Behavioral Outcome in Children with a History of Neonatal Encephalopathy following Perinatal Asphyxia

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Objective To examine the effects of mild and moderate neonatal encephalopathy (NE) on behavioral functioning, and prevalence of psychiatric diagnoses at 9–10 years. **Methods** The Child Behavior Checklist (CBCL), Teacher's Report Form (TRF), Diagnostic Interview Schedule for Children IV (DISC-IV), and the Children's Social Behavior Questionnaire (CSBQ) were used to assess behavioral outcome of 34 children with mild NE, 47 children with moderate NE, and 53 typically developing controls. **Results** Both children with mild and moderate NE showed more problematic behaviors than controls, which are related to a diversity of behavioral domains: elevated rates of social problems, anxiety and depression, attention regulation problems, and thought problems. No group differences were found in percentages of children with a DISC-IV (DSM-IV) classification. **Conclusions** NE has a mildly negative effect on behavioral functioning, but does not lead to elevated levels or specific patterns of developmental psychopathology.

Key words asphyxia neonatorum; behavioral problems; developmental psychopathology; hypoxia-ischemia; brain.

Neonatal encephalopathy (NE) following perinatal asphyxia (PA) has been known to have an impact on both short- and long-term development of its survivors. Estimates of the incidence of NE vary between 1 and 8 per 1000 live births (American College of Obstetrics and Gynecology: Task force on Neonatal Encephalopathy, 2003). The prognosis of children with NE varies widely and depends on the severity of their neonatal condition. In general, children with mild NE (NE1 according to the classification system of Sarnat and Sarnat, 1976) show a positive long-term development. Their motor and cognitive functioning at school age are comparable to those of healthy peers (Barnett et al., 2002; Robertson & Finer, 1988; Robertson, Finer, & Grace, 1989). In contrast, children with severe NE (NE3 according to Sarnat's classification) nearly always die or develop severe impairments such as cerebral palsy (CP), mental retardation, epilepsy, and in some cases, cortical visual or auditory impairment (American College of Obstetrics and Gynecology: Task force on Neonatal Encephalopathy, 2003). Children with moderate NE (NE2 in the Sarnat system) are a more heterogeneous group with respect to developmental outcome, but on average, their level of functioning at school age is between that of children with mild NE and severe NE (van Handel, Swaab, de Vries, & Jongmans, 2007). Death and disability rates of 5% and 15%, respectively, are reported for this group (Robertson, Finer, & Grace, 1989). Cognitive abilities of survivors with moderate NE who do not develop CP are in the average range but less well developed than those of children with mild NE and healthy peers (Marlow, Rose, Rands, & Draper, 2005; Robertson & Finer, 1988).

Long-term outcome of NE should be considered within the context of the dynamic interactive nature of development. Dynamic models of human development stress the ongoing interaction between genetic expression, brain function, neurobehavioral aspects, and environment (cf. Anderson, 2001). Early brain damage can influence development by changing the expression of genetic vulnerabilities that interact with other characteristics of the child,

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such as cognitive abilities and behavior, and its environment. In this view, a shared experience, such as an early hypoxic event resulting in neurological dysfunction, can influence development directly and indirectly, leading to different developmental pathways in children. Behavioral adjustment in daily life is one of the developmental aspects of children with a history of NE that has received little attention so far. From a dynamic developmental perspective, NE is likely to affect behavioral outcome, but the questions are whether this influence results in abnormal functioning and whether there are systematic patterns of behavioral abnormalities. The few studies that have been performed so far found an elevated rate of hyperactivity in children with moderate NE, but not in children with mild NE (Marlow et al., 2005; Moster, Lie, & Markestad, 2002; Robertson & Finer, 1988). In addition, one study reported an unexpectedly high proportion of children with moderate and severe NE who developed an Autism Spectrum Disorder (Badawi et al., 2006). However, in the last study, the causes of the NE were not limited to PA.

