Prospective Cohort Study of Neurodevelopmental Outcomes following Extreme Neonatal Hyperbilirubinaemia

ANGELA MCGILLIVRAY (✉ angelajmcgillivray@hotmail.com)
RPA HOSPITAL

Jan Polverino
RPA HOSPITAL

Nadia Badawi
Cerebral Palsy Alliance Research Foundation https://orcid.org/0000-0001-6828-1636

Nicholas Evans
University of Sydney

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Abstract

Objective

To describe the incidence and neurodevelopmental outcomes following extreme neonatal hyperbilirubinaemia in an Australian cohort.

Study Design

A prospective cohort study of neurodevelopmental outcomes up to 3 years of age of infants born between 2010 and 2013 at ≥34 weeks’ gestation with TSB ≥450µmol/L and/or clinical signs of acute bilirubin encephalopathy. Kernicterus was defined as two consistent signs of adverse neurodevelopment consistent or bilateral lesions of the basal ganglia or midbrain on MRI.

Results

Follow-up assessment data was available for 26 out of 56 children. Three children had neurodevelopmental impairment: one has GMFCS level 4 CP, audiological deficiency and visual impairment, the second has GMFCS level 1 CP and the third, global developmental delay with autism spectrum disorder. The estimated incidence of kernicterus in this cohort is 0.35 per 100 000 live births.

Conclusion

Kernicterus continues to occur in high-income settings. Healthcare should be optimised to achieve prevention.

Introduction

Neonatal hyperbilirubinaemia is common but fortunately, for the vast majority of infants, inconsequential. Significantly impaired neurodevelopment remains a risk, predominantly in the setting of extremely high levels of unbound bilirubin, and often in the context of individual patient susceptibility to neurotoxicity due to an array of clinical and physiological risk factors. A number of studies have tracked the developmental progress of children following severe or extreme neonatal hyperbilirubinaemia. These studies are methodologically varied – applying a wide range of neonatal hyperbilirubinaemia definitions, (serum bilirubin ≥280 to ≥450µmol/L) and neurodevelopmental assessment follow-up modalities and timeframes. Overall, the existing literature reflects that most children, without associated risk factors and without signs of acute bilirubin encephalopathy, who receive appropriate timely assessment and treatment, will not suffer serious adverse neurodevelopmental sequelae. There remains a significant disparity in outcomes between low and high-resource settings. In order to evaluate the Australian context, our preceding prospective surveillance study, estimated the incidence of extreme neonatal hyperbilirubinaemia by means of prompted voluntary paediatrician reports, to be approximately 9.4 per 100 000 live births. This compares to an international incidence estimate of 7 to 700 per 100 000 according to variably defined levels of extreme hyperbilirubinaemia in high-income countries. The subsequent follow-up study, and the focus of this paper, was initiated to ascertain the nature of long-term neurodevelopmental sequelae following extreme neonatal hyperbilirubinaemia in Australia.

Methods
This study aimed to follow the neurodevelopmental outcomes of cases of extreme neonatal hyperbilirubinaemia identified by our preceding prospective surveillance study which utilised voluntary clinician reporting of cases in collaboration with the Australian Pediatric Surveillance Unit (APSU).\textsuperscript{19} The APSU contact approximately 1400 clinicians by email each month to request reporting of rare conditions and infectious disease outbreaks.

**Study population**

Cases were defined as: an infant of 34 weeks gestation or more with a peak total serum bilirubin (TSB) of $\geq 450\mu$mol/L or with clinical and/or magnetic resonance imaging consistent with bilirubin toxicity. Of the 87 cases identified in the surveillance study, 56 were eligible for enrolment in this follow-up study. Thirty of the original surveillance study cases were located in states where follow-up study assessments were not available. One child from the surveillance cohort died in infancy of unknown cause.

