0.371. The letter b represents the single attribute utility score for a specific attribute at a specific functional level.\textsuperscript{16} *Reference population from Raat et al.\textsuperscript{19}*

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Archivist

Treatment for cryopyrin-associated periodic syndrome

The term cryopyrin-associated periodic syndrome (CAPS) embraces several rare, inherited, inflammatory disorders including the familial cold autoinflammatory syndrome, the Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disorder (otherwise known as the congenital infantile neurologic, cutaneous and articular syndrome). Common features include onset in infancy, severe fatigue, fever, myalgia, anaemia, and inflammation of skin, eyes, bones, joints and meninges. Sensorineural deafness and intellectual impairment may occur and systemic AA amyloidosis develops in about a quarter of all patients. CAPS is caused by mutations in the cryopyrin gene, NLRP3, causing overproduction of interleukin-1β. Now (Helen J Lachmann and colleagues. New England Journal of Medicine 2009;360:2416–25; see also Editorial, ibid: 2467–70) a human anti-interleukin-1β monoclonal antibody (canakinumab) has been shown to be a highly effective treatment for CAPS. Thirty four of 35 patients (four aged 4–16 years) responded completely to a single dose of canakinumab. Of the responders, 31 were then randomised to canakinumab or placebo every 8 weeks for up to 24 weeks. Patients continuing canakinumab remained in remission but disease flares occurred in 13/16 in the placebo group. Concentrations of C-reactive protein and serum amyloid A protein returned to normal on treatment with canakinumab. The incidence of suspected infections was greater with canakinumab and two serious adverse events occurred during treatment, one of urological sepsis and one of vertigo.

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