In contrast to the lack of studies on the behavioral development after NE, there is a growing body of literature on the effects of NE on brain structure. Various patterns of brain damage have been found in this group of children, which have been related to adverse development (Ferriero, 2004; Miller et al., 2005;). Some of these brain lesions are of interest when studying behavioral development after NE. One of the brain structures that are highly sensitive to hypoxic-ischemic damage is the hippocampus (Azzarelli, Caldemeyer, Phillips, & Demyer, 1996; Maneru et al., 2003). Reductions in hippocampal volume have been associated with memory deficits, and in addition, relationships have been found with the risk for psychiatric disorders. Several researchers hypothesized that hippocampal volume plays a role in the association between PA and the vulnerability to develop schizophrenia (Boog, 2004; de Haan et al., 2006; van Erp et al., 2002;). In addition, hippocampal dysfunction and volume reduction have been associated with the development of autism (DeLong, 1992; Nicolson et al., 2006). Another relevant brain–behavior relationship that has been proposed is that between perinatal striatal injury and the risk for ADHD (Toft, 1999; Zappitelli, Pinto, & Grizenko, 2001). Animal studies have suggested that striatal neurons are particularly vulnerable to the effects of PA (Mallard et al., 1995), and evidence of hyperactivity and impulsivity has been found in animal experiments with PA (Adriani et al., 2006; Weitzdoerfer, Pollak, & Lubec, 2004). In addition, retrospective studies of children with ADHD have found higher percentages of pre-, peri-, and postnatal insults, compared to unaffected children (Zappitelli et al., 2001).

In conclusion, studies so far indicate a serious developmental risk of NE following PA. It is known that the risk of a negative outcome is very high after severe NE. Relatively little is known about the behavioral developmental outcome of children with mild and moderate NE. In the current study, we aimed to examine this behavioral outcome at school age, in a stepwise manner. Firstly, we examined behavioral functioning in daily life, i.e., the prevalence of specific problem behaviors. Secondly, we examined the presence of clinical psychiatric diagnoses (also referred to as ''psychiatric classifications'' or ''psychopathology'') and whether specific patterns of psychopathology exist.

We expected that children with moderate NE would show more problem behaviors and a higher prevalence of psychopathology than children with mild NE, who, in turn, would show more problem behaviors and psychopathology than children without NE.

Methods

Participants

This study was approved by the Medical Ethical Committee of the University Medical Centre, Utrecht. Participants in this study were drawn from the Neonatal Intensive Care Unit (NICU) of the Wilhelmina Children's Hospital in the Netherlands, between 1993 and 1997. Most of the children were referred to the NICU from a local hospital when they needed ventilatory support. In addition to developing NE during the first days of life, to be included patients had to meet at least three of the following criteria: (1) signs of fetal distress (late decelerations on fetal monitoring or meconium staining), (2) Apgar score below seven at 5 min, (3) arterial umbilical pH below 7.10, (4) delay in onset of spontaneous respiration, (5) multiorgan failure (Cowan et al., 2003). Because of the differential patterns of brain injury observed in prematurely versus term-born children with NE (Volpe, 2001), gestational age (GA) was restricted to 37–42 weeks. Exclusion criteria were: dysmaturity (a birth weight below the 10th percentile), congenital or acquired chronical illness, and malformations of the central nervous system that are known to be associated with developmental delays. A careful maternal history was taken. None of the mothers were known with antenatal substance use. The children were classified as mild NE (NE1) when their symptoms lasted less than 24 hr. NE1 was characterized by hyperalertness, uninhibited Moro and stretch reflexes, sympathetic effects, and a normal EEG. Moderate NE (NE2) was marked by obtundation, hypotonia, strong distal flexion, and multifocal seizures. The main

distinction between NE1 and NE2 was the presence of neonatal seizures. All infants had continuous EEG recording during the first 72 hr and seizures were therefore not only clinically detected but also electrographically. This made the distinction between grade I and II more reliable than usually reported in the literature. Of the original 170 eligible children, 46 died in the neonatal period and 5 had to be excluded (1 because of a congenital syndrome and 4 because of dysmaturity). Seven families moved and could not be traced. The parents of the remaining 112 children received a written invitation to participate in the follow-up study, and were subsequently contacted by phone. The parents of 87 children gave written informed consent. The remaining parents refused participation of their child because they considered the examination too demanding for their child or themselves. Six children could not be adequately tested with the selected test instruments because of severe motor or sensory problems, or a general developmental delay. The patient sample that eventually participated in the follow-up consisted of 81 children with a history of NE1 ($N = 34$) or NE2 ($N = 47$). Fifty-three comparison children (CO), matched for age and gender, were recruited from the schools of the patients and other schools in the region of the Wilhelmina Children's Hospital in Utrecht. Additional exclusion criteria for the comparison group were: any pre- or perinatal complications, assisted instrumental delivery, and referral to a pediatrician or admission to a hospital in the first month of life.

