Adult neurobehavioral outcome of hyperbilirubinemia in full term neonates – a 30 year prospective follow-up study

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Abstract

Background. Neonatal hyperbilirubinemia (HB) may cause severe neurological damage, but serious consequences are effectively controlled by phototherapy and blood exchange transfusion. HB is still a serious health problem in economically compromised parts of the world. The long term outcome has been regarded favorable based on epidemiological data, but has not been confirmed in prospective follow-up studies extending to adulthood.

Methods. We studied the long term consequences of HB in a prospective birth cohort of 128 HB cases and 82 controls. The cases are part of a neonatal at-risk cohort (n=1196) that has been followed up to 30 years of age. HB cases were newborns ≥ 2500 g birth weight and ≥ 37 weeks of gestation who had bilirubin concentrations > 340µmol/l or required blood exchange transfusion. Subjects with HB were divided into subgroups based on the presence (affected HB) or absence (unaffected HB) of diagnosed neurobehavioral disorders in childhood, and compared with healthy controls. Subjects were seen at discharge, 5, 9 and 16 years of life and parent’s and teacher’s assessments were recorded. At 30 years they filled a questionnaire about academic and occupational achievement, life satisfaction, somatic and psychiatric
symptoms including a ADHD self-rating score. Cognitive functioning was tested using ITPA, WISC, and reading and writing tests at 9 years of life.

**Results.** Compared to controls, the odds for a child with HB having neurobehavioral symptoms at 9 years was elevated (OR=4.68). Fortyfive per cent of the HB group were affected by cognitive abnormalities in childhood and continued to experience problems in adulthood. This was apparent in academic achievement (p<0.0001) and the ability to complete secondary (p<0.0001) and tertiary (p<0.004) education. Also, the subgroup of affected HB reported persisting cognitive complaints e.g. problems with reading, writing and mathematics. Childhood symptoms of hyperactivity/impulsivity (p<0.0001) and inattention (p<0.02) were more common in HB groups, but in adulthood the symptoms were equal. The affected HB had lower scores in parameters reflecting life satisfaction, more poorly controlled drinking, but not increased substance abuse.

**Discussion.** Our results indicate that neonatal HB has negative consequences in adult age. A prospectively collected cohort with strict inclusion criteria enables to control most of the bias factors involved with retrospective data. The control and HB groups were remarkably similar at birth in terms of medical data, and the growth environment of the children, as well as the parents’ social groups, education, size of family, type of housing at birth and at 9 years of age. Our findings bear resemblance to disorders of the fronto-striatal network, and also symptoms of the ADHD spectrum were frequent in the HB group suggesting a link of HB to other neurodevelopmental disorders.
Background

Neonatal hyperbilirubinemia (HB) is a well-recognized risk for severe neurological disability and death (Ip, et al., 2004). While it is at present reasonably well controlled in the developed countries, it is still a concern in economically compromised areas (Sgro, Campbell & Shah, 2006; Kaplan, Bromiker, & Hammerman, 2011). The pathogenesis of encephalopathy by unconjugated bilirubin is poorly understood but neuronal damage may be linked to oxidative stress and a disruption of the blood-brain barrier (Palmela et al., 2011). Kernicterus refers to the severe neurodevelopmental consequences, but more subtle forms of bilirubin encephalopathy also exist (Shapiro, 2003; Johnson & Bhutani, 2011). The type and severity of the effects of HB have mostly been studied in relatively short follow-up studies ranging up to school age, where mild to moderate neonatal HB has appeared to be relatively, if not totally, benign (Culley, et al., 1970; Newman & Klebanoff, 2002; Ip, et al., 2004; Gamaleldin et al., 2011). There is still controversy however on the risks for neurodevelopmental disorders in later childhood (Shapiro, 2003; Kuzniewicz & Newman, 2009; Johnson & Bhutani, 2011; Koziol, Budding, & Chidekel, 2013). To date, there are very few studies on neonatal hyperbilirubinemia followed up to early adulthood, and none beyond 20 years. The existing ones are based on retrospective analysis of birth data during military drafting of conscripts (Nilsen, et al., 1984; Seidman et al., 1991; Ebbesen, et al., 2010).

