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Five and Nine Year Check-up of 314 Children with Neonatal Hyperbilirubinaemia

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This is a part of a prospective follow-up study of 1196 newborn infants with certain neonatal high risk factors. About one third of the group consisted of children with neonatal hyperbilirubinaemia; they had a serum bilirubin value > 340 mmol/l or had had blood exchange transfusions. They were born in 1971–74 at the State Maternity Hospital, Helsinki. Thirteen children were severely handicapped and excluded from the series and 54 were not traced or parents refused to bring them to the check-up. 314 children were examined at the age of five and/or nine years. The control series comprised 72 children. The results indicated that the children with neonatal hyperbilirubinaemia managed less well in neurological and psychological tests than the control group, they had poorer school marks and more often attended special classes for somatic and psychic handicaps or for the mentally retarded. Their results were, nevertheless, often better than those for the rest of the risk group.

KEY WORDS: Neonatal hyperbilirubinaemia, follow-up study, neuro-developmental examination.

MODERATELY high concentrations of serum bilirubin are common in normal newborn infants. This slight degree of jaundice, often termed "physiological jaundice", tends to appear on the second to third day of life in fullterm infants and disappears within a few days; among premature infants the rise tends to be a little slower and the symptoms are of longer duration. When total bilirubin levels reach close to 300 mmol/l during the first week of life, hyperbilirubinaemia is considered present. High concentrations can lead to a neurological syndrome, kernicterus, which causes a choreoathetoid type of cerebral palsy, seizures, mental retardation, high tone hearing loss, and other neurological defects in infancy and childhood. Subtle forms

of brain damage, such as impairment in neurological and cognitive functions, have been reported to be late sequelae of this syndrome (Hansen & Bratlid, 1986; Hyman *et al.*, 1969), and premature infants are considered particularly susceptible (Ritter *et al.*, 1982).

At the time of the birth of the infants in our study series, in the beginning of the 1970s, an unconjugated serum bilirubin concentration of 340 mmol/l (20mg%) or more during the first 5–6 days of life was taken as the level at which treatment with blood exchange transfusions was indicated. These were repeated as frequently as necessary to keep bilirubin levels below 340 mmol/l. During the first days of life exchange transfusions were made at lower levels as well according to an internationally accepted standard procedure (Allen & Diamond, 1957).

At the end of the 1960s exposure to increased intensities of light, particularly blue light, had been found to increase oxidation of bilirubin to other products. Phototherapy was also started in Finland and was first available at the State Maternity Hospital (former Institute of Midwifery), Helsinki, where this study was carried out at the end of 1973. Before then it was used at the Helsinki University, Children's Hospital, where the infants received blood exchange transfusions as well.

Some children in our study group had had higher serum bilirubin values and a longer duration of hyperbilirubinaemia than is nowadays acceptable. It can therefore be assumed that if hyperbilirubinaemia causes central nervous system impairment this is more likely to be found in the children of the present series. The aim of this study was to evaluate probable minor sequelae of hyperbilirubinaemia, which tend to go undetected before preschool or school age. The children were therefore checked at the ages of five and nine years. Children with severe handicaps were excluded from the results.

SAMPLE

The children in the study series were born at the State Maternity Hospital, Helsinki, in 1971–74. Included were all children who had had at least two serum bilirubin values > 340 mmol/l in the neonatal period or who had been given blood exchange transfusions. Most mothers at risk, such as those with Rh-immunization, gave birth at the Obstetric Department of the University Hospital.

was given at the State Maternity Hospital from the end of 1973, and before then at the Children's Hospital.

At the ages of five and nine years the children were checked at the Children's Hospital. At the five-year examination they were given a neurodevelopmental screening examination developed by Bax and Whitmore (1973) and modified by our research group, which measures motor function, perception, articulation, language skills, behaviour and vision. A score of 0 was given for faultless performance and scores from 1–8 for faults. The points were counted for a total score. The Illinois Test of Psycholinguistic Abilities (ITPA, Kirk et al., 1968) and the Marianne Frostig Test of Visual Perception (1966) were also given. Additionally the children were asked to draw a man (Goodenough, 1926) and write their name (Reimer et al., 1975). The articulation and muscle function of the lips and tongue were also evaluated.