Mean age was 120.3 months in the CO group ($SD = 5.8$), 118.8 months in the NE1 group ($SD = 6.3$), and 117.4 months in the NE2 group ($SD = 6.5$) [$F(2, 131) = 2.645$, $p = .075$]. The three groups did not differ in gender [χ^2 (2) = .060, $p = .971$]. Boys were slightly overrepresented in all groups (CO: 29/53; NE1: 19/34; NE2: 25/47). To operationalize socio- economic status, maternal educational level was measured on a five-point scale (1. no education or primary school, 2. lower technical or vocational training, 3. lower secondary education, 4. higher secondary education, 5. higher education e.g., university) (Kunst et al., 2005). Maternal education was highest in the CO group (CO: mean = 4.2, median = 4.0; NE1: mean = 3.5, median = 4.0; NE2: mean = 3.7, median = 4.0; H (2) = 6.537, $p = .038$).

Measures

Behavioral Functioning

The parents and the classroom teacher completed the Dutch adaptation of the *Child Behavior Check List (CBCL)* (Verhulst, van der Ende, & Koot, 1996) and the *Teacher's Report Form (TRF)*, respectively. The CBCL and TRF are standardized questionnaires of problematic behavior of a child in the past 6 months. These questionnaires deliver scores that indicate problems within several specific areas of functioning, as well as a total problem score that indicates if the problematic behavior reaches clinical levels, meaning that the same amount of problems can be found in children with psychopathology according to classification systems for psychiatric diagnoses like the well-known Diagnostic Statistical Manual (DSM). The questionnaires were scored with the computerized scoring program Assessment Data Manager (ADM, version 6.5). The Dutch version of the CBCL has acceptable reliability and validity (Evers, Van Vliet-Mulder, & Groot, 2000). The parents of one child with mild NE failed to complete the questionnaire because of language difficulties. One teacher of a child with mild NE and seven teachers of comparison children did not return the questionnaire.

A second parent questionnaire, the *Children's Social Behavior Questionnaire (CSBQ, in Dutch: Visk)* (Hartman, Luteijn, Serra, & Minderaa, 2006) was used to describe a broad range of social problem behaviors that may be related to pervasive developmental disorders. The CSBQ is a 49-item questionnaire. The total score consists of the sum of six scales: ''Behavior/emotions not optimally tuned to the social situation,'' ''Reduced contact and social interest,'' ''Difficulties in understanding social information,'' ''Orientation problems in time, place, or activity,'' ''Stereotyped behavior,'' and ''Fear of and resistance to changes.'' The CSBQ has sufficient reliability and validity (Hartman et al., 2006). Internal consistency (Cronbach's α) is .94, interrater reliability (Intraclass Correlation Coeffient) is .86, and test-retest reliability (Pearson's r) is .9. Hartman et al. estimated construct validity by performing a combined factor analysis of the CSBQ and CBCL subscales. The patterns of factor loadings that were found indicated that the CSBQ has good convergent and divergent validity. Because of language problems, the parents of one child with NE1 and one with NE2 could not complete this questionnaire.

Psychiatric Classifications/Psychopathology

We investigated the prevalence of psychiatric classifications with the *National Institute of Mental Health Diagnostic Interview Schedule for Children version IV—Dutch translation (DISC-IV)* (Ferdinand & van der Ende, 1998). This is a highly structured interview to obtain DSM-IV classifications. A psychologist (M.H.) used the parent version (DISC-IV-P) to interview one of the parents. The parents of four children with mild NE could not be interviewed, in one case because of language problems, and in three cases no appointment could be made within the time frame of