**Study Methods**

Parents were contacted by the local paediatrician (whom had made the surveillance study report) and offered enrolment of their child in the neurodevelopmental follow-up study. The study comprised multiple assessments planned at 1 and 3 years of age and included: a medical review and neurological examination by a paediatrician; the Ages and Stages Questionnaire, 3rd edition\textsuperscript{21} and the Bayley Scales of Infant and Toddler Development, 3rd edition.\textsuperscript{22} Families were offered follow-up assessments at the local study-site which, most commonly, were arranged at the facility where their child's hyperbilirubinaemia and neonatal intensive care treatment had been managed. For remotely-located families, home-visits were arranged with the study team. As per usual clinical practice, therapeutic recommendations were made and implemented for any children with clinical concerns by the assessing team.

Kernicterus was defined on the basis of neonatal bilirubin levels $\geq 450\mu$mol/L and either: two signs of adverse neurodevelopment consistent with kernicterus or abnormal MRI findings with bilateral lesions of the basal ganglia or midbrain. The live birth denominator for the states included in follow-up (New South Wales, Queensland and Western Australia) was determined as per the previous surveillance study, using Australian Institute of Health and Welfare and the Australian Bureau of Statistics data.

**Ethical approval**

The study was approved by the Human Ethics Committees of: Sydney Local Health District (approval number X11-0075), King Edward's Memorial Hospital Perth (approval number 2014009EW) and the Mater Hospital, Brisbane (approval number 1897M). The study was performed in accordance with the Declaration of Helsinki.

**Results**

Complete neurodevelopmental follow-up data was available for 26 children. Nine infants were known to undergo neurodevelopmental assessment but the study team were unable to obtain written consent through the original surveillance study reporting-paediatrician consent process. The remaining 21 were lost to follow-up. Of the 26 children for whom neurodevelopmental follow-up data was available, all underwent neurological examination and formal developmental assessment at a mean age of 31 months (range 12–41 months). One child underwent a Griffiths developmental assessment\textsuperscript{23} instead of BSID-III due to local team preference. Table 1 summarises the clinical and demographic characteristics of surveillance study subjects who were enrolled in follow-up compared with those for whom formal outcome data was not available. Median peak serum bilirubin levels ($\mu$mol/L) did not differ significantly between the groups: 484 (range 454–669) vs 492 (range 370–760). Gestational ages and clinician-
determined ethnicity were comparable between the groups; as was mode of delivery and primary feeding modality in the first week after birth. Neonatal jaundice of idiopathic aetiology was significantly more common amongst the follow-up study group: 65% vs 43% ($P< 0.05$); whereas those without formal follow-up data were more likely to have an identified pathological cause for their neonatal jaundice, for example, a haematological aetiology such as ABO incompatibility, G6PD deficiency or Rhesus isoimmunisation (23% vs 57%; $P< 0.05$). There was a non-significant trend for females to be more likely to receive follow-up (54% vs 40%). Table 2 provides an overview of neurodevelopmental outcomes for the 26 enrolled follow-up study subjects, categorised according to each assessment method. Mean BSID-III scores were: cognition 10.3 (SD 1.5), receptive communication 9.4 (SD 1.8), expressive communication 9.2 (SD 2.4), fine motor 10.4 (SD 2.6) and gross motor 9.2 (SD 2.3).

