

## The relationship between ophthalmic deficits and functional ability in low birth weight children

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### Abstract

**Aim:** To review the current literature on long-term ophthalmic deficits and behavioural and/or cognitive outcomes occurring in low birth weight (LBW) children and to determine whether there is any link between the ophthalmic deficits and functional outcome.

**Methods:** A literature search was performed focusing mainly on publications from the past 10 years.

**Results:** LBW children are at an increased risk of a large number of ophthalmic deficits, including reduced visual functions (acuity, visual field, colour vision, stereo-acuity and contrast sensitivity), increased prevalence of strabismus and all types of refractive error. These deficits are not restricted to the smallest children; they can occur with increased frequency in all LBW children. As a group LBW children have increased risk of cognitive and behavioural deficits, which can affect them throughout their education. There is evidence of an association between ophthalmic outcome and many aspects of functional ability (e.g. IQ, reading ability). Further research is required to discover whether there is a common aetiology.

**Conclusion:** The evidence discussed supports the need for long-term ophthalmic monitoring, and treatment where necessary, due to the potential impact of LBW on education and development. Currently there is no standardised approach for this. Further discussion is required to optimise the long-term care of all LBW children.

**Key words:** Contrast sensitivity, Colour vision, Eye movements, Low birth weight (LBW), Preterm children, Refractive error, Stereo-acuity, Strabismus, Visual acuity, Visual field

### Introduction

The increasing survival of babies born prematurely has

resulted in an increase in children with long-term disabilities.<sup>1</sup> Infants classified as extremely low birth weight (ELBW = <1001 g) frequently have clear pathology that can be directly linked to impairment. The research focus, however, has turned to the relatively larger low birth weight (LBW) (<2500 g but ≥1501 g) babies who are frequently discharged from neonatal care with no known pathology, but who later may exhibit a wide range of more subtle disabilities. Over the past five decades the survival rates have increased for smaller babies, with conditions such as retinopathy of prematurity (ROP) now affecting a different, lower birth weight population.<sup>2</sup> Therefore, to reflect the deficits of current LBW children this review, where possible, will be based on more recent publications.

Preterm infants are at an increased risk of many types of problems encompassing many areas of function including developmental abnormalities of physical, cognitive and behavioural measures. Included in the large list of potential problems are a number of ophthalmic deficits, such as reduced acuity and an increase in the prevalence of strabismus and refractive error. In many cases these deficits do not occur in isolation. How the ophthalmic deficits affect functional ability and interact with other types of deficit (e.g. cognitive deficits) is not fully understood. The aim of this review is to evaluate the literature that has reported a relationship between the ophthalmic deficits and the functional outcome,<sup>3</sup> while accepting that it may not be possible to establish a causal relationship between the two.

### Methods

A search of scientific literature databases, including Pubmed and Web of Knowledge, was performed using the key words preterm children, low birth weight (LBW), visual acuity, contrast sensitivity, colour vision, visual field, strabismus, stereo-acuity, eye movements, refractive error; and the terms educational, behavioural and cognitive outcomes. After identification of relevant articles the references from those articles were reviewed and also a forward citation search of articles more than 5 years old was performed using Web of Knowledge. The search was limited, predominantly, to the last 10 years.

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## Visual function

### Visual acuity (VA)

Unocular, binocular, near and distance visual acuity are reduced in the LBW population compared with children born at term.<sup>4-6</sup> This deficit persists even when cases with amblyopia are removed from the analysis.<sup>7-9</sup> Although the mean difference in binocular VA between the LBW cohort and controls is small (0.04 logMAR in one study<sup>7</sup>) and the majority of LBW children had acuity of 6/6 or better (76%), 20% of LBW children had VA between 0 and 0.3 logMAR (6/6-6/12).<sup>10</sup>

There are many factors that affect the development of acuity in the preterm infant, encompassing all parts of the visual pathway. The most common cause of VA deficits in LBW children is neurological impairment.<sup>11-15</sup> The most common site of brain injury related to hypoperfusion in premature infants is the periventricular white matter<sup>14</sup> and it has been shown that visual impairment is more common in cases with ischaemic lesions such as periventricular leucomalacia (PVL) and infarcts, than with haemorrhage.<sup>16</sup> In contrast to the majority of studies, Cooke *et al.*<sup>9</sup> reported no association between periventricular haemorrhage (PVH) and PVL and adverse visual outcomes. However, their sample contained only 3 children (1.1%) with cystic PVL, and they identified the defects using cranial ultrasound, which may not be sufficiently sensitive to detect all abnormalities.