this study. The DISC-IV consists of seven modules of which we selected three because of time constraints and expected diagnostic prevalence: ''Anxiety disorders,'' ''Mood disorders,'' and ''Disruptive disorders.'' Classifications were assigned if a parent report met full diagnostic criteria using the DISC-IV scoring algorithms. For ease of analysis and to facilitate transformation into categories of DSM-IV diagnoses, separate diagnoses were grouped into broader categories. ''Anxiety disorders'' included social phobia, separation anxiety, specific phobia, panic disorder, agoraphobia, and generalized anxiety disorder. The second category, ''Mood disorders,'' consisted of major depression, dysthymia, and (hypo)mania. We considered ADHD to be a separate diagnostic category, and ODD and CD combined formed the category ''Disruptive disorders.'' This choice is based on the difference between attention deficit and hyperactive/impulsive behavior on the one hand and the behaviors that are associated with ODD or CD on the other hand. The former are not the result of intentional resistance of the child (Matthys, 1996) and can therefore be differentiated from the latter. Because the DISC-IV does not include a module to assess symptoms of pervasive developmental disorders, we used a cut-off point based on the CSBQ total score to decide whether psychopathology in this domain was present. We used recently revised norms for typically developing Dutch children ($N = 582$) to create the cut-off point to identify the children in the study sample who showed abnormally high levels of social problems like those found in pervasive developmental disorders (Hartman CA: personal communication, 2007).

Intellectual Functioning

Child IQ was estimated to provide information on general intellectual ability. The Wechsler Intelligence Scale for Children-III Dutch version was used (WISC-III Nl: Kort et al., 2005). The subtests Similarities, Vocabulary, Block Patterns, and Object Assembly were used to estimate IQ (Sattler, 1988).

Statistical Analyses

Because of the group differences found in age and educational level of the mother, we examined the relation of these variables with the behavioral variables to determine whether age and maternal education should be included as covariates. The correlations with the continuous variables of the CBCL, TRF, and CSBQ were measured with Spearman's r_s and Pearson's r, as appropriate. Logistic regression analysis was used to examine whether age and maternal education significantly predicted outcome on the dichotomous variables of the DISC and CSBQ.

To examine behavioral functioning, group means were compared on all scales of the CBCL and TRF, and the total score of the CSBQ. Analysis of the CBCL and the TRF incorporated the eight syndrome scales, the ''broad band'' scales ''Internalizing'' and ''Externalizing,'' and the Total problems score. When overall differences between the groups were found, post hoc tests were performed to determine which groups differed specifically from each other. The next step was to examine the prevalence of psychopathology according to the DSM-IV among the three groups. Percentages of DISC-IV classifications and percentages of children who scored above the 95th percentile of the CSBQ norms (an indication of pervasive developmental disorder) were described for the groups separately. For the statistical analyses, SPSS 12.0.2 was used. A p value $<.05$ was regarded as statistically significant, and multi-testing corrections were applied as appropriate. All analyses were two-tailed. The distributions of scores of the continuous variables were examined for each group to determine whether parametric or nonparametric statistical analyses had to be applied. Normality of distribution and homogeneity of variances could be assumed for the broad band scales ''Internalizing'' and ''Externalizing,'' and the Total Problems score of both the CBCL and the TRF. Differences in these variables among the groups were tested using one-way analyses of variance (ANOVA) and Tukey HSD post hoc tests. When normality and homogeneity of variances could not be assumed, or when groups of children were compared according to levels of variables of ordinal measurement scale, Kruskal–Wallis tests were performed. These were followed up by Mann–Whitney U-tests. Chi square (χ^2) analyses were used to test differences between the groups in the percentages of children who obtained a DSM-IV (DISC-IV) classification, the percentages of children who scored above the clinical cut-off criterion of the CBCL and TRF and above the 95th percentile of the norms for typically developing children of the CSBQ, and the percentages boys and girls in the study sample. Effect sizes (Pearson's r) were calculated for post hoc, pair wise comparisons (Field, 2005). According to widely accepted criteria, $r = .10$ was considered a small effect, $r = .30$ a medium effect, and $r = .50$ a large effect (Cohen, 1988).

