ORIGINAL ARTICLE

# Cognitive development at 5.5 years of children with chronic lung disease of prematurity

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**Background:** Preterm infants with chronic lung disease (CLD) had impaired cognitive development and poorer eye-hand coordination at 10 months of age.
**Aims:** To study whether this effect of CLD persisted until school age and whether the severity of CLD affected outcome.
**Method:** Cognition and visual-motor skills were examined (Wechsler preschool and primary scale of intelligence, and tests from the Nepsy scale) in 60 very preterm children, without intraventricular haemorrhage or periventricular leucomalacia, at 5.5 years of age. Thirty two children suffered from CLD and 28 were controls.
**Results:** The groups did not differ significantly in cognitive outcome. Children with CLD and controls attained a full scale intelligence quotient (IQ) of 94.4 and 99.1, a verbal IQ of 99.6 and 101.5, and a performance IQ of 90.9 and 96.7 respectively. Similarly, no difference was found in tests of eye-hand control. However, the children with the most severe form of CLD had significantly lower performance (84.8) and full scale(87.6) IQs and worse visual-motor performance than the controls. CLD grade III, together with the need for glasses or lenses, had a significant impact on the explained variance.
**Conclusions:** At school age, children born very preterm and who experienced severe CLD had deficits in cognition, visual-motor perception, and performance. The findings suggest a need to consider intervention programmes for such infants.

The prevalence of neurological sequelae among preterm children with chronic lung disease (CLD) is significantly higher than among preterm children without CLD.[1] Recently it has been reported that CLD per se, even in the absence of ultrasound evidence of significant brain lesions, exerts an unfavourable effect on postnatal development. In a previous study, we reported impaired cognitive functions and poorer eye-hand coordination in 10 month old infants with CLD,[2] and Singer *et al*[3] reported suboptimal motor performance at 3 years of age.

An important question is whether such early suboptimal cognitive and motor development might lead to significant deficiencies at a later age, or whether they are overcome in time and therefore not manifest by school age. Our follow up study was designed to investigate this at 5.5 years of age.

We focused primarily on cognition and eye-hand coordination—that is, skills found previously to be affected negatively by CLD at an early age.

Visual abnormalities may affect perception and, in consequence, the development of fine motor control. Many infants born preterm suffer from retinopathy of prematurity (ROP), which, even in its regressed form, is associated with compromised visual function.[4] Thus, we also examined the possible impact of ROP and the use of glasses or contact lenses, other neonatal or medical risk factors as well as maternal education.

## METHODS

### Subjects

We selected 70 children with CLD from a population based study group of 291 very low birthweight (VLBW) children (birth weight < 1500 g), born between September 1988 and March 1993. A developmental check up had been carried out at 10 months of age. We have described previously the inclusion criteria, dropouts, and neonatal medical data for this index group.[2] At 5.5 years of age (± 2 weeks), the cognitive abilities of all children remaining from the population based group were assessed. Eleven children from the initial index group had moved away so were lost to follow up. The intelligence test (Wechsler preschool and primary scale of intelligence-revised (WPPSI-R)) was not performed on five of the children, because of a delay in the decision to include this test in the protocol. Thus, the final group consisted of 60 VLBW children, 32 of whom had been diagnosed with CLD, and 28 controls (fig 1). The diagnosis of CLD had been based on the occurrence of acute pulmonary injury during the first week of postnatal life: radiographic findings—that is, regions of hyperlucency interspersed with pulmonary scarring and atelectasis—and oxygen dependency for more than 28 days.[5] We classified CLD into three grades according to criteria described by Toce *et al*.[6] Grade I (two children) and II (11 children), representing relatively mild CLD, were combined into one group, and grade III (19 children) constituted the group with severe CLD. We selected controls from among consecutively born "healthy" VLBW children without CLD. No child had intraventricular haemorrhage/periventricular leucomalacia (PVL) of a grade > 2.