Another common cause of poor VA in preterm infants is ROP. Severe ROP, classified as stage 3 onwards, has a definite impact on VA, with the increasing severity of ROP being inversely proportional to the VA.<sup>17,18</sup> However, in mild ROP (stages 1 and 2), despite the presence of retinal changes which involve the fovea,<sup>19</sup> there has been no deficit of VA found.<sup>7,9</sup>

In addition to the damage caused by preterm birth, changes in the environment also have an impact on development; one example is change in nutrition. Docosahexaenoic acid (DHA, a long chain polyunsaturated fatty acid) is said to be an important component in the development of the eye structure, with lipids making up 60% of the structural material in the photoreceptor outer segments and visual cortex.<sup>20</sup> DHA can be found in cholesterol and phospholipids, is present in breast milk and is now available in infant food.<sup>21</sup> Without a dietary source of DHA, preterm infants showed both poor retinal function and acuity when compared with both breast-fed preterm and full-term infants.<sup>22</sup> However, no long-term studies have been carried out to determine whether this is a permanent effect.<sup>20</sup>

The functional implications of poor acuity are obvious; the defined level of acuity required for driving is a clear example of how a deficit can affect function. It is not clear whether acuity better than driving standard but below the age-matched average has any impact on function, for example in the 20% of cases with binocular VA between 0.0 and 0.3 logMAR.<sup>7</sup>

Two studies have reported an association between reduced visual acuity, reduced IQ, reading ability and increased learning difficulties in preterm children when compared with normal birth weight (NBW) children.<sup>3,13</sup> However a statistical association does not differentiate

whether the VA deficit and reduced cognitive ability have a common aetiology or whether the cognitive deficit is due, in part or entirely, to the VA deficit.

Could the association between moderate/severe ROP (stage  $\geq 3$ ) and VA be used as a prognostic indicator of later visual function? Whilst stage 3 ROP was associated with reduced acuity and significantly poorer scores on motor, total and verbal IQ, when the gestational age (GA) was standardised the differences only became borderline.<sup>9</sup>

### Contrast sensitivity (CS)

LBW children also show reduced contrast sensitivity across a range of spatial frequencies (1.5-18 cycles/deg),<sup>23</sup> with the lowest CS found in cryotherapy treated eyes, but no reduction found in eyes with mild ROP.<sup>7,9</sup> Although no association was found with known neurological deficits,<sup>7</sup> charts such as the Pelli-Robson use large letters (low spatial frequency) specifically to allow measurement of cortical function in the presence of retinal damage. Reported reductions in CS scores are therefore consistent with subtle, undetected neurological deficits.

Assessing visual function across a range of contrasts provides valuable information on the ability to detect a variety of objects in daily life,<sup>24</sup> particularly in the presence of normal VA. For example, the level of CS has been shown to be a good predictor of reading rate.<sup>25</sup> A direct relationship between CS and motor skills has also been found in a LBW cohort, where reduced CS proved to be a better predictor of reduced motor skills than VA.<sup>8</sup>

### Colour vision

LBW children have a higher tendency to a blue-yellow colour defect compared with children born at term.<sup>26</sup> While colour deficits might cause difficulties in school, no evaluation of the impact of colour deficits was found in the literature.