In a Norwegian study reporting results of 39 male conscripts at 18 years of age, the mean intelligence scores were comparable to the total conscript cohort, but seven subjects with a more severe hyperbilirubinemia had significantly lower scores than the national average (Nielsen, et al 1984). A study from Israel with a much larger sample (n=1948) found no linear association between neonatal bilirubin levels and intelligence test scores or school achievement at 17 years of age, but the risk for low intelligence test scores was higher among full term males (but not females) with serum bilirubin levels above 342 µmol/l (Seidman, et al., 1991). The most recent study was from Denmark, where no association between higher bilirubin levels and
the risk of obtaining a neuropsychiatric diagnosis, or scoring lower in the cognitive
test used in the drafting was seen in males with a median age of 18.8 years (Ebbesen,
et al., 2010). There was however a larger proportion of men found unfit for military
service in the HB group. Also, only 25 subjects (6% of all hyperbilirubin cases) in
the Danish study were exposed to bilirubin levels above 342 µmol/l, the cut-off value
that has previously been regarded significant.

These studies have mainly relied on IQ data and only offer limited outcome
information. Intelligence scores are often insensitive to executive dysfunction,
learning deficits and affective disorders (Johnson & Bhutani, 2011). An association
between neonatal jaundice and neurodevelopmental syndromes e.g. ADHD has been
suggested (Jangaard, et al., 2008) but not proven (Kuzniewicz, Escobar, & Newman,
2009). Also a link to autism and other disorders of psychological development has
been presented in HB (Jangaard, et al., 2008; Maimburg, et al., 2010). In a national
cohort from Denmark, full-term children exposed to jaundice as neonates had 56% to
88% greater risks of psychological development disorders, compared with children
not exposed to jaundice (Maimburg, et al., 2010). The conclusion of HB being of
benign nature based on intelligence test findings may therefore be inaccurate. Very
little is known about the vocational and social outcome of hyperbilirubinemia in
adults.

We report here the 30 year results of a prospective follow-up study on a birth cohort
of full term and normal weight newborns with hyperbilirubinemia (HB >340 µmol/l)
as the only birth risk factor whose adult outcome is compared to healthy, typically
developed controls similarly followed-up. Our aim was to study if the cognitive and
behavioral problems discovered in childhood continue in adulthood, and if they affect
the educational, occupational, and social functioning as well as health and wellbeing
of the adult subjects

Material & methods

Material
The birth risk cohort originates from a single maternity hospital in Helsinki Finland. During the recruitment period 1971-74, there were 22,359 consecutive births in this hospital, out of which 1196 (5.4%) neonates had at least one predefined risk:

- APGAR score lower than 7 at 5 or 15 minutes (n=372), birth weight under 2000 grams (n=317), jaundice with bilirubin > 340 µmol/l (n=368), severe respiratory difficulties necessitating external ventilation (n=161), neurological symptoms (n=195), maternal diabetes (n=95), infant hypoglycemia (n=104), and severe infection (n=36); 19% had more than one risk factor (Michelsson, et al., 1978).

For the present study only full term neonates with hyperbilirubinemia were included. For inclusion, at least two serum bilirubin values of 340 µmol/l (20 mg/100ml) or more were required. Children who had received blood exchange transfusion because of rapidly increasing serum bilirubin values were also included. Those who died during early childhood and those with severe disabilities (incl. kernicterus) were excluded from follow up (Michelsson, et al., 1988). Additional exclusion criteria for the present study included gestational age below 37 weeks, or birth weight below 2500 g. There were 238 HB cases fulfilling these inclusion and exclusion criteria. All subjects were Caucasian and the families spoke Finnish.

The control subjects, also prospectively studied from childhood, were born in the same hospital during the study period, attended the same schools, and were free of any perinatal risk factors. For the present study those with gestational age at or above 37 weeks, birth weight at or above 2500 g and full assessment information from 9 years of age are included (n=104).

Ethical review has been conducted over the course of the longitudinal study, and the latest approval was obtained from the Ethical Review Board of the Helsinki and Uusimaa hospital district in May 2013 (number 147/13/3/00/2013). All participants gave their written consent to the study.

**Methods and procedures**
The family’s social and economic status, maternal risk factors, genetic traits, medical data about delivery and delivery complications was recorded prospectively. The socio-economic status was defined as the father’s occupational level (1 to 5, 1 being the highest category). Psychosocial distress score was formed to include poor housing conditions, divorces, relocations, alcohol abuse, unemployment, family conflicts, domestic violence, imprisonment, severe diseases or mental problems in family. The assessment methods at 5, 9 and 16 years of age have been described in detail elsewhere (Hokkanen, Launes, & Michelsson, 2013).

