

# Confidence in the prediction of neurodevelopmental outcome by cranial ultrasound and MRI in preterm infants

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EDITOR'S CHOICE

## INTRODUCTION

Preterm birth is increasing and the rate of neurodevelopmental impairment in survivors remains high.<sup>1,2</sup> Clinicians routinely need to provide parents and carers with prognostic information for their vulnerable infants, and most do this with the aid of some form of neuroimaging. Cranial ultrasound is cheap, safe and can be performed at the cot side by the attending neonatologist or paediatric radiologist. MRI is less widely available, more expensive and requires transportation to an imaging unit, but provides anatomically richer data. However, it is not clear how comparable the images are, nor can we be sure about the predictions made by either imaging method.

In September's issue of the journal, the analysis by Horsch *et al*<sup>3</sup> of contemporaneously acquired cranial ultrasound and MR images at term corrected age in a cohort of infants born at <27 weeks gestation found close concordance between the two imaging methods, with only marginal, if any, additional information with MRI. However imaging findings were normal or showed mild MRI changes in >80% of infants and only 3/72 (4%) showed severe abnormality, reducing confidence in any comparison. In fact the prognostic power of each imaging modality was undefined as neurodevelopmental outcome was not reported.

To provide practicing clinicians with pragmatic estimates of the confidence

limits appropriate when interpreting cranial ultrasound and MRI, we searched the literature for studies that allowed reasonable quantitative estimates of prognostic value, ensuring that repeated publications of individuals were excluded by contacting researchers directly where necessary. From the surprisingly small number of suitable studies we selected and aligned information as objectively as possible with familiar imaging and neurodevelopmental outcome classifications, with outcomes, usually determined at about 2 years of age, categorised broadly as abnormal neuromotor development (estimated as the presence of cerebral palsy or a low Bayley Psychomotor Developmental Index of below 70) or cognitive impairment (estimated as a low Bayley Mental Developmental Index of below 70 or a Griffiths Developmental Quotient of below 85).

To combine multiple studies into single estimates, we used Meta-Disc4 software<sup>4</sup> to calculate pooled likelihood ratios with 95% CIs and then applied a Bayesian approach to calculate the pooled probability, together with 95% CIs, that particular imaging appearances would be associated with specific neurodevelopmental outcomes. Bayesian analysis allows a background probability (called the prior probability) to be modified by new information from a test to provide an updated post-test or posterior probability. We used the overall background risks described in the recent Epipage study<sup>5</sup> as the prior probability and calculated the post-test probability given the neuroimaging result.

We offer these results as positive predictive values (PPV; the proportion of subjects with a positive test result who have the outcome being tested for) or the pooled post-test probability (the probability that a patient with a given test result will have a particular neurological outcome)

together with 95% CIs for the estimates. These data should indicate to clinicians how much confidence can be placed in a prognosis assigned after neuroimaging.

## CRANIAL ULTRASOUND

Images were interpreted as normal if there was no haemorrhage in the germinal matrix, ventricles or brain tissue, no evidence of brain tissue destruction and no marked ventricular dilatation. Peri- and intraventricular haemorrhage (IVH) was classified according to the scale of 1–4 after Papile *et al*<sup>6</sup> or the broadly similar scale developed by Volpe<sup>7</sup> with cerebellar haemorrhage considered separately. We grouped together images that suggested focal or multifocal tissue destruction due to cystic periventricular leukomalacia (PVL). In the absence of precise measurements in many studies, we made pragmatic decisions on defining moderate and severe ventricular dilation. The probabilities of cerebral palsy associated with specific imaging findings are given in table 1, together with the 95% CIs for those estimates.

## Normal scan

A series of studies over a 30-year period have shown that a normal ultrasound scan provides considerable confidence that an infant will have normal neuromotor development. The predictive accuracy is high and confidence limits narrow: in one typical study the PPV was 99% (95% CI 98% to 99%)<sup>8</sup>; combining suitable studies, the pooled probability for normal outcome was 94% (95% CI 92% to 96%),<sup>8–12</sup> although heterogeneity between studies was high ( $I^2$  88%). Cognitive impairment is excluded slightly less effectively: in a typical large study, a normal ultrasound scan predicted normal cognitive function with a PPV of 77% (95% CI 74% to 80%),<sup>13</sup> and the pooled probability of a normal cognitive outcome with a normal ultrasound scan is 82% (95% CI 79% to 85%).<sup>11,13</sup>

