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

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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, Beeny 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...
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).

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 \( \chi^2 \) test was used for comparing categorical data. Test results were compared with population norms using the one sample t-test. Statistical analysis was 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 available. 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%).
Table 2 Results of the WISC-R

<table>
<thead>
<tr>
<th>WISC-R, n = 31</th>
<th>Score, mean (SD)</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>
</tr>
<tr>
<td>Total performance IQ</td>
<td>100.6 (14.5)</td>
<td>95.2</td>
<td>106.0</td>
</tr>
<tr>
<td>Total IQ</td>
<td>100.0 (13.2)</td>
<td>95.0</td>
<td>104.9</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.

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 S).

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 AS5, duration of ventilation and use of a patch for closure of CDH.

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 showed a significantly lower score in CDH patients, implying CDH survivors might be at risk for attention and concentration deficits. Although mean behaviour problem scores were comparable to reference norms, it was remarkable that 20% of the CDH patients (versus 10% of the Dutch general population) appeared to have clinically relevant behavioural problems.

So far only a few studies have reported on the long term cognitive development of CDH patients not treated with ECMO (roughly 50% of the high risk CDH patients are not treated with ECMO36–38) and most of these studies describe children with a maximum age of only 4 years.39 Bouman et al studied a small sample of CDH survivors (11 patients, aged 8–12 years) with comparable patient characteristics and found a mean IQ of 85, while almost half of the children obtained IQ scores around or more than 1 SD below normal. The discrepancy might be due to the small sample size, which may also have resulted in a potential selection bias.39 However, despite our, on average, good test results, it has to be noted that participation of CDH patients in special education (12%) was more frequent than in the general Dutch population (4%).39 20 compatible with the lower HUI single attribute score on cognition, suggesting that CDH patients learn and/or remember school work more slowly than classmates and sometimes require special education.

It has been suggested that neurological abnormalities in CDH patients might (also) be due to CDH repair, since surgery induces a significant inflammatory response, which may provoke cerebral white matter injury. White matter injury, which has been described in infants asphyxiated at term35 as well as in CDH patients,37 38 might result in cognitive impairment.39 In addition, children who underwent surgery in the neonatal period because of oesophageal atresia, imperforate anus or abdominal wall defects, had more learning, emotional and behavioural problems,39–40 implying that surgery in the neonatal period might play a role.

In this study approximately one fifth of the mothers and the teachers of CDH survivors reported significant emotional and behavioural problems, especially in the internalising broad-band grouping. Sub-analysis showed that according to their mothers, most children had a deviant score on the item somatic complaints without a physical cause. A possible explanation is that parenting a child with a potentially life-threatening congenital anomaly is stressful, since follow-up studies of children with other serious congenital anomalies (eg, oesophageal atresia, abdominal wall defects) also have also found increased levels of emotional and behavioural problems.39–40 However, this does not explain the relatively high incidence of

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 95% CI difference (SD)</td>
<td>n (%) T score ≥63 95% CI difference (SD)</td>
</tr>
<tr>
<td>Total problem score</td>
<td>6 (21%) −3.8 (6.0)</td>
<td>3 (13%) −2.4 (8.6)</td>
</tr>
<tr>
<td>Internalising problem score</td>
<td>6 (21%) −3.1 (6.5)</td>
<td>5 (21%) −2.2 (9.4)</td>
</tr>
<tr>
<td>Externalising problem score</td>
<td>3 (11%) −5.6 (2.9)</td>
<td>2 (8%) −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 (18.6)</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>
<tr>
<td>General behavior</td>
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<td>0.66</td>
<td>0.11</td>
</tr>
<tr>
<td>Mental health</td>
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<td>76.5 (15.4)</td>
<td>0.29</td>
<td>0.26</td>
</tr>
<tr>
<td>Self esteem</td>
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<td>74.7 (12.2)</td>
<td>0.06</td>
<td>0.47</td>
</tr>
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<td>0.09</td>
<td>0.42</td>
</tr>
<tr>
<td>Family cohesion</td>
<td>78.4 (21.0)</td>
<td>70.6 (23.5)</td>
<td>0.19</td>
<td>0.33</td>
</tr>
</tbody>
</table>

CDH, congenital diaphragmatic hernia; CHQ, Child Health Questionnaire.
Values are mean (SD). 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
*Reference population from Raat et al.29 †Reference population from Raat et al.30

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.
Table 5 Results of the HUI-3

<table>
<thead>
<tr>
<th>Attribute</th>
<th>CDH patients, n = 33</th>
<th>Reference population, n = 1435*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision</td>
<td>0.981 (0.050)</td>
<td>0.994 (0.038)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hearing</td>
<td>1.000 (0.000)</td>
<td>0.996 (0.037)</td>
<td>0.58</td>
</tr>
<tr>
<td>Speech</td>
<td>0.964 (0.092)</td>
<td>0.971 (0.082)</td>
<td>0.58</td>
</tr>
<tr>
<td>Ambulation</td>
<td>1.000 (0.000)</td>
<td>0.998 (0.036)</td>
<td>0.70</td>
</tr>
<tr>
<td>Dexterity</td>
<td>0.995 (0.031)</td>
<td>0.999 (0.022)</td>
<td>0.36</td>
</tr>
<tr>
<td>Emotion</td>
<td>0.984 (0.035)</td>
<td>0.977 (0.067)</td>
<td>0.57</td>
</tr>
<tr>
<td>Cognition</td>
<td>0.938 (0.112)</td>
<td>0.970 (0.080)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pain</td>
<td>0.986 (0.045)</td>
<td>0.976 (0.076)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Multivariate utility score, mean (SD)

<table>
<thead>
<tr>
<th>CDH patients</th>
<th>Reference population</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.906 (0.133)</td>
<td>0.929 (0.124)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

CDH, congenital diaphragmatic hernia.

The HUI-3 multi-attribute utility score (u) is calculated according to the following formula: 
\[ u = 1.371 \times b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + b_7 - 0.371 \times b_8. \]

The letter b represents the single attribute utility score for a specific attribute at a specific functional level. *Reference population from Raat et al.*

problems in the internalising 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 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

Original article


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 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.

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

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