To analyze the persistence of symptoms discovered in childhood, the subjects were categorized into two groups (affected and unaffected), based on their evaluations at 5 years and/or 9 years. We used the clinical classification that had been done prospectively for purposes of previous publications describing the children’s prior development (Lindahl & Michelsson, 1986, 1987; Lindahl, Michelsson, & Donner, 1988; Michelsson, Ylinen, & Donner, 1981; Michelsson, Donner, & Lindahl, 1988; Michelsson & Lindahl, 1984, 1987, 1988, 1993; Michelsson & Noronen, 1983). The diagnostic classification in the HB group were as follows: 21% had minimal brain dysfunction (MBD) - a diagnosis in use at the beginning of the cohort study implying several concomitant deficits - 30% had dyslexia, 27% perceptual disabilities (auditory, visual or undefined), 27% had motor impairment, 15% hyperactivity and attention deficit, 11% significant psychiatric and psychosomatic symptoms, 9% had neurological signs, and 5% had speech and language abnormalities (not including dyslalia only). A combined score of all the developmental findings was constructed and those with a score of 1 or above were considered to be affected with at least one of the diagnoses. The Illinois Test of Psycholinguistic Abilities (Kirk, McCarthy & Kirk, 1969), Reading and spelling tests (Ruoppila, Roman & Vasti, 1968, 1969) as well as the Wechsler Intelligence Scale for Children (WISC, Wechsler 1949) had been used in these evaluations. Information had also been obtained from parents and teachers.

When the subjects were 16 years of age, the families were contacted with a questionnaire and information regarding school performance as well as general health
and social wellbeing was inquired. The parents reported their child’s school marks that were graded by the teacher from 4 (failed) to 10 (excellent).

Long term outcome at the age of 30 years was assessed with an extensive questionnaire. The following domains are reported here: cognitive complaints (persisting learning difficulties, writing difficulties, reading difficulties, perceptual problems, mathematical problems, speech problems, motor/dexterity problems), educational and occupational achievement (graduation from school, highest degree completed, the type of present employment), general health (subjective health, use of prescribed sedatives or hypnotics, past traumas, fractures and concussions), psychiatric symptoms (diagnosed depression, anxiety disorder, panic disorder, obsessive-compulsive traits, manic-depression, sleep disorders), social well-being (general life satisfaction, social adaptability) substance use (illicit drugs, alcohol consumption). Social inadaptability score included items of reported difficulty in making friends, maintaining social relationships, perceiving them as unsatisfactory and perceiving the social support received as unsatisfactory. General unhappiness score included items of reported dissatisfaction to life and the social environment. Alcohol consumption score included items of reported drinking regularly more than once a month, perceived excessive use expressed by family members, perceived excessive use estimated by self and reported incidences of driving while intoxicated.

The questionnaire also included the ADHD Current Symptoms Scale as well as the ADHD Childhood Symptoms Scale with each of the 18 DSM-IV (American Psychiatric Association, 1994) diagnostic symptom criteria scored from 0 to 3 depending on the severity of symptoms (Barkley & Murphy, 1998).

Of the cases fulfilling the criteria of the present study, 128 HB cases (54%) and 82 controls (79 %) returned an adequately completed questionnaire at the age of 30 years. We analyzed the possible attrition bias caused by the 54% compliance in the HB group by comparing the responders and the non-responders. At birth, there was no difference between the groups in the parity, the percentage of small-for-date, apgar points, gestational weeks, birth weight, head circumference, gender ratio,
mother’s smoking habits during pregnancy, or the family socio-economic status. The developmental classification score at the age of 9 years was similar in both groups.

Statistical analysis

Statistical analysis was performed using the STATISTICA analysis software (StatSoft, Inc. 2013). For continuous outcome variables, a multiple analysis of variance (MANOVA) was used in four separate models that included variables of for birth data, cognitive tests at 9 years of age, social variables at 30 years, and ADHD symptom scores at 30 years. Missing data was replaced by mean values of relevant groups. Differences between three groups were further tested by univariate analysis of variance (ANOVA) and pair-wise comparisons. Due to multiple comparisons, we used the Bonferroni method post-hoc test because of the conservative estimates it produces. The Kruskall-Wallis nonparametric analysis of variance was used for ordinal variables or when the distribution was skewed. For testing significance of two independent variables, the Mann-Whitney-U or the Kolmogorov-Smirnov two sample tests were used. Frequencies were calculated from contingency tables and Fisher’s exact test was used to test the significance in 2 x 2 tables.

Results and discussion

There were 57 HB cases with at least one neurobehavioral disability used for classification at 9 years of life (the affected-HB group) and 71 with no disabilities (the unaffected-HB group). The controls were similarly classified into unaffected (n=70) and affected (n=12) groups. The odds ratio was calculated as OR=4.68 (95% confidence interval 2.21 – 10.11) for a subject with HB of belonging in the affected group as compared to controls.