## Grade 1 or 2 IVH

In one major study, images with only grade 1 or 2 IVH showed a low risk of abnormal neuromotor development with narrow confidence limits: PPV 6% (95% CI 4% to 9%).<sup>9</sup> Combining studies together produced broadly similar findings but with wider confidence limits, the pooled probability of abnormal neuromotor development being 9% (95% CI 4% to 22%).<sup>9,14</sup>

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**Table 1** Prediction of abnormal neuromotor function by cranial ultrasound

| Ultrasound test result    | Cerebral palsy       |                            |                                |                                  |
|---------------------------|----------------------|----------------------------|--------------------------------|----------------------------------|
|                           | Pre-test probability | Likelihood ratios (95% CI) | Post test probability (95% CI) | Heterogeneity among studies (I2) |
| Normal scan               | 9%                   | 0.5 (0.4 to 0.7)           | 5% (4% to 6%)                  | 90%                              |
| Grade 1 or 2 IVH          | 9%                   | 1 (0.4 to 3)               | 9% (4% to 22%)                 | 88%                              |
| Grade 3 IVH               | 9%                   | 4 (2 to 8)                 | 26% (13% to 45%)               | 82%                              |
| Grade 4 haemorrhage (any) | 9%                   | 11 (4 to 31)               | 53% (29% to 76%)               | 84%                              |
| Cystic PVL                | 9%                   | 29 (7 to 116)              | 74% (42% to 92%)               | 90%                              |
| Ventricular dilatation    | 9%                   | 3 (2 to 4)                 | 22% (17% to 28%)               | 0%                               |
| Hydrocephalus             | 9%                   | 4 (1 to 13)                | 27% (10% to 56%)               | 97%                              |

Normal scan refers to absence of haemorrhage within the brain parenchyma or ventricles, cysts or ventricular dilation. The grade of IVH (intraventricular haemorrhage) is given according to the Papile classification. PVL indicates periventricular leukomalacia. Ventricular dilation indicates moderate to severe ventricular dilation not meeting the criterion for hydrocephalus. Hydrocephalus indicates massive ventricular dilation >4 mm above the 97th centile. Pre-test probability refers to the prevalence of cerebral palsy based on the Epipage study.<sup>4</sup> The likelihood ratio is the probability that a patient with cerebral palsy has a positive test (abnormal ultrasound result). Post-test probability is the probability that a patient with a specific abnormality on cranial ultrasound will have abnormal neuromotor function. Heterogeneity is a measure of similarity between studies and the validity of statistical pooling.

### Grade 3 IVH

In one typical study, the presence of grade 3 IVH was associated with a modest increase in the risk of abnormal motor development but wide confidence limits, with PPV 24% (95% CI 12% to 42%).<sup>8</sup> However, combining studies produced a pooled probability of abnormal motor development being 26% (95% CI 13% to 45%).<sup>8 11</sup>

### Grade 4 IVH

In a typical large study, these lesions (also called parenchymal haemorrhagic infarction or cerebral venous infarction) predicted abnormal motor development with an appreciably increased risk PPV of 47% (95% CI 31% to 64%).<sup>8</sup> The pooled probability for abnormal motor development estimated by combining suitable studies was 53%, but again with wide confidence limits (95% CI 29% to 76%), probably in part due to the variability in both site and size of lesions.<sup>8 10 11</sup>

### Cystic PVL

In a typical large study, images showing cystic PVL were predictive of cerebral palsy with a PPV of 77% (95% CI 59% to 89%), although the rarity of the finding was reflected by wide confidence limits.<sup>3</sup> The combination of studies suggested that the pooled probability for abnormal neuromotor outcome with cystic PVL is 74%, but again there is considerable uncertainty in individual cases (95% CI 42% to 92%).<sup>8 9</sup>

### Ventricular dilatation

Definitions of moderate and severe ventricular dilatation differ widely in the literature. We defined ventricular dilatation pragmatically, and ventricular dilatation

at or near term was modestly predictive of major disability. In one typical study, the PPV was 27% (95% CI 15% to 43%),<sup>15</sup> while the pooled probability for abnormal motor development was 22% (95% CI 17% to 28%).<sup>13 15</sup>