### Procedures

#### Assessment of cognitive functions

We assessed cognition using WPPSI-R,[7] applicable to children 3–7 years of age. This test consists of a verbal and a performance subscale, and the results are given in three measures, full scale intelligence quotient (IQ), verbal IQ, and performance IQ, with means of 100 and standard deviations of 15. When

**Abbreviations:** CLD, chronic lung disease; ROP, retinopathy of prematurity; VLBW, very low birthweight; PVL, periventricular leucomalacia; WPPSI-R, Wechsler preschool and primary scale of intelligence-revised; IQ, intelligence quotient

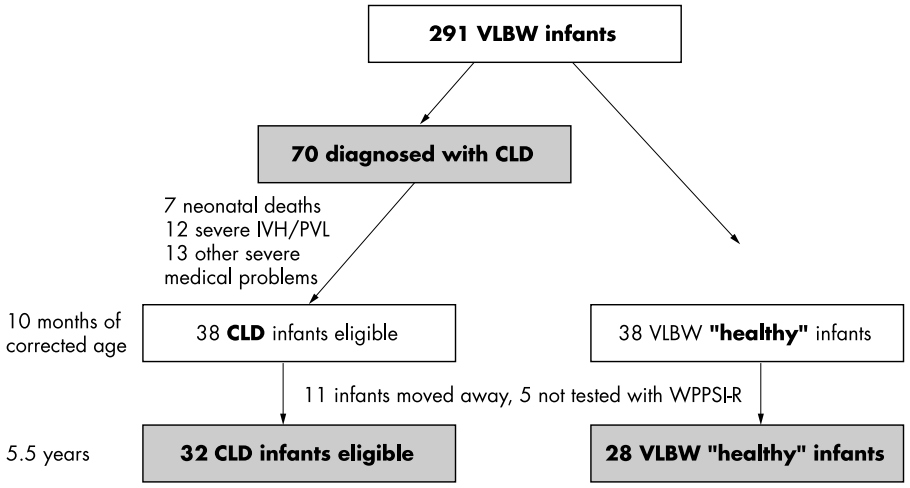


**Figure 1** Selection of study subjects. CLD, Chronic lung disease; VLBW, very low birthweight; PVL, periventricular leucomalacia; IVH, intraventricular haemorrhage.

calculating individual IQs, we used the corrected age of every child—that is, the chronological age less the number of weeks preterm (= conception age). The Swedish norm data of the test were used.

### Eye-hand coordination

All children were examined with the complete Nepsy neuropsychological test battery (46 subtests).[8] However, to specifically study eye-hand coordination and visual-perceptional skills, we included in our analysis only relevant subtests.

(1) Manual speed. A pegboard and an open box containing 10 pegs were placed in front of the child, who was told to put the pegs into the holes as fast as possible. Each hand was tested individually and the process repeated. The score was the total time required to perform these tasks.

(2) Three dimensional construction. The examiner constructed a bridge of three wooden cubes in front of the child and then asked him to copy this construction with his three cubes. The child was then shown pictures of other constructions and asked to duplicate these. If the child failed, the examiner demonstrated how to perform the construction, subsequently pulled the cubes apart, and asked the child to make a second attempt. Each construction was given a score of 2 (successful on the first try), 1 (on the second try), or 0 (unsuccessful).

(3) Tracking. The test material consisted of two identical papers with railway tracks printed on them. The child was asked to follow these railroad tracks with his pencil, remaining in the middle without crossing the rails or stopping or lifting the pencil. We recorded the time and sum of the pencilled area outside the tracks. In the second trial the railway track was a mirror image of the first one.

From the WPPSI-R scale we applied the animal pegs subtest, which is optional and not included in the IQ calculation.

(4) Animal pegs. The child was required to place pegs of a certain colour in the holes below pictures of four different animals. The raw score was a combination of the number of correct placements and time used.

One additional test was included:

(5) Bead threading. We recorded the shortest time (in seconds) required to thread six wooden beads on to a shoelace.

**Table 1** Medical data on children with chronic lung disease (CLD) and controls in the neonatal period and at 5.5 years of age: analysis of group differences