The result indicates that the odds for a subject with neonatal HB of being in the affected group was nearly five-fold compared to the controls. As ADHD, dyslexia and other developmental disabilities are each found in about 5% - 10% of the general
population (Shaywitz & Shaywitz, 2005; Polanczyk, et al., 2007; Willcutt et al 2010), finding individuals affected with e.g. reading or writing impairment, motor difficulties, and attentional problems in our control group as well was expected. HB however greatly increases this risk. To be able to study if the neurobehavioral difficulties of childhood improve or disappear in adulthood, we continued to examine the affected and unaffected subgroup separately. The subgroups were based on categories that had been formed prospectively, independently from the present study. Because the aim was to compare the HB group with typically developed healthy subjects, controls affected with developmental disabilities were excluded from further analyses. The rationale was that a control group containing both affected and unaffected individuals would have created a bias in favor of unaffected HB and in disfavor of affected-HB cases, obscuring the potential differences.

The management of neonatal hyperbilirubinemia

Table 1 shows the perinatal background data in the three groups. A statistically significant difference was found in MANOVA for the continuous variables (Wilks’ Lambda p<0.0001) but in univariate ANOVAs only the 5min apгар differed between the groups, with the control group actually being the lowest. There was a slight but statistically not significant over representation of girls in the control group (57%) and boys in the affected (61%) and unaffected (55%) HB group.

No difference between the affected-HB and unaffected HB-groups was found in parity, the percentage of small-for-date, mother’s smoking habits during pregnancy, maternal diabetes, the number of x-ray investigations during pregnancy, past miscarriages, maternal blood pressure, mother’s weight gain during pregnancy, glycosuria, toxemia, mother’s marital status or the hereditary traits (diabetes, neurological, sensory deficits). Among all cases with HB, 54 received phototherapy and 79 had blood exchange transfusions (in six cases more than one transfusion). The number of treatments was equal in the affected-HB group (46 treated, 11 non-treated)
and the unaffected-HB HB group (55 treated, 16 non-treated). Neither were there any significant differences in the start time, duration of HB or the peak bilirubin value. ABO blood group incompatibility was present in 40 cases and Rh incompatibility in one. The treated and non-treated HB subjects were equal in terms of cognitive testing, school performance, and other assessments at 9 years of age indicating that treatment decisions did not explain the measured outcome differences.

**Medical events and development at birth, 9 and 16 years of life**

There were no differences in the children’s hospitalizations, traumas, or other somatic complaints and diseases in follow-up. The groups did not differ in the amount of reported past developmental problems within the family (44% in the affected-HB, 28% in the unaffected-HB and 34% in the controls). The body-mass-index BMI of the child was comparable in the three groups at age 9 years.

The family’s socio-economic status was the highest and the social distress scores the lowest in the unaffected HB group differentiating it from the affected HB group but not from the control group in pair-wise comparisons. The affected-HB group did not differ from the controls. The significance levels were low and considering the multiple tests performed, the findings are not considered meaningful.

The performance of the groups in cognitive tests performed at the age of 9 years is presented in Table 2 demonstrating significant differences between the three groups (MANOVA Wilks’ lambda p<0.0001). In pair-wise comparisons the affected-HB group differed from the controls in all tests conducted; the unaffected-HB group differed from the controls only in spelling test (p<0.003). The frequency of remedial instruction in preschool and school until nine years of age had been 86% in affected-HB, 44% in unaffected-HB, and 28% in the control groups (p<0.0001).

At 16 years of age the mean of all school marks (the total average of all subjects graded from 4 to 10) was 7.3 (95% confidence interval 7.1-7.5) for the affected-HB,
8.4 (8.2-8.6) for the unaffected-HB and 8.5 (8.3-8.6) for the controls, F(2,207)=41.5, p<.0001, the affected-HB group differing from the other two groups.

The results show that despite similar medical history and growth pattern, many children in the HB group managed less well in the psychological tests than the control group. This is in line with a previous cross-sectional study of this cohort (Michelsson, et al., 1988). In that study, where also cases under 2500 g and 35 – 36 weeks at birth were included, half of the HB group presented with writing difficulties at the age of 9 years (Helenius, 1987). They also had more problems at school, had lower grades, and more often attended special classes (Michelsson, et al., 1988). In the present study, where the pre-term cases were excluded, cognitive tests showed the same result. As expected based on the classification performed, the affected-HB children also needed more special education and help in school. Thus, the negative effect of HB to cognition was not caused by the borderline cases of low weight and gestational age.