### Post haemorrhagic hydrocephalus

The outcome for children with more precisely defined post haemorrhagic hydrocephalus is also variable. In the selected group of patients in the recent Drift study,<sup>16</sup> the children receiving standard treatment could be predicted to have abnormal neuromotor function with PPV of 69% (95% CI 50% to 83%). Combining studies together produced a lower estimate but emphasised this uncertainty: the pooled probability of abnormal neuromotor outcome was 27% (95% CI 10% to 56%).<sup>10 11 16–18</sup>

### Cerebellar haemorrhage

Cerebellar haemorrhages are not commonly reported. They are often detected in association with supratentorial lesions although they can rarely occur in isolation. In the previous issue of the journal, Horsch *et al* found that ultrasound failed to detect cerebellar lesions.<sup>3</sup> However, O'Shea *et al* found that the presence of cerebellar haemorrhage on ultrasound predicted abnormal neuromotor outcome, but with wide CIs: PPV 71% (95% CI 42% to 90%).<sup>13</sup>

### MAGNETIC RESONANCE IMAGING

Relatively few studies have attempted to determine the value of MRI for predicting abnormal motor development or cognitive impairment<sup>19–23</sup> and, like the ultrasound studies, they use different imaging and outcome criteria. We have again pragmatically selected and aligned

results, focusing on studies using widely available MR techniques.

### White matter abnormalities

Woodward *et al* evaluated the presence of white matter injury using a combination of imaging appearances to predict long-term neurodevelopmental outcome.<sup>21</sup> Using a white matter grading score ranging from normal to moderate-severe, the PPV of moderate-severe white matter abnormalities for abnormal motor development was 31% (95% CI 17% to 49%) and for cognitive impairment was 34% (95% CI 20% to 52%). Combining studies with reasonable overlap between the image categorisations suggested that moderate-severe white matter abnormalities predicted abnormal neuromotor development with a pooled probability of 35% (95% CI 19% to 55%),<sup>20 21</sup> and cognitive impairments with a pooled probability of 52% (95% CI 36% to 67%).<sup>21 23</sup>

### Ventricular enlargement

In one study, ventricular enlargement with a ventricular diameter >8 mm predicted long-term neurodevelopmental impairment with a PPV of 86% (95% CI 42% to 99%).<sup>23</sup> Another study found that a combination of ventriculomegaly and white matter abnormality predicted abnormal motor development with a PPV of 55% (95% CI 23% to 85%).<sup>22</sup> Unfortunately, the diagnostic categories used prevented combination of these data, and the wide confidence limits suggest caution in the clinical application of these data.

### Abnormalities of the posterior limb of the internal capsule

When a supratentorial lesion is visualised, evaluation of the posterior limb

of the internal capsule (PLIC) might be expected to improve diagnosis of motor deficits because of its importance as a conduit of motor signalling. One group has suggested that in the presence of PVL, an abnormal appearance of the PLIC predicts abnormal motor development with a PPV of 90% (95% CI 54% to 99%), and with IVH a PPV of 78% (95% CI 40% to 96%), although the small number of patients studied means that the confidence limits are very wide.<sup>19 20</sup>

## CONCLUSION

Knowledge of the prognostic value of cranial ultrasound and MRI rests on a relatively small set of reports; often the meta-analysis could only be performed using two studies, and even then measures of heterogeneity were high. The values provided in this review are pragmatic rather than definitive. In particular, we did not feel that the data were sufficient to calculate separate estimates for different gestational ages, despite the large differences in prior probability of later problems over gestation. Nevertheless, for those who might wish to use age-specific priors (available from the Epipage study<sup>5</sup>) we provide likelihood ratios in table 1.

However, these indicative results have clinical relevance. While a normal ultrasound scan confidently predicts a reduced risk of later motor problems, the prognostic values of many specific abnormalities detected by both ultrasound and MRI have wide confidence limits. In the recent paper by Horsch *et al*, infants with a normal cranial ultrasound scan had normal or mild white matter changes only on MRI.<sup>3</sup> Together with the results of the study by Horsch *et al*, our review suggests that the risk of abnormal motor outcome is low and can be determined with some confidence for the majority of preterm infants, but is less certain in the 10–20% of infants with moderate abnormalities, irrespective of the imaging modality

used. While some of this uncertainty is due to the small number of patients available for some analyses, the inherent imprecision of imaging and later childhood influences that affect neurodevelopment must also be contributing factors. Wise clinicians have always known that individual tests rarely provide certainty, and they continue to use neuroimaging with circumspection.

**Competing interests** None.

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