Results

Covariates. Age was not significantly correlated with scores on the CBCL and TRF and did not predict outcome on the DISC and CSBQ. Therefore, the analyses were not corrected for age. Educational level of the mother did not

predict outcome on the DISC and CSBQ, and was not significantly related to the continuous behavioral variables except CBCL social problems ($r_s = -.17$, $p = .047$) and attention problems ($r_s = -.17$, $p = .049$). Replacing the Kruskal–Wallis analyses on these outcome variables with ANCOVA's with maternal education as a covariate did, however, not substantially change the results.

Intellectual functioning. Mean estimated IQ differed significantly between all groups [$F(2, 130) = 22{,}897$, $p < .001$] (CO: $M = 109.0$, $SD = 12.0$; NE1: $M = 98.10$, $SD = 12.29$; NE2: $M = 86.5$, $SD = 21.7$).

Behavioral functioning: Overall problem behavior. CBCL and TRF scores are presented in Tables I and II. In general, the comparison group obtained the lowest problem scores. On the TRF, the three groups differed significantly on the Total Problems scale [$F(2, 123) = 8.928$, $p < .001$]. On post hoc tests, the NE2 group appeared to have significantly more problems than the CO group ($p < .001$, $r = .448$).

Table I. Behavioral Functioning: Teacher ratings (TRF)

	CO $N = 46$ Mean[a] (SD)	NE1 $N = 33$ Mean (SD)	NE2 $N = 47$ Mean (SD)	p*	Post hoc; p** CO-NE1	CO-NE2	NE1-NE2
TRF							
Anxious/depressed	52.9 (4.9)	55.7 (7.0)	56.5 (6.6)	**.005**	.030	**.002**	.435
Withdrawn/depressed	53.6 (5.3)	55.8 (7.8)	55.9 (6.2)	.17			
Somatic complaints	50.8 (2.2)	54.8 (8.6)	53.6 (6.2)	.03			
Social problems	52.1 (4.5)	55.6 (7.8)	57.6 (7.5)	**<.001**	**.011**	**<.001**	.108
Thought problems	51.7 (4.0)	55.5 (9.0)	54.4 (6.7)	.06			
Attention problems	51.6 (2.7)	53.9 (6.8)	54.9 (5.2)	**.001**	.247	**<.001**	.041
Rule-breaking behavior	51.7 (3.1)	53.6 (6.2)	53.6 (5.2)	.20			
Aggressive behavior	52.9 (4.1)	54.9 (8.7)	55.7 (6.6)	.14			
Internalizing problems	48.0 (7.8)	53.1 (11.1)	53.2 (10.5)	.02			
Externalizing problems	48.7 (7.3)	50.4 (10.7)	53.0 (8.6)	.06			
Total problems	46.7 (7.6)	51.4 (11.7)	54.6 (8.1)	**<.001**	.063	**<.001**	.269

Note. Bold printed values are considered significant.

[a]Mean *T*-score.

Critical *p (after multi-testing correction) = .005; critical **p (after multi-testing correction) = .017.

Table II. Behavioral Functioning: Parent Ratings (CBCL + CSBQ)

	CO $N = 53$ Mean[a] (SD)	NE1 $N = 33$ Mean (SD)	NE2 $N = 47$ Mean (SD)	p*	Post hoc; p** CO-NE1	CO-NE2	NE1-NE2
CBCL							
Anxious/depressed	53.9 (5.7)	56.8 (8.6)	54.0 (5.0)	.28			
Withdrawn/depressed	53.9 (5.2)	56.2 (6.4)	56.3 (6.9)	.08			
Somatic complaints	53.9 (5.1)	57.5 (8.9)	55.8 (5.8)	.12			
Social problems	53.4 (5.2)	56.0 (6.7)	56.6 (8.4)	.08			
Thought problems	54.0 (5.7)	59.8 (9.0)	57.1 (8.8)	**.004**	**.001**	.059	.12
Attention problems	54.0 (5.9)	55.9 (6.9)	57.7 (10.3)	.09			
Rule-breaking behavior	53.5 (5.7)	54.3 (6.5)	54.3 (5.6)	.70			
Aggressive behavior	53.1 (5.7)	54.7 (6.6)	56.3 (8.6)	.19			
Internalizing problems	48.7 (10.3)	53.7 (11.0)	51.2 (11.6)	.12			
Externalizing problems	47.1 (10.6)	49.1 (11.3)	51.1 (11.8)	.20			
Total problems	47.0 (11.7)	52.2 (12.0)	52.3 (12.2)	.05			
CSBQ total score[b]	9.2 (9.1)	15.2 (13.4)	19.2 (17.9)	**.003**	**.012**	**.002**	.541

Note. Bold printed values are considered significant.