The nine-year examination consisted of The Test of Motor Impairment (TMI, Stott et al., 1972), ITPA (7 subtests for children born in 1972 and 1973, and for the others all 12 subtests). Teachers were questioned about the childrens' school marks in reading, writing, arithmetic, art, handicraft and gymnastics and the school marks scored 0 for good performance, 1 for average and 2 for poor. The points were counted for a total score.

A clinical diagnosis of neurodevelopmental dysfunction was made at group sessions with participation of the paediatrician or child neurologist, child psychologist, speech therapist and nurse who had investigated the children. A diagnosis of MBD was made when the children were found to have impairment in motor function as well as behavioural problems and learning or perceptual disabilities.

Statistics were measured with BMDP software (1983). The number of children to whom the tests were given varies somewhat depending on refusals, on the fact that the test items varied slightly each study year and were therefore not set for all children, and that some items are not yet finally analyzed.

RESULTS

Ninety-eight of the children with hyperbilirubinaemia were born in 1971, 118 in 1972, 104 in 1973 and 48 in 1974. High serum bilirubin values were first noted at the age of 0–2 days for 91 children, at 3–4 days for 185 and at 5 days or later for 35 children. Serum bilirubin

The children with neonatal hyperbilirubinaemia formed part of a group of 1196 newborns considered to be at risk. Criteria for inclusion in this risk group were apart from hyperbilirubinaemia, Apgar scores of $\leq$ 6 at 5 min of age, severe respiratory problems, birth weight $\leq$ 2000 g, neurological symptoms, hypoglycaemia, septic infections and mother with diabetes.

The children with **neonatal** hyperbilirubinaemia totalled 368; some could also have had one or more other risk factors as well. Fifty-nine were not traced or parents refused to bring them to the check-up. One child had died in the neonatal period and one later. Six had known severe handicaps and were not invited. A further seven with severe handicaps came to the check-up but the results were excluded.

The study series totalled 314 children; 306 attended the check-up at age five years but 39 of these were not investigated at age nine. The nine-year check-up was attended by 275 children; 8 who had not been checked at age five came to the nine-year control. Fifty-three children had had other risk factors as well.

The study group was compared with 549 children without hyperbilirubinaemia in the neonatal risk group who had been checked at five or nine years and were not severely handicapped and with a control series of 72 children. This control series comprised 53 children born in 1971–74 and selected as non-risk infants from the State Maternity Hospital and 19 who were healthy twins of children included in the risk group; 55 were examined at the age of nine. The risk group comprised 147 children with neonatal asphyxia (Apgar scores $\leq$ 6 at 5 min of age), 37 with hypoglycaemia (at least two values $<$ 1·67 mmol/l for fullterm and $<$ 1·21 mmol/l for prematures), 50 with neurological symptoms, 120 with a birth weight $<$ 2000 g, 5 with septic infections and 47 were born to mothers with diabetes, 120 had several of these risk factors.

METHODS

The obstetric and neonatal data were collected from the maternity wards of the State Maternity Hospital and/or the two wards where premature and fullterm infants under observation or needing paediatric care were treated. Infants with more severe disorders were transferred to the Children's Hospital; respirator care and blood exchange transfusions, for example, were given there. Phototherapy

values of ≥ 340 mmol/l lasted 2 days or less in 229 children, 3–4 days in 63 and 5 days or more in 16. A serum bilirubin value of 340–399 mmol/l was noted for 166 children, 400–450 mmol/l for 89 and > 450 mmol/l for 22. Blood exchange transfusions were given to 193 (62·1%) of the children; to 181 once and to 12 twice or more. Phototherapy was given to 135 children (49·2%), 94 of whom had exchange transfusions as well. The cause of hyperbilirubinaemia was Rh-immunization in 9 children, in the others diagnosed or suspected ABO-incompability or unknown aetiology.

Table I shows the results of the five-year check-up. The neuro-developmental examination was significantly worse in the children with neonatal hyperbilirubinaemia than in the controls; 22·6% versus 5·3% with a score of ≥ 24 and 15·2% versus 2·1% with a score of ≥ 30. There were no significant differences between the children with hyperbilirubinaemia and the risk group.