Table 3 provides a summary of outcomes, hyperbilirubinaemia aetiology and presenting clinical characteristics of those with adverse neurodevelopment. All 26 children underwent medical assessment and neurological examination. Three children had neurodevelopmental abnormalities. The most severely affected child (case 1 table 3) has GMFCS level 4 cerebral palsy, severe auditory deficiency requiring cochlear implant and visual impairment following a total bilirubin level of 630µmol/L and presentation with acute intermediate ABE. One child (case 2) has GMFCS level 1 cerebral palsy and a third (case 3) has global developmental delay with autism spectrum disorder. On the basis of the two cases of confirmed cerebral palsy following severe neonatal hyperbilirubinaemia, the incidence of kernicterus in this Australian cohort is estimated to be 0.35 per 100 000 live births. Twenty children had hearing assessments, 19 of which were normal on newborn screening assessment. One child required a cochlear implant for hearing impairment detected by means of a ‘bilateral refer’ result on newborn screening. Twenty-five children were assessed using the Bayley-III. The mean age of their most recent assessment was 31 months (range 12–41). Mean subscale scores for BSID III were: cognition 10.3 (SD 1.5), receptive communication 9.4 (SD 1.8), expressive communication 9.2 (SD 2.4), fine motor 10.4 (SD 2.6) and gross motor 9.2 (SD 2.3). 22 children had ASQ-3 questionnaires completed on their behalf. The mean age of latest ASQ assessment was 25 months (range 12–42). Four children were assessed as having one or more areas of development in the ‘refer’ (-2SD) category and ten children had one or more areas in the ‘monitor’ category (-1SD).

**Discussion**

This study followed the long-term developmental progress of children who were exposed to extreme neonatal hyperbilirubinaemia in Australia. The data is largely reassuring. The majority of infants for whom long-term follow-up results were available, did not suffer long-term neurodevelopmental sequelae. The estimated incidence of kernicterus ostensibly compares favourably with international estimates of 0.4 to 2.7 per 100 000 live births.²⁻¹⁸ There are however significant methodological variations to consider, both within this study and its comparators. The majority of kernicterus incidence reports to date have been retrospective population-based record review studies of adverse neurodevelopment diagnoses following variably defined neonatal hyperbilirubinaemia. For example, Alkén and colleagues’ recent Swedish large population cohort study of almost 1 million children estimated a kernicterus incidence of 1.3 per 100 000 based on medical record review up to 2 years of age of children who had TSB of ≥ 510µmol/L in the newborn period.² Wu and colleagues also conducted an extensive medical record review study in a Califomian population of 525,409 infants born between 1995 and 2011³ with serum bilirubin levels at, or above the American Academy of Pediatrics (AAP) exchange transfusion threshold.²⁵ A pediatric neurologist blinded to bilirubin levels, reviewed medical records for diagnostic evidence of CP secondary to kernicterus based on magnetic resonance image (MRI) findings and clinical evidence of dyskinesia. Ninety percent of the cohort had follow-up to 15 months of age. The incidence of CP incidence was 0.4% amongst ‘exposed’ infants compared to 0.1% in the ‘unexposed’. Three children in the ‘exposed’ group have cerebral palsy consistent with kernicterus. In contrast,
Thomas Newman and colleagues' large, nested case-control study of Californian infants identified 140 cases from a population of 106,627 who had a peak TSB of $\geq 427\mu\text{mol/L}$ and compared their developmental outcomes with 419 controls. Follow-up data to 2 years of age was available for 94% of the cases and 89% of the controls. Formal evaluations were completed in 59% and 40% of cases and controls respectively to a mean age of 5.1 years of age ± 0.12 SD. The study did not find any cases of kernicterus in this cohort and there were no differences in neurological abnormalities, parental cognitive concern or reported behavioural problems. The Canadian Pediatric Surveillance Unit most recently reported a national kernicterus incidence of 2.7 per 100,000 based on a prospective study of paediatrician reports. Kernicterus was defined on the basis of neonatal bilirubin levels $> 425\mu\text{mol/L}$ and either: two signs of adverse neurodevelopment consistent with kernicterus and/or enamel dysplasia of deciduous teeth; or abnormal MRI findings with bilateral lesions of the basal ganglia or midbrain. Ninety percent (18 out of 20) cases met criteria on the basis of MRI brain abnormalities. Outcome data for 14 of the 20 cases was gathered by way of a study-specific paediatrician-completed questionnaire at 12–18 months of age. Chronic bilirubin encephalopathy was evident in eleven. Three cases with abnormal neonatal MRIs had normal development and two cases with normal MRIs had abnormal neurodevelopment. The UK study estimated incidence of 0.9 per 100,000 live births was based on a definition of severe hyperbilirubinaemia as $\geq 510\mu\text{mol/L}$ and associated neonatal encephalopathy (impaired consciousness, hypotonia, opisthotonus and seizures). Five suspected cases of kernicterus were reported at 12 months of age by means of an unvalidated questionnaire completed by reporting clinicians. With regards to the risks associated with bilirubin encephalopathy, Ebbesen and colleagues' population-based study of 502,766 infants utilising linked national data found bilirubin levels $> 450\mu\text{mol/L}$ without associated intermediate or advanced ABE carried little risk of adverse neurodevelopmental sequelae. In this Australian study, of the children with known adverse outcomes, the most severely affected child presented with intermediate ABE in association with a bilirubin level of 630$\mu\text{mol/L}$ secondary to haemolysis (case 1). With regards to the BSID-III findings of 25 cases in our study, all mean subscale results measured within the normal range of the standardised US population of this assessment tool. However, when considered in the local context, the performance of this cohort on BSID-III, might be considered lower than expected. Since its introduction in 2006, a tendency for the BSID-III to overestimate early childhood development has been documented by a number of authors. Peter Anderson and colleagues' study of 202 healthy term Australian children at 2 years of age found all BSID-III mean scores were above the US normative means and thus rates of developmental delay much lower than expected. Chinta and colleagues also reported the 3 year BSID-III performance of 156 healthy term Australian infants. Of particular relevance to our study, there was no significant difference on the gross-motor scale performance amongst the Chinta cohort compared with the US norms. One child (case 3) in this study has been diagnosed with global developmental delay and Autism Spectrum Disorder (ASD) in the context of a family history. ASD and other disorders of psychological and behavioural development, including attention-deficit disorder (ADHD) have been observed by some authors. Whilst further research is required to further explore this relationship, behavioural development of children affected by severe or extreme neonatal hyperbilirubinaemia should certainly be considered in their long-term surveillance and care.