[a]Mean *T*-score.

[b]Mean total score.

Critical *p (after multi-testing correction) = .005; critical **p (after multi-testing correction) = .017.

The NE1 group obtained problem scores that were higher than those of the CO group but lower than those of the NE2 group. These differences, however, were not significant.

Behavioral functioning: Teacher ratings of specific problem behavior. Significance testing of the scores of the three groups on the syndrome scales of the TRF yielded the following results. The groups differed significantly on the scales ''Anxious/depressed'' [$H(2) = 10.500$, $p = .005$], ''Social problems'' [$H(2) = 20.194$, $p < .001$], and ''Attention problems'' [$H(2) = 14.553$, $p = .001$]. The NE2 group obtained the highest problem scores on these scales, followed by the NE1 group and the CO group. In post hoc testing, the scores of the children with NE2 differed significantly from those of the CO group on all three scales (p values; Anxious/depressed: $p = .002$, $r = .325$, Social problems: $p < .001$, $r = .466$, and Attention problems: $p < .001$, $r = .396$). In addition, the Social problems scale showed a significant difference between the NE1 and the CO group ($p = .011$, $r = .285$).

Behavioral functioning: Parent ratings of specific problem behavior. The CBCL showed significant group differences on the syndrome scale ''Thought problems'' [$H(2) = 11.109$, $p = .004$]. On this scale, the NE1 group showed the highest problem scores. Post hoc tests revealed that this group showed significantly higher problem scores than the CO group ($p = .001$, $r = .354$). The NE2 group did not differ significantly from the NE1 and the CO group on this scale.

The CSBQ total score differed significantly between groups [$H(2) = 11.498$, $p = .003$]. On post hoc tests, both the NE2 and the NE1 groups appeared to have significantly more problems than the comparison group (NE2-CO: $p = .002$, $r = .310$; NE1-CO: $p = .012$, $r = .273$). No significant difference existed between the NE2 and the NE1 group.

Psychiatric classifications/psychopathology. With respect to psychiatric classifications, percentages of children who obtained one or more classifications on any of the DISC-IV clusters, and percentages of children who scored above the 95th percentile of the CSBQ norms are presented in Table III. Eighteen (38.3%) children with NE2 obtained one or more DISC-IV classifications, compared to six (20.0%) children with NE1 and 12 (22.6%) CO children [$\chi^2(2) = 4.202$, $p = .122$]. Eight (17.0%) of the NE2 children, three (8.8%) of the NE1 children, and two children of the CO group (3.8%) scored above the CSBQ cut off point [$\chi^2(2) = 5.030$, $p = .081$].

For reasons of comparison, percentages of children who obtained scores in the clinical range on the Total problems score of the CBCL and TRF are presented below. The cutoff was set at the 90th percentile. On the TRF, 5/47 (10.6%) of the children with NE2, 3/33 (9.1%) of the children with NE1, and 0/46 (0%) of the CO children scored above the clinical cut off [$\chi^2(2) = 4.990$, $p = .082$]. On the CBCL, 10/47 (21.3%) of the children with NE2, 6/33 (18.2%) of the children with NE1, and 4/53 (7.5%) of the CO children scored above the clinical cutoff [$\chi^2(2) = 4.015$, $p = .134$].

Discussion

General conclusions

This study aimed to examine behavioral outcome at school age in children with mild or moderate NE. We first examined behavioral functioning in daily life. At an overall level, children with NE, particularly those with moderate NE, showed more problematic behavior than a peer group. Looking at specific domains of behavioral functioning, both children with mild and moderate NE showed higher levels of social problems. In addition, children with moderate NE showed more anxious/depressed behaviors and attention problems, and children with mild NE had higher levels of thought problems.

