



# The ability of early serial developmental assessment to predict outcome at 5 years following neonatal hypoxic-ischaemic encephalopathy



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## ABSTRACT

**Background:** Neurodevelopmental difficulties in children following hypoxic-ischaemic encephalopathy (HIE) may not emerge until school age.

**Aims:** To evaluate the value and stability of early serial developmental assessments in predicting long-term outcome.

**Study design:** Prospective study of infants with neonatal HIE and early continuous EEG at birth.

**Subjects:** Term infants with HIE were recruited at birth. Development was measured at 6, 12 and 24 months using the Revised Griffiths' Scales (GMDS-R).

**Outcome measures:** Intellectual abilities at age five were measured using the Wechsler Preschool & Primary Scale of Intelligence (WPPSI-III<sup>UK</sup>) and the 'numbers' subtest from the Children's Memory Scale. Overall five-year outcome was also reported.

**Results:** IQ outcome was available in forty-seven surviving children (28 male, 19 female: mean (SD) age 64.0(5.7) months. Mean processing speed ( $p = 0.01$ ) and short-term verbal memory ( $p = 0.005$ ) were below the norm. Global development (GDQ) at 6, 12 and 24 months correlated ( $p < 0.01$ ) with five-year global, verbal and performance IQ with improved correlation over time. Normal GDQ throughout early childhood predicted normal IQ at 5 years (24 month AUROC value = 0.941,  $p = 0.001$ ). An abnormal early GDQ score at any stage in the first 24 months had excellent negative predictive values, superior to those for neonatal Sarnat and EEG grading.

**Conclusions:** Normal early development predicts normal 5 year IQ with prediction increasing over time. Repeated measurement is warranted due to instability of findings across the first two years. Follow-up for children with abnormal early development is warranted given high sensitivity for school-age global abnormal outcome.

## 1. Introduction

Hypoxic-ischaemic encephalopathy (HIE) occurs following approximately 3 per 1000 term births. It remains one of the leading causes of neonatal death, with survivors at risk of significant neurological disability including cerebral palsy, epilepsy, intellectual disability, and sensory loss [1]. Longer term outcome studies have reported more

specific neurodevelopmental sequelae that may not emerge until after 24 months [2–4]. These include delayed educational attainment and specific deficits in language, sensorimotor and selected memory domains [5,6]. In particular, working memory, long-term episodic and specifically verbal learning and retention are lower in children with moderate and severe HIE [7,8].

The challenge lies in the early identification of children for whom

**Abbreviations:** HIE, Hypoxic ischemic encephalopathy; EEG, Electroencephalograph; SWC, Sleep wake cycle; IBI, Inter-burst interval; GDQ, Griffiths Global Developmental Quotient; GMFCS, Gross Motor Function Classification System; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; FSIQ, Full Scale Intelligence Quotient; VIQ, Verbal IQ; PIQ, Performance IQ; PSQ, Processing Speed Quotient; GLC, General Language Composite; CMS, Children's Memory Scale; CP, Cerebral palsy; ASD, Autism Spectrum Disorder; ADHD, Attention Deficit Hyperactivity Disorder; DCD, Developmental Co-ordination Disorder; Lang D/O, Language Disorder; CS, Caesarian section; BD, Base deficit; MD EI, Multi-disciplinary early intervention

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later-emerging deficits are more likely to occur. Research studies have outlined the importance of follow-up of affected children into their school years to capture the full impact of early injury [9].

The ability of early standardised developmental assessment to predict later cognitive outcome is clear at the extremes of developmental progress because a severe insult has a suppressor effect across multiple development domains [10]. However the prediction of more subtle deficits, most amenable to intervention, poses a greater challenge. Prediction studies observing clinical samples of infants tend to report low sensitivity and high specificity for later intellectual difficulties [11–13]. Development progresses rapidly in the first years of life and the range of “normal development” is wide. Little information is available regarding the temporal stability of repeated early developmental assessments [14]. Stability is likely to depend upon the patterns of development in the underlying domains of motor skills, language and cognition. The optimal time to assess these domains in early childhood remains unclear and the importance of serial assessment is acknowledged [15].

The use of the Bayley Scales [16], predominates in this field, and knowledge of predictive properties of other standardised development assessments such as the Griffiths scales is less well understood, especially for infants following neonatal HIE.

This study sought to record the temporal stability of serial developmental assessment in children following HIE at 6, 12 and 24 months and to determine the role of age at assessment for the prediction of (i) cognitive abilities and (ii) overall outcome at five years.