In contrast to our observations, studies reporting childhood outcomes of HB have mostly found no significant consequences (Culley, et al.m 1970; Newman, T. B. & Klebanoff, M. 2002; Ip, et al., 2004; Gamaleldin et al., 2011). In our cohort 55% of the HB subjects belonged to the unaffected group and these subjects were comparable to controls in most variables studied, supporting the general view. However, a smaller percentage was affected, resembling the cohort in Denmark (Maimburg, et al., 2010), emphasizing the need to identify separate subgroups. Conflicting findings may also depend on the different ages of children studied. An important factor influencing the clinical picture is the maturation of frontal cortices, which is not complete until after adolescence, perhaps in the ages between 15 to 20 years of age (Paus, 2005). The rate of this development is poorly known, and maturation rates may differ between genders, which should be considered when interpreting results of follow-up studies. The association of the cortical maturation with IQ scores is also unclear (Burgaleta, et al., 2014). A third potential factor is the Hawthorne effect: very active treatment is likely to be given in centers where also
research is done, which may skew results in the direction of less serious consequences.

**Academic and occupational achievement reported at 30 years of age**

All but 2 subjects in all groups combined had graduated from first level education (the first compulsory nine years). However, 11% of the affected-HB subjects reported having required remedial teaching or a special class during those nine school years, in contrast to only one child in the control group and none in the unaffected-HB group (p<0.004). The proportion of subjects who had received the diploma at the end of the secondary education (12 years of school) was 30% in the affected-HB group, 70% in the unaffected-HB and 75% in the control group (p<0.0001). Within the HB group, the relative risk of not completing secondary education was more than two-fold (RR=2.49, 95% confidence interval 1.65-3.73, p<0.0001) for a person with affected-HB compared to an unaffected-HB.

At the point of school graduation the mean of all school marks (the total average of all subjects) was significantly different in the three groups F(2,207)=29.1, p<.0001, the affected-HB group having the lowest grades (see Fig 1).

The proportion of subjects who by the age of 30 had completed an academic degree was 11% in the affected-HB group, 32% in the unaffected-HB and 31% in the control group (p<0.0001). When also other forms of tertiary education (applied universities) were included, the relative risk of not completing tertiary education was still elevated (RR=1.57, 1.13-2.13, p<0.004) for a person with affected-HB compared to an unaffected-HB.

At 30 years of age 86%, 93% and 90% of the groups (affected-HB, unaffected-HB and controls, respectively) were working or studying full time, showing a similar outcome. At the other end of the spectrum however, 11% of the affected-HB, 3% of the controls and none of the unaffected-HB groups were unemployed (p<0.006).
The results indicate that the subgroup of affected-HB had poorer academic achievement, i.e. lower mean school grades, and less potential to graduate from secondary or tertiary education. There was also a greater risk for later unemployment. Corresponding findings in academic and occupational failure are reported in other causes of high birth risk e.g. low birth weight and asphyxia (Hack 2006, Arpino, et al., 2010; Stuart, Otterblad Olausson & Källen, 2011). The academic achievement is widely regarded as an objective and a sensitive measure, and it is influenced not only by general intelligence but also by memory, motivation, executive functions and social skills. Similar course of underachievement has been found e.g. in adults with ADHD who may have significantly less education than expected based on their IQ, and lower occupational levels than expected based on their education (Biederman et al., 2008).

Social competence, health and substance use at 30 years of age

Marital status and number of offspring was equal in all groups. Subjective happiness however was lower and the problems in social adaptability (see Table 3) were more frequent in the affected-HB group compared to the controls in pair-wise comparison. The general subjective health was similar in the three groups and there were no differences in the reported incidences of traumas, fractures and concussions. Alcohol consumption was more uncontrolled in the affected-HB group compared to the controls in pair-wise comparison. Past episodes of driving while intoxicated were reported by 20% of the affected-HB group and by 6% and 9% in the unaffected-HB and control groups respectively (p<0.04, Fisher’s exact test). Five percent of the affected-HB, 10% of the unaffected-HB, and 8% of the controls evaluated their alcohol consumption as excessive as estimated by themselves or by a family member. The use of illicit drugs was similar in the three groups, 10% of all reported having used at any time in the past.

The results indicate higher alcohol consumption in the affected-HB group. Similar tendencies in association with developmental deficits have also been observed.
Excessive alcohol consumption may be a significant confounding factor in analyzing vocational outcome. The affected-HB group had the highest average in a score measuring alcohol use but the number of subjects reporting consumption at a level that could be classified as abuse however was small. There were only a few current users of illicit drugs at the time the questionnaire was completed and the frequency of ever using any substance was also low. Incidence of substance abuse in Finland has been among the lowest in Europe for decades, although a rise has occurred in the last 10 years (Varjonen, et al., 2012). We conclude, that alcohol and substance abuse does not explain the differences observed in vocational outcome.