| | CLD children (n=32) | Control children (n=28) | p Values |
|---|---|---|---|
| Neonatal period | | | |
| Gestational age at birth (weeks)* | 25 [2] | 27 [[3]] | 0.004 (Kruskal-Wallis ANOVA) |
| Birth weight* | 809 [206] | 852 [[370]] | 0.22 (Kruskal-Wallis ANOVA) |
| SGA* | 0 | 4 | |
| BW ratio* | 0.97 [0.15] | 0.93 [[0.2]] | 0.10 (Kruskal-Wallis ANOVA) |
| No ROP | 8 | 7 | 0.77 ($\chi^2$ with Yates correction) |
| ROP I–II* | 15 | 17 | 0.42 ($\chi^2$ with Yates correction) |
| ROP III+ cryotherapy* | 9 | 4 | 0.33 ($\chi^2$ with Yates correction) |
| 5.5 years | | | |
| Body weight (kg) | 18.7 (2.9) | 19.0 (3.0) | 0.70 (Student's *t* test) |
| Length (cm) | 112.8 (5.2) | 112.2 (5.3) | 0.66 (Student's *t* test) |
| Maternal education, level 0–6 | 5.0 [3.0] | 4.5 [2.5] | 0.70 (Kruskal-Wallis ANOVA) |
| Correction (glasses/lenses)* | 9 | 10 | 0.72 ($\chi^2$ with Yates correction) |
| Hand dominance* | | | |
| Right | 26 | 20 | 0.55 ($\chi^2$ with Yates correction) |
| Left | 4 | 7 | 0.36 ($\chi^2$ with Yates correction) |
| Shifting | 2 | 1 | |
| Asthma - medication* | 6 | 2 | 0.35 ($\chi^2$ with Yates correction) |

Values are mean (SD), number, or median [quartile range]. The group of children with CLD was made up of 13 with grade I–II and 19 with grade III.
*Medical risk factors.
SGA, Small for gestational age; BW, body weight; ROP, retinopathy of prematurity; ANOVA, analysis of variance.

**Table 2** Influence of CLD and grades of severity on WPPSI-R IQ

| | | | | | | CLD grade | |
|---|---|---|---|---|---|---|---|
| WPPSI-R | CLD group IQ | Control group IQ | p Value | CLD grade I–II IQ | CLD grade III IQ | p Value | Differences |
| Full Scale | 94.4 (17.2) | 99.1 (13.8) | 0.25 | 104.6 (15.1) | 87.6 (15.4) | 0.01 | 0, I–II≠III |
| Verbal | 99.6 (15.7) | 101.5 (13.7) | 0.62 | 108.4 (11.7) | 93.7 (15.6) | 0.02 | I–II≠III |
| Performance | 90.9 (17.4) | 96.7 (14.0) | 0.17 | 99.8 (15.3) | 84.8 (16.5) | 0.01 | 0, I–II≠III |

Values are mean (SD).
CLD, Chronic lung disease; WPPSI-R, WPPSI-R, Wechsler preschool and primary scale of intelligence-revised.

The raw scores of each test were used for analysis of differences between the groups.

The entire examination, including motor assessment and neurological examination (described elsewhere) except for the psychological tests, was performed on two consecutive mornings, with each session lasting three to four hours.

### Statistical analysis

We collected data on the following neonatal and medical risk factors:

- birth weight;
- gestational age at birth;
- small for gestational age;
- birthweight ratio: the ratio between birth weight and expected weight for gestational age,[9] a measure of intrauterine growth;
- CLD grade;
- regressed ROP: stage 1–2 (mild), 3 (moderate), and 3+ (severe);
- vision aid such as glasses and contact lenses;
- asthma requiring medication;
- hand dominance.

We also included maternal education.[10]

We used the Shapiro-Wilk W test to determine whether the variables could be adequately modelled by a normal distribution. Variables that were normally distributed and had an equal variance were tested for difference between groups using Student's *t* test. Otherwise we applied the Kruskal-Wallis analysis of variance by ranks and, subsequently, the Mann-Whitney U test. For categorical data, we used $\chi^2$ test with Yates correction for small samples. We analysed possible correlations between risk factors and IQ scores using Spearman's correlation of ranks. We applied multiple regression analysis to analyse the link between medical risk factors and outcome measurements. A backward stepwise regression was carried out to find the significant factors contributing to the explained variance.

## RESULTS

### Developmental risk factors and IQ

We made a particular effort to recruit at 10 months of age a population of children with CLD and "healthy" VLBW children comparable in gestational age and birth weight. These neonatal similarities were lost because of the loss of 16 children from the study; those with CLD who remained at 5 years of age were born at a significantly lower gestational age ($p = 0.004$) than the remaining controls (table 1). Statistical analysis showed that gestational age at birth was only significantly correlated ($p = 0.03$) with performance IQ. However, when other medical risk factors were also considered in multiple regression analysis (see table 3), gestational age at birth no longer exerted any significant impact on performance IQ.