Whilst the results of this prospective long-term outcomes study to 3 years of age using validated standardised assessment tools are reassuring, there are important methodological issues to consider. The voluntary reporting nature of enrolment, the indirect consent process and loss to follow-up led potentially to a significant underestimation of the incidence of impaired neurodevelopment. The study team were bound to the indirect consent process as the follow-up study was established as an adjunct to the original APSU surveillance study. In retrospect and in regards planning of future studies, enrolment in the follow-up study would have been offered at the time of the initial report. Similarly, nationwide follow-up centres and services would have been confirmed prospectively to ensure
not only maximal cohort follow-up, but most importantly, all children and families received optimal early childhood surveillance and therapeutic intervention and support. Furthermore, minor neurological neurological dysfunction (MND)\textsuperscript{29} and abnormal general movements\textsuperscript{30} have been associated with neonatal hyperbilirubinaemia and we suggest future studies should not miss the opportunity to study General Movements in this patient population, in order to further proactively identify and treat early objective signs of abnormal neuromotor development.

The issues faced by the study team in setting up this ambitious study highlight complex barriers experienced by rare-disease researchers in establishing prospective national long-term outcomes studies. Long-term neurodevelopmental outcome data is key to determining the impacts of therapeutic interventions, not least in the field of perinatal research. In the context of an observational, non-interventional study such as this, the need to navigate complex local, state and national ethical approval processes seems unjustified. In fact, in order to progress our knowledge of long-term developmental outcomes in general, consideration of a central national ethics body in warranted.