Cognitive and psychiatric status at 30 years of age

Ongoing cognitive problems were more frequent in the affected-HB group compared to the two other groups. Sixteen per cent of the affected-HB group reported reading difficulty, 9% writing, 9% speech and 9% mathematical difficulty, and smaller percentages other learning or perceptual problems. All symptoms combined, 23% in the affected-HB subjects had cognitive complaints, in contrast to 10% in the unaffected group and 7% in the control group (p<0.03).

In the subjective ADHD symptom rating scales (see Table 3) the three groups differed significantly (MANOVA Wilks’ lambda, p<0.004). The affected-HB group scored higher for childhood inattention compared to both the unaffected-HB and the control groups (p<0.001), and also higher for childhood hyperactivity/impulsivity compared to the controls (p<0.01). The unaffected-HB group scored higher in childhood inattention compared to the controls (p<0.002). The difference was not significant for the current symptoms rating scales.

Based on the self-rating, three cases fulfilled the new DSM5 (American Psychiatric Association, 2013) criteria symptom count for ADHD in adulthood: one with the hyperactive/impulsive and two with the combined type ADHD. When the count was done for childhood symptoms, eight cases fulfilled the criteria: three with the
inattentive, two with the hyperactive/impulsive and three with the combined type. In the unaffected-HB group one case reported childhood symptoms of the inattention type, followed by adult symptoms of the combined type; another case reported symptoms of the hyperactive/impulsive type in childhood only. In the control group one case reported combined type symptoms for both childhood and adulthood.

No differences in self-reported depression, anxiety, tendency towards compulsive or manic behavior, bizarre thoughts, or psychotic ideation between the groups were found. Quality of sleep as well as the use of sedatives or hypnotics was reportedly similar in all groups.

The results indicate that the various learning disabilities found in a subgroup of the HB cases in childhood continue into adulthood. In our study, 23% of the affected-HB subjects reported persisting cognitive complaints at the age of 30 years, reading difficulties being reported most frequently. This is in line with the previous results at 9 years of age (Helenius, 1987). In addition to learning disabilities, the subjects reported subjective ADHD symptoms more frequently than the controls. In the retrospective childhood ADHD symptom rating scale both HB groups (affected and unaffected) reported higher scores of inattention than controls, but the difference was no longer significant in adulthood. The childhood hyperactive/impulsive symptoms were higher in the affected-HB group, but they too levelled off by adulthood, resembling the typical pattern for ADHD symptoms (Biederman, Mick & Faraone, 2000; Wilens, Biederman & Spencer, 2002). ADHD is suggested to be more common among subjects with pre- and perinatal risk factors (Strang-Karlsson et al., 2008; Gustafsson & Källén, 2011; Halmøy, Klungsøy, Skjærven, & Haavik, 2012) although contradictory findings have also been reported (Silva et al 2013). Similarly mixed evidence has emerged regarding the link between ADHD and hyperbilirubinemia (Jangaard, et al., 2008; Kuzniewicz, Escobar, & Newman, 2009). In our study, the ADHD diagnosis cannot reliably be made based on questionnaire data, but ADHD symptoms appeared to be a part of the disability spectrum.
Conclusions

Our aim was to study long term consequences of neonatal hyperbilirubinemia at 30 year-old adults followed up from birth. To exclude the confounding effects of preterm birth, we included only newborns ≥ 2500 g birth weight and ≥ 37 weeks of gestation. The subjects with neonatal hyperbilirubinemia were divided into subgroups based on the presence (affected HB) or absence (unaffected HB) of diagnosed cognitive or behavioral disabilities in childhood, and compared with healthy controls. Our results indicate that neonatal HB has negative consequences in adult age. Nearly half of the HB group were affected by cognitive abnormalities in childhood and continued to experience problems in adulthood. This was apparent in academic achievement and the ability to complete secondary and tertiary education. Also, the subgroup of affected HB reported persisting cognitive complaints e.g. problems with reading, writing and calculus. Childhood symptoms of hyperactivity/impulsivity and inattention were more common in HB groups, but in adulthood the symptom levels were equal. The affected HB still perceived lower levels of subjective wellbeing as well as social adaptability, and reported more poorly controlled drinking; findings that may reflect a more profound tendency of poor adjustment.