Birth weight, small for gestational age, and birthweight ratio did not differ between the CLD group and the control group ($p = 0.22$). At 5.5 years of age, the length and weight of the children with CLD and the control group were comparable ($p = 0.66$ and $p = 0.70$ respectively), and so was maternal education ($p = 0.70$) (table 1).

The prevalence of different levels of regressed ROP was no different in children with and without CLD. Hand dominance, defined as the preferred hand for writing and painting, was the same in both. Similarly, the prevalence of children requiring correction of vision and those suffering from asthma was the same (table 1). Thus, the similar prevalence of potential confounding factors in the two groups ruled them out as contributing to the possible difference in cognitive outcome between the CLD and control children.

### CLD and cognitive functions

Comparison of the IQ values for children with CLD and the control group showed no significant differences (table 2). We tested the hypothesis that the severity of CLD may affect outcome and found lower IQ values in all scales for children with CLD grade III (table 2). Furthermore, CLD grade III, together with the need for glasses/lenses, contributed significantly to the explained variance (table 3).

**Table 3** Multiple regression analyses of dependent variables (backward stepwise regression)

| Dependent variable | Predictor | B* | SE of B | P for B | Explained variance (%) |
|---|---|---|---|---|---|
| FSIQ† | CLD III | –12.7 | 3.8 | 0.002 | 13.8 |
| | Glasses/lenses | –12.5 | 3.8 | 0.002 | 12.6 |
| VIQ‡ | CLD III | –9.6 | 3.9 | 0.02 | 8.3 |
| | Glasses/lenses | –8.2 | 3.9 | 0.04 | 5.4 |
| PIQ§ | CLD III | –15.8 | 3.9 | <0.001 | 13.1 |
| | Glasses/lenses | –13.2 | 3.7 | <0.001 | 14.4 |
| | BW ratio | 0.3 | 0.1 | 0.03 | 4.7 |

*Regression coefficient; †Adjusted $r^2 = 0.264$; SE of estimate = 13.5; ‡Adjusted $r^2 = 0.137$; SE of estimate = 13.6; §Adjusted $r^2 = 0.322$; SE of estimate = 13.2.
CLD, Chronic lung disease; BW, body weight.

**Table 4** Eye-hand coordination subtests: analysis of group differences

| Subtest | CLD *v* nCLD p Value | CLD grade 0, I–II and III | |
|---|---|---|---|
| | | p Value | Difference |
| Manual speed | 0.93 | 0.04 | I–II≠III |
| Three dimensional construction | 0.27 | 0.21 | |
| Tracking | | | |
| Time | 0.31 | 0.6 | |
| Failures | 0.53 | 0.76 | |
| Animal pegs | 0.53 | 0.05 | I–II≠III |
| Bead threading | 0.34 | 0.49 | |

CLD, Chronic lung disease.

### CLD and eye-hand coordination

No test of visual-spatial skills showed a significant difference between CLD and control children (table 4). However, subdivision of the CLD group on the basis of severity showed significant differences in two subtests, manual speed and animal pegs, for children with CLD grade III. The lowest median scores were observed in all tests for this subgroup.

## DISCUSSION

In a previous study we reported that CLD was associated with a less favourable cognitive development at 10 months of corrected age.[2] We found similar results in school age children but only in those with grade III CLD. The children with mild CLD and the control group performed within normal range of IQ scores.

In a study with similar design, O'Shea *et al*[11] reported differences in full scale and performance IQs, but not in verbal IQ. In our study, both the children with CLD and the controls achieved higher IQ values in all three measures than those studied by O'Shea *et al* (table 5). A possible explanation is that we used corrected age, whereas O'Shea *et al* used chronological age. Therefore, we reanalysed our IQ data in relation to chronological age: a difference remained. It is also possible that outcomes differed as our patients were born five years later than those studied by O'Shea *et al*, so may have benefited from general improvements in neonatal care. Furthermore, possible differences in family socioeconomic status and education as well as different test norms may have influenced outcomes.

Our former study also found severe CLD to be related to eye-hand coordination.[2] Deficiency in eye-hand coordination in neurologically normal extremely low birthweight children at 3 years of age has also been reported by Bowen *et al*.[12] In the present study, children with CLD grade III were over-represented among the poorest performers, although significant differences in performance were obtained in connection with only two tests, manual speed and animal pegs.