The mean ITPA of the children with hyperbilirubinaemia did not differ from the controls although some of the subjects showed significant differences; these were three auditory and two visual subtests. When the results were compared with the risk group no significant differences were found. The Frostig perceptual test was poorer for the children with hyperbilirubinaemia than for the controls. It was, however, somewhat better than for the risk group. The drawing of a person was poorer for the children with hyperbilirubinaemia than the controls but better than the risk group. Seven children with hyperbilirubinaemia had scores of <80 and 43 had scores of 80–100. None of the control children had a score <80 but three had scores between 80–100. 234 children in the study group and 474 in the risk group drew a person and were scored. In the control series 56 did draw a person. The name writing was scored 0 if the children had drawn a person but not written their name; 22·5% in the study group, 24·7% in the risk group and 4% of controls did not write their name.

There were no significant differences in any of the groups in height, weight and head circumference at either five or nine years of age.

Table II shows the results of the nine year examination. The TMI was significantly worse in the children with hyperbilirubinaemia than the controls but not than the risk group.

The WISC intelligence test gave scores of <100 for 10·5% of the children with hyperbilirubinaemia and 2·8% of the controls. A score <90 was recorded in 4·9% of the children with hyperbilirubinaemia

but in none of the control children. Performance IQ was poorer in children with neonatal hyperbilirubinaemia than in the controls but the means of the verbal and total IQ showed no differences.

Table 1

Results of the 5-year examination for children with neonatal hyperbilirubinaemia, controls and the risk group. Some children refused to draw a person or write their name, the numbers of children who performed these tests are shown in brackets after the items.

The results from the Frostig test are only for the years 1972 and 1973 (n = 73, controls 52). The children with hyperbilirubinaema were compared with the controls and the risk group.

Test item	Hyperbilirubinaema (296)	Controls (72)	Risk group (501)
Neurodevelopmental examination	19.2 + 15.9	11.4 + 6.4***	19.2 + 13.6
ITPA			
Auditory reception	40.2 + 8.6	41.4 + 6.8	39.5 + 7.9
Visual reception	34.3 + 5.5	34.4 + 4.6	33.3 + 5.4
Auditory association	37.3 + 6.6	38.7 + 5.5	36.6 + 6.8
Visual association	35.4 + 6.8	36.4 + 5.6	35.4 + 7.5
Verbal expression	36.2 + 7.1	36.4 + 4.3	35.9 + 7.2
Manual expression	33.2 + 6.4	35.1 + 3.2**	32.7 + 6.1
Grammatic closure	37.8 + 7.0	39.6 + 7.6*	37.1 + 7.4
Visual closure	35.7 + 6.6	38.6 + 5.4***	34.9 + 6.4
Auditive seq. memory	35.3 + 6.9	34.6 + 4.2	34.3 + 5.8
Visual seq. memory	35.3 + 6.6	34.6 + 4.2	34.3 + 6.6
Auditory closure	35.4 + 7.2	37.8 + 5.1**	34.6 + 7.6
Sound blending	31.6 + 4.8	34.0 + 3.8***	30.9 + 5.1
ITPA mean	35.7 + 4.0	37.1 + 5.9	35.6 + 4.2
Dubowitz test (121)	34.4 + 9.6	38.9 + 6.8***	34.2 + 4.2
Draw-a-man test (234)	121.8 + 26.1	133.8 + 28.7***	117.4 + 27.5*
Name writing (270)	8.5 + 5.5	12.3 + 3.0***	8.6 + 5.4
Frostig			
I	10.2 + 2.1	11.6 + 2.3***	9.9 + 2.4
II	8.6 + 1.9	11.2 + 2.4***	8.4 + 1.9
III	9.5 + 3.4	10.8 + 2.2**	9.3 + 3.2
IV	10.5 + 2.2	11.5 + 2.7*	9.9 + 2.3**
V	10.5 + 2.1	11.3 + 2.3*	10.1 + 2.1*
PQ	106.1 + 12.6	109.7 + 10.6*	103.7 + 14.2*

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

Table 2
Results of the 9-year examination for children with neonatal hyperbilirubinaemia, controls and the risk group. The children with neonatal hyperbilirubinaemia were compared with the controls and the risk group. Five of the ITPA subtests were given only to children born in 1971 and 1974. The WISC intelligence test was given to 244 children with hyperbilirubinaemia, 44 controls and 348 in the risk group.