The strength of our study is that our control and HB groups were remarkably similar at birth in terms of medical data and absence of risk factors, other than HB. Our base cohort’s limit for inclusion in the low birth weight group was 2000 g and inclusion to any group did not have a fixed limit of weeks of gestation. Consequently, there were a few neonates both in the control and the HB groups, whose gestational age was 35-36 weeks and / or birthweight between 2000 – 2500 g. In order to avoid any further bias we also excluded these borderline cases. The growth environment of the children was also very similar in the groups, as the parents’ social status, education, size of family, type of housing were comparable at birth and at 9 years of age. Further, the children were born in the same hospital, lived in the same metropolitan area, and attended the same schools. We also tested for attritional bias, and found none. Therefore we think that confounding factors are well controlled without need for
statistical modeling. Our results should be well generalizable in otherwise uncomplicated HB cases, even in the era of more modern therapeutic possibilities.

A limitation in our study is that a questionnaire is a rather insensitive tool that has sampling and data processing challenges (Gilbody, House, & Sheldon, 2001; Olsen et al., 2001; Jaddoe et al., 2006, 2010). However, mailed inquiries are widely used and allow statistical comparison of parallel groups. Furthermore, in our study the cases had also been clinically carefully examined from birth up to age 9 years, which increases the reliability of our data. The main outcomes reported here, i.e. need for remedial teaching, low school grades and academic underachievement, are objective and we regard the differences between our groups credible. Still, although statistically significant differences were found, the results are indicative rather than proof of specific types of cognitive consequences due to the low specificity of a questionnaire.

The symptoms we found, e.g. decreased social adjustment, symptoms of the ADHD spectrum, and the ability to achieve goals when in an instructive environment (primary education with special tuition) but not when independent planning and execution of tasks are required (higher education or occupational environment) bear resemblance to impairment of the fronto-striatal system. The pathogenesis of encephalopathy by unconjugated bilirubin is poorly understood but it seems to involve oxidative stress, a disruption of the blood-brain barrier and the consequent damage of neuronal cells (Palmela et al., 2011). Brain pathology typically following bilirubin neurotoxicity has been suggested to involve the basal ganglia, particularly globus pallidus, as well as subthalamic nuclei, hippocampus, diencephalon, midbrain, pontine and brain stem nuclei and cerebellum (Johnson & Bhutani, 2011; Koziol, Budding, & Chidekel, 2013), locations which take part in a wide variety of motor, sensory and cognitive functions. Fronto-subcortical circuits (Cummings, 1993) connect the frontal cortex to the basal ganglia and these circuits participate in executive functions (attention control, response inhibition, planning and execution). In this respect, HB has common elements with the processes that are active in other perinatal disorders that cause brain damage, e.g. ischemia-asphyxia and immaturity and/or low birth weight (e.g. Volpe, 2005, 2012). Clearly, speculations on
frontal dysfunction in HB warrant further studies with thorough neuropsychological testing and neuroimaging.

We conclude that neonatal HB is a recognizable cause of adult age neurobehavioral problems, severe enough to have negative occupational and quality of life effects.

References


Jangaard, K. A., Fell, D. B., Dodds, L., & Allen, A. C. (2008). Outcomes in a population of healthy term and near-term infants with serum bilirubin levels of >or=325 micromol/L


Table 1. Description of the groups at birth. Means (95% confidence interval) and frequencies.

