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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. 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.

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. 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. CDH patients are predisposed to several factors, such as perinatal and postnatal hypoxia, hypercapnia and acidosis, that can interfere with central nervous system development and serious problems in long-term psychosocial functioning and behaviour can be expected.

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.

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

What is already known on this topic

- Small studies have shown significantly more emotional and behavioural problems than expected in congenital diaphragmatic hernia (CDH) survivors.
- CDH patients not treated with extracorporeal membrane oxygenation might also be at risk for cognitive problems.
- Despite significant CDH associated symptoms, a few quality of life studies in older patients suggest that the majority of patients enjoy quite healthy lives.

What this study adds

- CDH survivors have a near-normal level of cognitive functioning but are at risk for attention and concentration deficits.
- Many CDH survivors can have significant emotional and behavioural problems which may contribute to school failure.
- Perception of general health is reduced, indicating that parents and CDH survivors believe their health is poor and is likely to get worse.

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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).

Health related quality of life and health status were assessed
with the Child Health Questionnaire (CHQ) and the Health
Utilities Index 3 (HUI-3).

In order to create optimal conditions, all tests were performed
in the morning and all children were tested by the same
experienced child psychologist.

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 scores21 and is
validated for the Dutch population.22

Bourdon-Vos test
Selective attention was assessed with the Bourdon-Vos test.
This paper-and pencil test measures sustained selective atten-
tion and concentration in terms of speed and accuracy.23 The
validity, sensitivity and reliability of the Bourdon-Vos test
appear to be highly acceptable.24

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.25 The test has proven to be valid and reliable.26
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 con-
taining 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).27

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).28 Results of the CHQ-PF50 and the CHQ-CF87 were
compared with norm scores based on a representative sample of
355 Dutch schoolchildren aged 5–13 years29 and norm scores
based on a sample of 475 Dutch adolescents,30 respectively,
using the unpaired t test (see online supplementary data for
more information about the CHQ).

In order to indicate clinical relevance of statistically sig-
nificant 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

Figure 1 Exclusion and enrolment of patients. Eleven patients had late
presenting CDH and were therefore excluded. One patient was excluded
because of ECMO treatment. CDH, congenital diaphragmatic hernia;
ECMO, extracorporeal membrane oxygenation.
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 differences between the study population and the reference population or when there was a trend towards significance (p<0.1). 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 3 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 1

<table>
<thead>
<tr>
<th></th>
<th>Participating (n = 33)</th>
<th>Non-participating (n = 7)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21 (64%)</td>
<td>3 (43%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Age at follow-up (years)</td>
<td>10.2 (3.3)</td>
<td>11.4 (3.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.9 (2.0)</td>
<td>40.1 (1.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>5 min AS &lt;5</td>
<td>6 (18%)</td>
<td>1 (14%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Left sided CDH</td>
<td>28 (85%)</td>
<td>7 (100%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Ventilation (days)</td>
<td>15.3 (15.0)</td>
<td>12.3 (8.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>LOS hospital (median days)</td>
<td>24</td>
<td>27</td>
<td>0.77</td>
</tr>
<tr>
<td>LOS ICU (median days)</td>
<td>13.5</td>
<td>12.5</td>
<td>0.53</td>
</tr>
<tr>
<td>GERD</td>
<td>7 (21%)</td>
<td>2 (29%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>11 (33%)</td>
<td>4 (57%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Neurologic deficits</td>
<td>9 (27%)</td>
<td>1 (14%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Recurrent CDH</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

AS, Apgar score; CDH, congenital diaphragmatic hernia; GERD, gastroesophageal reflux disease; ICU, intensive care unit; LOS, length of stay.

Numbers indicate numbers of patients, except age at follow-up, gestational age, ventilation and length of stay. Variables are expressed as mean (SD) unless otherwise stated. Cardiac abnormalities were diagnosed in the neonatal period and included atrial septal defect, ventricular septal defect or a combination. All patients with neurological deficits had (motor) developmental delay in the first 2 years of life. GERD was demonstrated by gastrointestinal x ray series, pH-metry and/or endoscopy in the first 2 years after CDH repair. No significant differences were observed.

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).
Health related quality of life

CHQ

Parents of all 33 children completed the CHQ-PF50 (table 4). Only (Cohen’s) effect sizes for general health perceptions were 0.87 indicating a large effect on this domain (fig 2).

Sixteen of 17 children completed the CHQ-CF87 and one patient refused (table 4).

HUI-3

The parents of all 33 patients completed the HUI-3 questionnaire. Only cognition was significantly lower in the CDH group. Vision was lower in CDH survivors, although this was not significant (table 5).

Explaining outcome based on neonatal characteristics

In linear regression analysis associations were found only for the domain General Health Perceptions and the domain Physical Functioning of the CHQ-CF87. General Health Perceptions decreases 0.12 points for every day the child stayed in hospital (constant 92.70; R² = 0.259), and Physical Functioning decreased 0.06 points for every day the child stayed in hospital (constant 95.42; R² = 0.799) when corrected for Apgar score after 5 min, LOS or duration of ventilation.

DISCUSSION

In general, we found subtle cognitive problems in patients 6–16 years after CDH repair. Although CDH patients had a normal level of cognitive functioning, since mean IQ scores were comparable to the healthy population, the Bourdon-Vos test returned. Responders and non-responders did not differ as regards the peri- and postnatal variables mentioned in table 1. Six CDH patients (21%) had total problem scores in the clinical range on the CBCL, which is significantly more than the expected 10% of the reference population (x²; p = 0.003)²² (table 5). There were no differences between patients in the normal and in the clinical range of the CBCL for Apgar score after 5 min, LOS or duration of ventilation.

No significant differences were found when compared to the norm score.

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>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total verbal IQ</td>
<td>99.5 (14.0)</td>
<td>94.3</td>
<td>104.8</td>
<td></td>
</tr>
<tr>
<td>Total performance IQ</td>
<td>100.6 (14.5)</td>
<td>95.2</td>
<td>106.0</td>
<td></td>
</tr>
<tr>
<td>Total IQ</td>
<td>100.0 (13.2)</td>
<td>95.0</td>
<td>104.9</td>
<td></td>
</tr>
</tbody>
</table>

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

No significant differences were found when compared to the norm score.

Table 3 Results of the CBCL

<table>
<thead>
<tr>
<th>CBCL score</th>
<th>Mother (CBCL) (n = 28)</th>
<th>Teacher (TRF) (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) T score ≥63</td>
<td>95% CI difference (SD)</td>
</tr>
<tr>
<td>Total problem score</td>
<td>6 (21%)</td>
<td>−3.8 (6.0)</td>
</tr>
<tr>
<td>Internalising problem score</td>
<td>6 (21%)</td>
<td>−3.1 (6.5)</td>
</tr>
<tr>
<td>Externalising problem score</td>
<td>3 (11%)</td>
<td>−5.6 (2.9)</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.
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 internising broad-band grouping reported by teachers.

We found that health related quality of life was lower than in other studies. 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


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, 51 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.

Provenance and peer review: Commissioned; not externally peer reviewed.

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