Test item	Hyperbilirubinaemia (277)	Controls (55)	Risk group (520)
Test of Motor Impairment (277)	6.5 + 5.0	3.5 + 3.2***	7.2 + 6.0
ITPA			
Auditory reception (74)	38.3 + 5.8	38.2 + 5.9	34.1 + 6.3*
Visual reception	36.3 + 6.7	34.7 + 6.5	35.2 + 6.4***
Auditory association	36.7 + 7.1	37.1 + 5.9	35.9 + 6.9
Visual association (74)	38.5 + 5.5	38.1 + 5.5	36.2 + 5.8***
Verbal expression (74)	30.9 + 2.8	31.9 + 5.1	31.1 + 3.7
Manual expression	34.6 + 7.1	34.4 + 6.2	34.4 + 6.2
Grammatic closure (74)	36.9 + 6.7	37.3 + 3.6	35.3 + 8.6*
Visual closure (74)	37.6 + 5.8	36.0 + 5.7	36.0 + 7.2
Auditory seq. memory	35.7 + 6.0	35.8 + 6.1	35.1 + 6.4
Visual seq. memory	34.1 + 6.3	35.7 + 6.0	35.6 + 5.9**
Auditory closure	34.8 + 7.1	37.1 + 6.3	35.3 + 7.0
Sound blending	37.3 + 6.8	38.7 + 6.0	37.4 + 6.3
ITPA mean	35.6 + 4.1	36.3 + 3.5	35.6 + 3.8
WISC			
Information	12.3 + 3.6	12.5 + 3.2	11.9 + 3.3
Comprehension	12.9 + 3.7	13.9 + 3.1	12.8 + 3.6
Arithmetics	11.4 + 3.1	12.5 + 2.3	11.2 + 2.7
Similarities	13.9 + 2.8	14.3 + 3.0	14.0 + 2.5
Digit span	8.8 + 3.0	9.2 + 2.9	8.7 + 2.4
Picture completion	11.3 + 3.1	11.9 + 2.7	11.6 + 3.0
Picture arrangement	11.2 + 2.9	12.3 + 3.1	11.3 + 2.8
Block design	13.4 + 3.0	13.8 + 2.9	13.1 + 3.0
Object assembly	12.1 + 3.1	12.8 + 2.7**	12.5 + 3.0
Coding	10.8 + 3.0	12.3 + 3.0	11.1 + 2.8
Verbal IQ	111.7 + 15.9	114.9 + 13.1	110.6 + 13.0
Performance IQ	112.5 + 15.1	117.5 + 11.7*	113.1 + 13.8
Total IQ	114.0 + 15.4	117.8 + 12.6	113.0 + 13.1

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

The mean ITPA was not significantly different between the children with hyperbilirubinaemia and the control and risks groups,

but four of the 12 subtests were better and one poorer when the children with hyperbilirubinaemia were compared with the risk group.

The school placement (table III) was known for 286 of the children with hyperbilirubinaemia; 274 attended ordinary class and 13 of these had repeated a class or had the school start postponed. Four were in special classes for somatic handicaps such as cerebral damage or visual or hearing impairment, one was in a special class for the emotionally disturbed, and seven attended classes for the mentally retarded. Table III also shows the school placement for the risk group.

Table 3
School class placement for the children with neonatal hyperbilirubinaemia and the risk group.

Class	Hyperbilirubinaemia (286)	Risk group (510)
Normal class	91.2	88.1
Special class for		
somatic handicaps	1.4	2.0
emotionally disturbed	0.3	1.0
the mentally retarded	2.5	3.1
Has repeated one class	2.8	3.5
School start postponed 1 year	1.8	2.4

Articulation was impaired in the children with hyperbilirubinaemia at both 5 and 9 years (table IV). Articulatory errors when pronouncing words were noted in 51·5% of the children with hyperbilirubinaemia and in 32·5% of the controls. In hyperbilirubinaemia the articulatory errors were considered severe in 13·0% and in the controls in 5·3%. The muscle function of the lips and tongue was also worse in the children with hyperbilirubinaemia than in the controls. The differences were not significant when compared with the risk group.