### Visual field

There is an increase in visual field defects in LBW children which is attributable to neurological damage<sup>27</sup> and previous cryo/laser treatment.<sup>28</sup> Lindqvist *et al.*<sup>29</sup> however, reported no difference in the visual fields between LBW children and controls when tested at the age of 14 years. This contradiction with the findings from the CRYO-ROP group<sup>28</sup> may be accounted for by the different methods used to measure the visual fields and the fact that none of the subjects in Lindqvist *et al.*'s study were treated with cryotherapy.

It has been reported that the size of visual field required for efficient navigation varies depending on the average image contrast<sup>30</sup> and that when the field of view decreases, mobility performance is also reduced. Although this evidence shows that a reduction in the visual field has an impact on functional ability, the effects of a small reduction in a visual field (e.g. a 5-7% reduction in ROP cryo-treated eyes<sup>28</sup>) are not fully understood.

In one study, in which a very small cohort of subjects (7 children) with normal VA was tested in a general

**Table 1.** A summary of the rates of strabismus in low birth weight children

| Reference                 | Sample size | Age at assessment (months) | Type of strabismus      | Prevalence | Hospital/population based |
|---------------------------|-------------|----------------------------|-------------------------|------------|---------------------------|
| Pott <sup>59</sup>        | 265         | 6                          | Infantile esotropia     | 1.9%       | Hospital                  |
| Holmstrom <sup>4</sup>    | 239         | 19.1                       | Esotropia and exotropia | 13.5%      | Population                |
| Pennefather <sup>60</sup> | 558         | 24                         | Esotropia and exotropia | 12.5%      | Population                |
| Darlow <sup>5</sup>       | 313         | 84                         | Not stated              | 22%        | Population                |
| O'Connor <sup>58</sup>    | 293         | 120                        | All                     | 19.3%      | Population                |
|                           |             |                            | Esotropia               | 8.2%       |                           |
|                           |             |                            | Exotropia               | 9.8%       |                           |
| Holmstrom <sup>61</sup>   | 248         | 120                        | Not stated              | 16.2%      | Population                |
| VanderVeen <sup>62</sup>  | 366         | 6                          | Esotropia               | 20.3%      | Hospital                  |
|                           | 372         | 9                          | Exotropia               | 30%        |                           |
| Powls <sup>8</sup>        | 137         | 132-156                    | All                     | 9.5%       | Hospital                  |

paediatric clinic, 3 children exhibited defects in the lower visual field due to periventricular white matter injury.<sup>31</sup> This affected function, particularly when walking over uneven ground or going down stairs.

### Refractive errors

It has been reported that LBW children have an increased prevalence of all types of refractive error.<sup>32-36</sup> The failure to emmetropise has been linked to a number of factors, such as cryotherapy,<sup>36</sup> but it is the resultant refractive error and impact on function that will be focussed on here.

Hypermetropia is the most common refractive error in childhood but there is considerable variation in opinion as to what degree of refractive error requires correction.<sup>37-40</sup> High hypermetropia has been associated with a range of deficits such as poorer performance on visual and literacy tasks, reduced reading and writing ability and lower IQ.<sup>41,42</sup> These deficits were irrespective of any amblyopia or strabismus.<sup>43</sup> There is an increase in cognitive functional, behavioural and memory deficits in the LBW population.<sup>44-50</sup> While it is possible that an increase in hypermetropia is a contributing factor in poor cognitive ability, this has not been proven.

Myopia is a common finding in ex-preterm children, particularly those treated for sight-threatening stage 3 ROP,<sup>51</sup> with a reported prevalence that ranges from 6.3% to 22%.<sup>8,17,34,52,53</sup> The authors of one study found no association between myopia and poor spatial ability.<sup>3</sup> They attributed this to the fact that testing was carried out on subjects with their optical correction on and therefore acuity was normal. This is contrary to the association found with hypermetropic refractive errors, but could be related to the fact that not all cases of hypermetropia are fully corrected.