## 2. Materials and methods

### 2.1. Participants

Infants with hypoxic-ischaemic encephalopathy (HIE) were prospectively recruited between May 2003 and December 2005, from a maternity service with approximately 6000 deliveries per annum [17]. Children were recruited prior to the introduction of therapeutic hypothermia and were therefore not cooled. Ethical approval was granted from the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Ireland. Inclusion criteria were infants of  $\geq 37$  week gestations who met at least two of the following: (i) initial capillary or arterial pH  $< 7.1$ , (ii) Apgar score  $< 5$  at 5 min, (iii) initial arterial or capillary lactate  $> 7$  mmol/L, (iv) abnormal neurology or clinical seizures. Infants were excluded if they had co-existing congenital anomalies, or significant co-morbidity. Written informed consent was obtained from the parent(s) within 6 h of birth, or where relevant, with the onset of clinical seizures. Serial administration of neurological assessments, and continuous EEG monitoring was performed for 24–72 h duration. The EEGs were graded according to background activity, as follows: Grade 0 (normal) - continuous background pattern with normal physiologic features; Grade 1 (normal/mild abnormalities) - continuous background pattern with slightly abnormal activity (mild asymmetry, mild voltage depression, or poorly defined sleep wake cycle (SWC)); Grade 2 (moderate abnormalities) - discontinuous activity with inter-burst interval (IBI) of  $< 10$  s, no clear SWC, or clear asymmetry or asynchrony; Grade 3 (major abnormalities) - discontinuous activity with IBI of 10–60 s, severe attenuation of background patterns or no SWC; Grade 4 (inactive EEG findings) - background activity of  $< 10 \mu\text{V}$  or severe discontinuity with IBI of  $> 60$  s. A modified Sarnat encephalopathy grade was assigned at 24 h [18,19]. These methods have been described previously [20].

### 2.2. Outcome data

The Griffiths Mental Development Scales (0–2), 1996 revision [21], was used to obtain standardised developmental assessments. Children were seen at 6, 12 and 24 months by a Griffiths' certified trained paediatrician (DM) either at home or at the outpatients' clinic. A

neurological examination assessing peripheral tone, axial tone and deep tendon reflexes was completed.

The Griffiths is a standardised assessment of infant and child development and was chosen for its clinical utility, psychometric properties and ecological validity. The scales were scientifically constructed based on item analysis and developmental theory. Items are categorised into five subscales, ‘Locomotor’, ‘Hearing and language’, ‘Personal-social’, ‘Eye-hand co-ordination’ and ‘Performance’, with standardised subscale means ranging 100.2–101.1 (15.9–16.3) for the standardisation sample [21]. The overall Griffiths' developmental quotient (GDQ) mean is 100.5 (11.8). An ‘abnormal’ score in this study was considered a GDQ  $\leq 88$ .

At age five years, participants were contacted, and those that provided written consent for inclusion in the research study, were seen either at home or at a research facility, for intellectual assessment by a clinical psychologist (COC) blinded to the neonatal data and early Griffiths' assessments. Neurological assessment was undertaken by a research paediatrician who assessed muscle tone, power and deep tendon reflexes. A GMFCS (Gross Motor Function Classification System) score [22], was assigned to children with cerebral palsy. Medical and demographic information was included in a parent questionnaire. Intellectual ability was assessed using the Wechsler Preschool and Primary Scales of Intelligence – 3rd UK Edition (WPPSI-III<sup>UK</sup>) [23]. Scaled scores for subtests and Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance (non-verbal) IQ (PIQ), Processing Speed Quotient (PSQ), and General Language Composite (GLC) were calculated. All composite scores are standardised with a mean of 100(15). An ‘abnormal’ IQ was defined in this study as  $\leq 84$ . The ‘Numbers’ subtest of the Children's Memory Scale (CMS) [24], was also administered to include a measure of verbal working memory, and scaled scores calculated.

An ‘abnormal’ outcome at age five was defined as death, cerebral palsy (CP), significant hearing/vision loss, FSIQ  $\geq 1$ SD below the mean (i.e. IQ  $\leq 84$ ), a DSM-IV diagnosed neurodevelopmental disorder (autistic spectrum disorder (ASD), developmental co-ordination disorder (DCD), attention deficit hyperactivity disorder (ADHD), Language disorder (Lang D/O)) and/or requirement for multidisciplinary early intervention (MD EI) team. Referrals to relevant individual health professionals were also noted.

### 2.3. Statistical analysis

Statistical analysis was completed using IBM SPSS Statistics 20.0 for MS Windows (IBM Corporation, NY, USA) and VassarStats: Website for Computational Statistics (Lowry, R 1998–2012, Vassar College, NY, USA). Mann-Whitney (continuous) and Chi-square (categorical) correlations were used to explore normal/abnormal 5 year outcome data with birth and social data. Fisher's exact (and the Freeman Halton extension) statistics were used when the minimum expected cell frequency assumption was violated, i.e. cell numbers  $< 5$ . Spearman's rank correlation coefficients were analysed for all IQ quotients. One sample *t*-tests were used to compare observed scores to the WPPSI-III test norms. PPV, NPV, sensitivity, specificity, and AUROC curves with confidence intervals were calculated. All *p* values were two-tailed with statistical significance cut-off set at  $< 0.05$ .

## 3. Results

In total, 60 children were recruited to the study. The modified Sarnat grades assigned at 24 h were: 27 mild, 21 moderate, and 12 severe. Of these, by 24 months, 6 (all severe) had died, 1 (mild) was lost to follow-up and two had been excluded due to confounding medical conditions – one (mild) with a repaired congenital diaphragmatic hernia and the other (moderate) with a suspected genetic syndrome due to dysmorphic features and generalised hypotonia. The remaining 51 children were contacted at age five. Of these, 1 (moderate) was lost to follow-up and 3 (2 mild, 1 moderate) withdrew from the study. See

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