Table 4
Disturbances in articulation and muscle function of lips and tongue at the age of five years for children with neonatal hyperbilirubinaemia, controls and the risk group. The children with neonatal hyperbilirubinaemia were compared with the controls and the risk group.

Five year examination	Hyperbilirubinaemia (303)	Controls (72)	Risk group (398)
Articulation of vowels and consonants			
good	50.2	64.0**	49.9
slightly abnormal	37.8	27.2	39.4
definitely abnormal	12.0	5.3	10.4
Articulation of words	48.5	62.8***	47.9
	35.0	31.9	37.9
	16.5	5.3	14.2
Muscle function of tongue			
good	51.9	84.3***	52.0
slightly abnormal	36.4	14.8	37.4
definitely abnormal	11.9	0.9	10.6
Muscle function of lips			
good	80.7	93.9***	80.9
slightly abnormal	17.0	6.1	17.9
definitely abnormal	2.3	0	1.2

** $p < 0.01$
*** $p < 0.001$

School marks were significantly poorer for the children with hyperbilirubinaemia than for the controls ($p < 0{\cdot}001$). No differences were noted with the risk group. The mean of the school marks were $4{\cdot}6 + 2{\cdot}4$ for children with hyperbilirubinaemia, $3{\cdot}9 + 2{\cdot}4$ for controls and $5{\cdot}1 + 2{\cdot}4$ for the risk group. Table V shows the percentage of poor school marks in the different children groups. The table also shows the percentage of children who received extra help in school subjects or had had speech therapy.

After the five-year check-up 43% of the children with hyperbilirubinaemia were referred to further investigations or treatment; 14% to neurodevelopmental evaluation or rehabilitation, 22% to speech therapy, 5% to a special kindergarten and 2% to psychologic

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Disturbances in articulation and muscle function of lips and tongue at the age of five years for children with neonatal hyperbilirubinaemia, controls and the risk group. The children with neonatal hyperbilirubinaemia were compared with the controls and the risk group.

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definitely abnormal	12.0	5.3	10.4
Articulation of words	48.5	62.8***	47.9
	35.0	31.9	37.9
	16.5	5.3	14.2
Muscle function of tongue			
good	51.9	84.3***	52.0
slightly abnormal	36.4	14.8	37.4
definitely abnormal	11.9	0.9	10.6
Muscle function of lips			
good	80.7	93.9***	80.9
slightly abnormal	17.0	6.1	17.9
definitely abnormal	2.3	0	1.2

** $p < 0.01$
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School marks were significantly poorer for the children with hyperbilirubinaemia than for the controls ($p < 0{\cdot}001$). No differences were noted with the risk group. The mean of the school marks were $4{\cdot}6 + 2{\cdot}4$ for children with hyperbilirubinaemia, $3{\cdot}9 + 2{\cdot}4$ for controls and $5{\cdot}1 + 2{\cdot}4$ for the risk group. Table V shows the percentage of poor school marks in the different children groups. The table also shows the percentage of children who received extra help in school subjects or had had speech therapy.

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DISCUSSION

Our prospective follow-up study comprised all infants born with certain risk factors in 1971–74 at the State Maternity Hospital. The total group of 1196 comprised 5·3% of the live born infants, and those with hyperbilirubinaemia totalled 1·7% (Michelsson et al., 1978). The results of the check-ups at ages five and nine years have previously been reported for **children with low birth weight** (Michelsson et al., 1983, 1984). A comparison with the results of these premature infants showed that the infants with neonatal hyperbilirubinaemia did better in almost all test items.

The neurodevelopment screening examination which was given to the children with neonatal hyperbilirubinaemia has previously been evaluated for all the risk children (Michelsson et al., 1981). The results showed that the mean for the total group of children at risk was 19·6, and that children with many risk factors managed less well. The mean score of the children with hyperbilirubinaemia was the best of the whole group if the mean for a few children with septic infections was excluded. In other words they managed better than children with other neonatal risk factors. Our results of the ITPA and Frostig tests at the age of five indicate that the children with neonatal hyperbilirubinaemia have managed better than those with low birth weight, (Michelsson et al., 1977).