Conclusion

Despite the loss to follow-up in this cohort, we hope this study provides valuable information on the outcome of infants with this very rare condition. One case of kernicterus is always one case too many. Kernicterus is usually preventable\textsuperscript{2} and should be a ‘never event’ worldwide. All newborns should be protected from this rare yet catastrophic neurological injury through the provision of timely diagnostic and interventional healthcare. Healthcare services should aim to mandatorily report and systematically investigate cases of severe neonatal jaundice to minimise future recurrence risk. Furthermore, children exposed to severe neonatal hyperbilirubinaemia should, during childhood, undergo regular neurodevelopmental surveillance and receive early intervention where appropriate in order to detect and minimise the impact of adverse outcomes for them and their families. We suggest follow-up should include regular audiological assessment, General Movements Assessment and standardised developmental assessment to at least three years of age. Preventative health-system strategies including: universal transcutaneous bilirubin screening and perinatal healthcare worker and parental education offer the best existing opportunities to reduce the risk of kernicterus.

Abbreviations

TSB total serum bilirubin

ABE acute bilirubin encephalopathy

CP cerebral palsy

GMFCS gross motor function classification system

Declarations

Acknowledgements

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Conflict of Interest

The authors declare there are no competing financial interests in relation to the work described.

Contribution Statement

AM contributed to the study design, the acquisition and analysis of the data, drafting the initial manuscript and subsequent critical revision. JP contributed to the acquisition of the data and critically reviewed the manuscript. NB and NE contributed to the study design and critically reviewed the manuscript. All authors have approved the final manuscript prior to submission and are accountable for the integrity of the study.

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Tables

Table 1 Characteristics comparison of study subjects enrolled in follow-up compared to those without formal outcome data
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Follow-up study subjects</th>
<th>No formal follow-up subjects</th>
<th>$P$ value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks (mean, range)</td>
<td>38 (35-40)</td>
<td>38 (35-40)</td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>12 (46)</td>
<td>18 (60)</td>
<td></td>
</tr>
<tr>
<td>Peak bilirubin µmol/L (median,range)</td>
<td>484 (454-669)</td>
<td>492 (370-760)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity -clinician determined (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>13 (50)</td>
<td>16 (53)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>9 (35)</td>
<td>7 (23)</td>
<td></td>
</tr>
<tr>
<td>Indigenous</td>
<td>0</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (15)</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia aetiology (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>17 (65)</td>
<td>13 (43)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ABO incompatibility (DAT positive)</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ABO incompatibility (DAT negative)</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Rhesus isoimmunization</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other hematological</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(spherocytosis, oxidative hemolysis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hematological cause</td>
<td>6 (23)</td>
<td>17 (57)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Other (sepsis, cephalohematomata)</td>
<td>3 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vaginal</td>
<td>15 (58)</td>
<td>17 (57)</td>
<td></td>
</tr>
<tr>
<td>Vaginal breech</td>
<td>0</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Instrumental</td>
<td>7 (27)</td>
<td>6 (20)</td>
<td></td>
</tr>
<tr>
<td>Cesarean</td>
<td>3 (12)</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>1 (4)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Feeding Method in first week (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breastmilk only</td>
<td>17 (65)</td>
<td>20 (67)</td>
<td></td>
</tr>
<tr>
<td>Formula only</td>
<td>2 (8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>7 (27)</td>
<td>8 (27)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>3 (10)</td>
<td></td>
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<tr>
<td>Treatment (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment</td>
<td>Group 1</td>
<td>Group 2</td>
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<tr>
<td>-------------------------</td>
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<td></td>
</tr>
<tr>
<td>Phototherapy</td>
<td>23 (88)</td>
<td>29 (97)</td>
<td></td>
</tr>
<tr>
<td>Albumin therapy</td>
<td>2 (8)</td>
<td>9 (30)</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin infusion</td>
<td>1 (3)</td>
<td>3 (12)</td>
<td></td>
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<tr>
<td>Exchange transfusion</td>
<td>6 (23)</td>
<td>5 (17)</td>
<td></td>
</tr>
</tbody>
</table>

*a clinical characteristics compared using t test, values <0.05 stated, otherwise, non-significant