<table>
<thead>
<tr>
<th></th>
<th>Affected-HB n=57</th>
<th>Unaffected-HB n=71</th>
<th>Controls n=70</th>
<th>Univariate test across the three groups</th>
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<td>gestational age (weeks)</td>
<td>39.5 (39.1-39.8)</td>
<td>39.3 (38.9-39.6)</td>
<td>39.8 (39.5-40.2)</td>
<td>ns</td>
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<tr>
<td>birth weight (g)</td>
<td>3505 (3376-3633)</td>
<td>3469 (3354-3585)</td>
<td>3538.4 (3428-3649)</td>
<td>ns</td>
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<td>head circumference (cm)</td>
<td>34.6 (34.2-34.9)</td>
<td>35.0 (34.7-35.3)</td>
<td>35.0 (34.7-35.4)</td>
<td>ns</td>
</tr>
<tr>
<td>apgar 1min</td>
<td>8.6 (8.4-8.8)</td>
<td>8.5 (8.3-8.8)</td>
<td>8.9 (8.7-9.2)</td>
<td>ns</td>
</tr>
<tr>
<td>apgar 5 min</td>
<td>9.8 (9.7-10.0)</td>
<td>9.9 (9.7-10.0)</td>
<td>9.6 (9.4-9.7)</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>apgar 15 min</td>
<td>9.9 (9.9-10.1)</td>
<td>9.9 (9.8-10.0)</td>
<td>10.0 (9.9-10.1)</td>
<td>ns</td>
</tr>
<tr>
<td>maternal age (years)</td>
<td>25.4 (24.3-26.5)</td>
<td>26.0 (25.0-27.0)</td>
<td>26.8 (25.4-28.1)</td>
<td>ns</td>
</tr>
<tr>
<td>peak bilirubin value, distribution of cases</td>
<td>&lt;300 2 300-339 5 340-399 29 400-449 14 &gt; 450 3</td>
<td>&lt;300 1 300-339 3 340-399 32 400-449 23 &gt; 450 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gender m/f</td>
<td>35 / 22</td>
<td>39 / 32</td>
<td>30 / 40</td>
<td>ns</td>
</tr>
</tbody>
</table>
Table 2 Comparison of the groups at 9 years of age. Means (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Affected-HB n=57</th>
<th>Unaffected-HB n=71</th>
<th>Controls n=70</th>
<th>Univariate test across the three groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC VIQ</td>
<td>104.8 (102.0-107.6)</td>
<td>119.2 (116.6-121.7)</td>
<td>120.0 (117.4-122.5)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>WISC PIQ</td>
<td>109.1 (106.1-112.2)</td>
<td>118.2 (115.5-121.0)</td>
<td>122.4 (119.7-125.2)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>WISC FSIQ</td>
<td>107.4 (104.6-110.3)</td>
<td>121.0 (118.4-123.5)</td>
<td>123.3 (120.8-125.9)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>ITPA total</td>
<td>33.8 (33.0-34.7)</td>
<td>37.7 (36.9-38.4)</td>
<td>37.2 (36.5-38.0)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Reading test</td>
<td>8.3 (8.1-8.6)</td>
<td>8.8 (8.6-9.0)</td>
<td>8.8 (8.6-9.0)</td>
<td>p&lt;0.003</td>
</tr>
<tr>
<td>Spelling test</td>
<td>7.0 (6.8-7.3)</td>
<td>7.9 (7.6-8.2)</td>
<td>8.5 (8.3-8.8)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>29.8 (28.5-31.1)</td>
<td>31.6 (30.5-32.7)</td>
<td>31.5 (30.4-32.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Social distress score</td>
<td>4.3 (3.4-5.1)</td>
<td>2.7 (2.0-3.4)</td>
<td>3.1 (2.4-3.8)</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>2.4 (2.1-2.7)</td>
<td>1.9 (1.6-2.1)</td>
<td>2.0 (1.8-2.3)</td>
<td>p&lt;0.04</td>
</tr>
</tbody>
</table>

WISC= Wechsler Intelligence Scale for Children, VIQ=verbal intelligence quotient, PIQ=Performance intelligence quotient, FSIQ= Full scale intelligence quotient; ITPA= Illinois Test of Psycholinguistic Abilities; BMI= body mass index
Table 3 Results from the questionnaire at 30 years. Means (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Affected-HB n=57</th>
<th>Unaffected-HB n=71</th>
<th>Controls n=70</th>
<th>Univariate test across the three groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>General unhappiness score</td>
<td>2.8 (2.3-3.3)</td>
<td>2.2 (1.8-2.6)</td>
<td>1.6 (1.2-2.1)</td>
<td>p&lt;0.003</td>
</tr>
<tr>
<td>Social inadaptability score</td>
<td>0.8 (1.6-1.1)</td>
<td>0.6 (0.3-0.8)</td>
<td>0.3 (0.1-0.6)</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Alcohol consumption score</td>
<td>2.8 (2.0-3.5)</td>
<td>1.4 (0.7-2.1)</td>
<td>1.6 (0.9-2.3)</td>
<td>p&lt;0.03</td>
</tr>
<tr>
<td>Current inattention symptoms</td>
<td>2.78 (1.97-3.59)</td>
<td>2.56 (1.88-3.24)</td>
<td>1.91 (1.22-2.60)</td>
<td>ns</td>
</tr>
<tr>
<td>Current hyperactive-impulsive symptoms</td>
<td>2.96 (2.12-3.80)</td>
<td>2.86 (2.16-3.56)</td>
<td>2.36 (1.65-3.07)</td>
<td>ns</td>
</tr>
<tr>
<td>Childhood inattention symptoms</td>
<td>5.52 (4.34-6.70)</td>
<td>2.79 (1.79-3.78)</td>
<td>2.16 (1.15-3.17)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Childhood hyperactive-impulsive symptoms</td>
<td>4.40 (3.26-5.53)</td>
<td>2.68 (1.72-3.63)</td>
<td>2.25 (1.28-3.21)</td>
<td>p&lt;0.02</td>
</tr>
</tbody>
</table>
Figure 1. The average school grades at graduation