The group of children with neonatal hyperbilirubinaemia included 53 children with other neonatal risk factors. We did not, however, exclude these children from the final results as the statistical studies failed to show any significant differences between those with hyperbilirubinaemia alone and those with other risk factors as well.

Previous studies of children with neonatal hyperbilirubinaemia have usually comprised children with bilirubin levels below 20 mg%. Culley et al. (1970) reported neurological sequelae in a group of 104 non-haemolytic jaundiced infants. Rubin et al. (1979) in a series of 200 children found early signs of neurological abnormalities which, however, were not predictive of long-term cognitive development. ITPA at the age of five and WISC at the age of seven showed no significant differences from controls with bilirubin levels of 16–23 mg%. However, IQ was slightly lower in the most severely jaundiced group and an excess of mental retardation was noted. Crichton (1972) reported in a follow-up of low birth weight infants with neonatal jaundice that at the age of 4–11 years there were no

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significant differences in intelligence. Koch (1964) studied 68 prematures with jaundice at the age of seven years and noted that six of 27 with a serum bilirubin level over 20 mg% had brain damage, but there was no linear correlation between IQ and bilirubin level.

Some children in our study group had higher serum bilirubin levels than what was even acceptable in the beginning of the 1970s when the study was made. This was partly due to the fact that they had been referred to another hospital for blood exchange transfusions and the wait for laboratory results and transportation caused delays. At that time phototherapy was also sparsely used because of the few apparatuses available. When phototherapy was started at the State Maternity Hospital the number of infants with hyperbilirubinaemia decreased by 50%.

Our study series showed a significantly higher number of different types of impairment than the controls. The outcome, however, might also have been influenced by other factors as well; such as other perinatal risk factors, social group and type of day-care. High bilirubin values, over 400 mmol/l, was found in 111 of the study group children. Thirteen (11·8%) of these were diagnosed as having MBD and six had learning disabilities or perceptional disturbances. The proportion, however, was not more than found in those with lower bilirubin levels.

Hyman et al. (1975) found MBD in 4·9% in their series when the term included children with hyperkinetic behaviour syndrome, unusual clumsiness, fine hand tremor, learning disorders and delayed maturation without mental retardation. Ten of the 20 children with MBD had high bilirubin levels and it was suggested that this may have had an aetiologic relationship to MBD. Prematurity did not appear to influence the occurrence of MBD as there was only one premature infant in the group. There were 15 boys and five girls. Five of the children had had perinatal complications such as asphyxia and hypoglycaemia. No correlation was found between the bilirubin level and mental retardation except that three of the five children with subnormal mentality had bilirubin levels over 30 mg%. High bilirubin values were most frequently found to involve the auditory pathway and rote memory which were impaired in 39% in this study. Visual perceptual difficulties were seen in one third of the children. The children tested did not, however, show difficulties in conceptual thinking, perceptual organization, visuomotor coordination or distractibility.

Karlberg et al. (1969) found that the incidence of CNS abnormalities among 100 infants with bilirubin levels over 20 mg% was high. Sensory neural hearing loss and athetosis also showed a significant association with neonatal high (> 20 mg%) bilirubin levels.

Our study showed that the children with hyperbilirubinaemia were significantly impaired in both motor and psychological tests and in school progress. The children attended 2–3 times more often various special classes than Finnish school children usually, according to official statistics. It was also found that almost 5% had either repeated one class or the school start had been postponed. This was also true for the risk group children who also were found to be clumsier and more hyperactive and had adjusted poorer to school requirements (Michelsson and Lindahl, 1984).

We have lately checked all the risk group children in respect of clinical diagnosis of MBD, learning disabilities and behavioural problems (Michelsson and Lindahl, unpublished data). The preliminary results indicate that almost 20% of the children with neonatal high risk factors have signs of MBD, and another 20% clumsiness, learning disabilities, behavioural problems or articulatory disturbances. The children with neonatal hyperbilirubinaemia, even if, in some tests they managed less well than the controls, performed better than children with other neonatal high risk factors.

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