We advise cautious interpretation of our findings. It is problematic to monitor specific functions at various ages using different developmental scales because concordance may be lost. At an early age, only broad abilities such as general mental and motor function[13–15] can be assessed reliably. Therefore, the results we obtained at 10 months of age (using the Griffiths' scale[16]) should be interpreted as a kind of general developmental index, rather than as an assessment of highly specific functions. At 5.5 years of age, the WPPSI-R has proved a sensitive tool for assessing visual-spatial development, so the poorer performance by children with severe CLD indicates suboptimal development.

A variety of factors are associated with the genesis and severity of lung injury leading to CLD. Prenatal and postnatal infection and inflammation, mechanical ventilation, oxygen toxicity, hypoxia, poor nutrition, and treatment with glucosteroids have all been reported to promote lung disease (for overview see Jobe and Bancalari[17]). Some of these seem more likely than others to affect development. Perinatal hypoxia has been associated with impaired neurodevelopment.[18 19] The duration of hypoxaemia is closely related to metabolic acidosis ($pH < 7.15$) and is a significant predictor of delayed development.[19] In their analysis of neuropsychological consequences of perinatal asphyxia, Korkman and coworkers[20] found significant multiple and diffuse, rather than specific, developmental differences (employing the Nepsy test) that were correlated with very preterm birth. Children with severe CLD experience frequent episodes of hypoxia.[19 21–24] The delayed development of cognitive functions in these infants may be a consequence of suboptimal oxygenation during the neonatal period.

Furthermore, growth retardation caused by malnutrition that results in infants being small for gestational age has been associated with detrimental cognition and motor development.[25] However, poor intrauterine growth cannot explain the differences found in our study, as the prevalence of small for gestational age infants did not differ significantly between the groups, nor did birthweight ratio.

In addition to hypoxia and poor nutrition, there is increasing evidence that postnatal steroids may lead to neurodevelopmental impairment in preterm infants.[26] Besides a variety of short term negative effects, impaired growth of the cortical grey matter has been described. None of the children participating in our study was treated with steroids during the neonatal period, and thus postnatal steroids can be excluded as confounding factors.

The major handicap, cerebral palsy, is often a consequence of severe intraventricular haemorrhage and PVL, but the cause of minor, non-specific neurological dysfunctions in children born very preterm is unclear. Subtle neuromotor deficits seen more commonly in these infants than in children born at term appear not to have clear cut morphological correlates in the form of PVL, as diagnosed by magnetic resonance imaging.[27 28] Furthermore, no relation between deviant magnetic resonance imaging findings and IQ scores were observed in VLBW children at 6 years of age.[29] Therefore some minor cognitive deficits in preterm infants may not be due to acute brain lesions such as haemorrhage and PVL. Even though adverse mental development shows no obvious correlation with structural deviations in the brain, it has been suggested that gliosis in central occipital white matter—that is, in posterior visual pathways and occipital-thalamic tracts dealing

**Table 5** IQ medians (min–max) for children from the present study and the study by O'Shea *et al*[11]

| IQ | Present study | | | | O'Shea *et al* | |
|---|---|---|---|---|---|---|
| | Corrected age | | Non-corrected age | | Non-corrected age | |
| | CLD | Controls | CLD | Controls | CLD | Controls |
| Full scale | 98 (52–131) | 101 (73–122) | 92 (47–123) | 95 (63–120) | 83 (53–103) | 87 (70–111) |
| Verbal | 102 (62–130) | 103 (68–121) | 99 (59–124) | 100 (62–119) | 85 (61–109) | 87 (68–128) |
| Performance | 92 (51–124) | 97 (64–123) | 85 (47–117) | 90 (58–118) | 79 (48–104) | 90 (74–106) |

IQ, Intelligence quotient; CLD, chronic lung disease.

with visual-motor integration—could affect visual-perceptual performance.[29]

Our study was of an infant population born between September 1988 and March 1993. Because of large advances in neonatal care made during the last decade, our results may not be predictive of the outcome for children born today with CLD. However, our study has important clinical implications in highlighting the need for careful follow up of children who, although not clinically determined as neurologically compromised, have suffered from severe CLD. Recognition of cognitive deficits is required if we are to find ways of enhancing their competence and minimising their developmental deficits.

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