We expected to find a relation between grade of NE and behavioral outcome. At an overall level,

Table III. Psychiatric Classifications (DISC-IV Diagnoses, and Social Problems: above P95 on the CSBQ)

	CO ($N = 53$)	NE1 [$N = 30$ (DISC-IV)] [$N = 33$ (CSBQ)]	NE2 [$N = 47$ (DISC-IV)] [$N = 46$ (CSBQ)]	p
DISC-IV				
Any anxiety disorder	6 (11.3)	4 (13.3)	9 (19.1)	.53
Any mood disorder	0 (0)	0 (0)	1 (2.1)	.41
ADHD	7 (13.2)	3 (10.0)	7 (14.9)	.82
Any disruptive disorder (ODD or CD)	3 (5.7)	4 (13.3)	7 (14.9)	.29
Any DISC-IV diagnosis	12 (22.6)	6 (20.0)	18 (38.3)	.12
>P95 CSBQ	2 (3.8)	3 (8.8)	8 (17.0)	.08

Values are given as N (%).

significantly elevated levels of problem behaviors were found in children with moderate NE, but not in children with mild NE. On specific behavioral domains, however, children with mild NE also showed higher ratings of problem behaviors. Furthermore, none of the measures in this study yielded significant differences between the two patient groups. This outcome pattern suggests that the more subtle developmental effects of NE following PA can be seen in both children with mild and moderate NE. Potential problems in behavioral functioning are milder, but not absent in mild NE, as opposed to the common finding that long-term negative effects are limited to moderate and severe cases of NE.

In addition to daily-life behavioral functioning, this study examined developmental outcome after NE on the level of psychiatric classifications/psychopathology. The DISC-IV screening for DSM-IV classifications, and the CSBQ cut off (as an indication of pervasive developmental disorders) did not reveal any systematic differences between the groups in the percentages of children who reached the criteria for a DSM-IV classification. These results suggest that NE, although this condition affects the overall level of behavioral adjustment, does not lead to increased rates or specific patterns of psychopathology. So, we can conclude from this study, that NE does not lead to behavior disorders at the age of 10 years, and thus, that the general clinical prognosis of mild and moderate NE is good. However, we want to be cautious with this conclusion because we did find subtle effects of both mild and moderate NE on specific domains of daily-life behavioral functioning. This indicates that NE, as a perinatal condition, does have a developmental impact that lasts at least until middle school age. We argue that these findings have to be placed in a broader perspective, i.e., in the context of the long-term effects of NE on other developmental domains such as general intelligence, scholastic abilities, and specific cognitive skills such as memory and learning. Relatively small disadvantages that exist in these cognitive domains as a result of the perinatal condition can interact with subtle changes in behavioral functioning and, over time, result in clinically significant problems.

Current findings in relation to previous studies

In the studies of Robertson and Finer (1988), and Marlow et al. (2005) higher rates of hyperactivity were reported in children with moderate NE, based on parent and/or teacher questionnaires. Moster et al. (2002) reported high levels of ADHD-related diagnoses in a group of children with NE, but the authors did not provide a description of the diagnostic process nor did they record the grade of NE. In our study, ADHD classifications were not more frequent in NE than in normal controls, according to DISC-IV criteria. However, on the level of behavioral functioning, relatively high levels of attention problems were found in children with moderate NE. So, although the pathology level is not reached, there seems to be vulnerability for symptoms that contribute to the ADHD syndrome. One other previous study reported an elevated rate of Autism Spectrum Disorders in children with moderate and severe NE with heterogeneous etiology (Badawi et al., 2006). The diagnoses in this study were based on the clinical judgment of health professionals. Our study revealed higher levels of social problems upon systematic screening (CSBQ) in children with moderate NE and to a lesser extent in children with mild NE. Although the CSBQ measures symptoms of social impairment as can be found in pervasive developmental disorders, these findings alone certainly do not justify the conclusion that ASD are more common among children with NE.