Table 2 Overview of neurodevelopmental outcomes categorised according to assessment measures
Neurological Examination

n= 26
mean age 31.2 months (range 12-41)
1 child with GMFCS 4 cerebral palsy, cochlear implant and visual impairment
1 child with GMFCS 1 cerebral palsy
1 child with global developmental delay & autism spectrum disorder
23 normal

Hearing Assessment

n=20
1 child with cochlear implant following bilateral refer on newborn screening
19 'bilateral pass' on newborn screening

Bayley Scales of Infant and Toddler Development III

n=25
mean age 31.2 months (range 12-41)

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>10.3 (1.5)</td>
</tr>
<tr>
<td>Receptive Communication</td>
<td>9.4 (1.8)</td>
</tr>
<tr>
<td>Expressive Communication</td>
<td>9.2 (2.4)</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>10.4 (2.6)</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>9.2 (2.3)</td>
</tr>
</tbody>
</table>

Ages & Stages Questionnaire 3

n=22
mean age 25.2 months (range 12-42)
4 cases with 1 area or more <2SD (refer)
10 cases with 1 area or more <1SD (monitor)
8 cases normal

Table 3 Summary of cases with diagnosis of CP, any BSID-III scaled score <7 (1SD) and / or an ASQ-3 domain in the ‘refer’ zone
<table>
<thead>
<tr>
<th>Case</th>
<th>Maximum TSB µmol/L</th>
<th>Primary Aetiology</th>
<th>Clinical Characteristics</th>
<th>Hyperbilirubinaemia treatment</th>
<th>Neurodevelopmental Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>630 days 2-3</td>
<td>haemolysis of unknown cause</td>
<td>female Caucasian 40 weeks vaginal delivery thrombocytopenia lethargy &amp; poor feeding opisthotonic</td>
<td>Phototherapy XT</td>
<td>CP GMFCS 4 Cochlear implant Visual impairment</td>
</tr>
<tr>
<td>2</td>
<td>525 day 10</td>
<td>Rhesus isoimmunisation</td>
<td>male Caucasian 35 weeks ventouse hydrops PPHN hypoglycaemia thrombocytopenia conjugated hyperbilirubinaemia</td>
<td>Phototherapy immunoglobulin no XT : too unstable</td>
<td>CP GMFCS 1 dysarthria BSID III 40m: • gross motor 4 • fine motor 8 • expressive communication 4 • receptive communication 10 • cognitive 9 ASQ-3 12m fine motor: refer</td>
</tr>
<tr>
<td>3</td>
<td>499 day 4</td>
<td>ABO incompatibility (DAT+)</td>
<td>male Pacific Islander 40 weeks Caesarean section lethargy &amp; poor feeding</td>
<td>Phototherapy</td>
<td>Normal neurological examination 34 months 34 months: global developmental delay &amp; autism spectrum disorder (family history) bilateral hearing screen pass</td>
</tr>
<tr>
<td>4</td>
<td>598 day 16</td>
<td>large cephalohaematomas</td>
<td>female Middle Eastern 38 weeks ventouse asymptomatic</td>
<td>Phototherapy XT</td>
<td>Normal neurological examination 37m bilateral hearing screen pass clinically normal vision and hearing 12m</td>
</tr>
<tr>
<td>Day</td>
<td>ID</td>
<td>Diagnosis</td>
<td>Gender</td>
<td>Race</td>
<td>Weeks</td>
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<tr>
<td>5</td>
<td>455</td>
<td>idiopathic</td>
<td>male</td>
<td>Caucasian</td>
<td>39</td>
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<td></td>
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<tr>
<td>6</td>
<td>460</td>
<td>G6PD deficiency</td>
<td>female</td>
<td>Asian</td>
<td>38</td>
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<tr>
<td>7</td>
<td>454</td>
<td>idiopathic</td>
<td>female</td>
<td>Asian</td>
<td>40</td>
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• receptive communication
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