Limitations

One may argue that the implications of our findings must be considered with caution because of some limitations of the study. First, the results of this study are based on the long-term development of children born over a decade ago. Since then, new treatments have been introduced for children with neonatal encephalopathy following perinatal asphyxia that can alter their prognosis. Hypothermia, both systemic (total-body) and selective (head cooling), is applied to prevent the occurrence of secondary energy failure following the initial asphyxial insult. Recent studies have shown that hypothermia can increase survival rates and reduce the risk of developing moderate or severe disabilities (Jacobs, Hunt, Tarnow-Mordi, Inder, & Davis, 2007). This fairly new treatment may also affect the incidence and severity of milder developmental difficulties such as behavioral problems. Therefore the long-term development of children who have been treated with hypothermia may differ from the outcome presented in this study.

Secondly, the representativeness of our comparison group may be questioned. In this group we found a seemingly high prevalence of 22.6% of any psychiatric classification. It is possible that we attracted a somewhat unrepresentative sample of ''normal'' comparison children because we had to rely on volunteers. Such a sampling bias, if indeed present, could have led to an underestimation of the relative problems in the NE1 and NE2 group and would therefore increase the concerns raised by this study about the behavioral outcome after NE. This seemingly high prevalence of psychiatric classifications in typically developing samples, however, is not uncommon.

Verhulst, van der Ende, Ferdinand and Kasius (1997) found a psychiatric diagnosis in 21.8% of a national sample of Dutch adolescents, using the same method (DISC), suggesting that the comparison group in the current study is not atypical. When interpreting the findings obtained from the DISC, one has to bear in mind that the DISC classifications do not correspond directly to DSM diagnoses. The ''full diagnostic criteria'' of the DISC, which we used, do not include a criterion of functional impairment resulting from the psychiatric symptoms. Verhulst et al. (1997) found that including such a criterion lowered the percentage of adolescents with a disorder from 21.8% to 5.9%. Nevertheless, the relatively high rates in our comparison group of DISC symptoms related to anxiety, ADHD and disruptive behavior disorders, only stress the importance of the group differences we found on the TRF, in particular the higher rates of anxious/depressed behaviors and attention problems in the moderate NE group compared to the comparison group. So, although we did not find elevated rates of child psychiatric diagnoses, this study provides evidence of a developmental risk of behavioral problems after NE.

A third limitation of this study concerns the methodological choices we made. Although general intellectual functioning has been shown to be related to behavioral problems (Dekker, Koot, van der Ende, & Verhulst, 2002), in the present study, we chose not to correct for IQ differences. Since our main aim was to examine the developmental impact of NE, correcting for IQ would only be adequate if NE selectively affects those neonates who are genetically predisposed to become less intelligent children. In that case, IQ would be a confounding variable that could explain observed differences in behavioral problems. Current medical literature does not provide any evidence that this is the case. We do know that children who suffered from NE, on average, show lower general intellectual abilities than healthy peers and that severity of NE is negatively related to IQ. In this study, IQ is thus not a confounding variable but rather another representation of the effect of NE on later developmental outcome, which we aim to measure.

Summary

Both mild and moderate NE have a negative effect on daily life behavioral functioning at the age of 9–10 years. Teachers and parents judge the behavior of children with NE to be more problematic, which is related to a diversity of behavioral domains: elevated rates of thought problems, anxiety and depression, attention regulation problems and social problems. However, these problem behaviors do not lead to elevated rates of child psychiatric diagnoses or specific patterns of psychopathology. These findings suggest that, despite a positive clinical prognosis, both children with moderate and mild NE are developmentally vulnerable and could benefit from continued monitoring throughout childhood. In the context of dynamic models of human development, diffuse problems can be expected resulting from NE. These models state that an initial CNS insult may lead to the expression of genetic vulnerabilities. In addition, with ongoing development, several minor disturbances in different developmental domains can interact and lead to cumulative problems that come to expression in a pattern of global dysfunction. The results of this study suggest a risk for subtle, diffuse problems in behavioral functioning with special vulnerability of thought regulation, emotion, attention, and social skills. Social dysfunction may be a likely outcome of this dynamic, cumulative process. Social behavior can be considered highly demanding since it relies on adaptive behavior, based on subtle, complex information processing and subsequent behavior regulation during ongoing social interaction.

More research is needed to confirm the finding that NE has a subtle negative effect on behavioral functioning, and to determine whether this effect is indeed global or specific patterns of dysfunction can be detected.

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