In the general population myopia has been shown to be linked with higher IQ scores when compared with children with hyperopia;<sup>54</sup> however, in this report the levels of myopia were not stated in the results and it may be speculated that they did not reach the high levels of myopia that can be associated with preterm birth.<sup>55,56</sup> Therefore it is currently not possible to apply this finding to LBW children.

The prevalence of anisometropia in LBW children is reported to be approximately 9%; for astigmatism the reported prevalence ranges from 13.7% to 20.7%.<sup>34,57</sup> No links between anisometropia, astigmatism and functional ability were found.

### Strabismus

One of the most common ophthalmic deficits in LBW children is strabismus, although the prevalence is rather variable, as highlighted in Table 1. Although esotropia is the most common deviation observed in NBW children, LBW children can present with a range of deviations. One report found equal numbers of esotropia and exotropia in a group of LBW children.<sup>58</sup>

While other deficits, such as reduced VA, are associated with alteration in cognitive measures and reduced motor skills, the deficits associated with strabismus in the general population include an impact on psychological functioning. The importance of having straight eyes has been associated with numerous factors such as better self-image, self-esteem and quality of life and a perception of less discrimination when compared with people with strabismus.<sup>63,64</sup> Given the large increase in strabismus in this population it could be speculated that this would affect psychosocial outcome. However, studies of the psychological functioning of ex-preterm children<sup>65</sup> and adults<sup>66</sup> demonstrated no significant difference from those born at term in all areas assessed, but no ophthalmic data were presented for these cohorts.

### Stereo-acuity

Stereo-acuity is reduced in LBW children compared with children born at full term.<sup>13</sup> However, LBW children do have a higher incidence of strabismus and lower visual acuity, therefore this is not surprising. It is supported by the finding of O'Connor *et al.*<sup>58</sup> that after removal of the cases with strabismus from the analysis there was no longer any difference between the cohorts. Cooke *et al.*<sup>9</sup> also found a significant reduction in stereo-acuity in the LBW group; they found a small, but significant, relationship between better stereo-acuity and a slight increase in head size.

Strabismus may result in either reduced or absent stereo-acuity and Morris *et al.*<sup>67</sup> concluded from the current evidence that while stereopsis is beneficial, in some scenarios, it is not essential. While this may be the case for NBW children who have no other deficits, in LBW children who have multiple deficits there may be a cumulative effect.

Weak or absent stereo-acuity was shown to be associated with poorer performance on perceptual-motor tasks. However, the authors highlighted the fact that

there were a large number of children with abnormal stereo-acuity but normal motor skills.<sup>68</sup> This emphasises the multifactorial nature of the deficits occurring in the LBW population.

### Control of eye movement

Eye movement control (as opposed to eye alignment) has received little attention in LBW children. Children with severe and moderate PVL have been noted to have 'significant abnormalities' with fixation and smooth pursuit.<sup>69</sup> Additionally, inappropriate smooth pursuit, difficulty following a target and inability to elicit voluntary saccades to visually presented targets have been reported.<sup>70</sup> However, many studies either did not use quantitative measurement techniques or did not report quantitative data. Studies that have employed quantitative methods have found LBW children to have reduced smooth pursuit gain,<sup>71</sup> relatively normal saccades, but increased antisaccade directional error rates.<sup>72,73</sup> Pursuit deficits may arise from the white matter lesions in PVL causing injury to the arcuate fibre bundles connecting the striate cortex with the middle temporal visual area.<sup>74</sup> Increased antisaccade error rates indicate a problem with the voluntary control of saccades with an inability to inhibit a reflexive saccade. This is suggestive of a diffuse lesion in the frontal cortex which may be associated with behavioural problems such as ADHD (attention deficit hyperactivity disorder) and executive dysfunction,<sup>75</sup> both of which have increased incidence in LBW children.<sup>49,76</sup>

There has also been some conflicting evidence concerning the control of eye movements in LBW children and the association with reading difficulties. Ek *et al.*<sup>77</sup> investigated reading ability in 4 LBW children who had PVL and associated visual impairment. All children had nystagmus, strabismus and clinical evidence of impaired motility. In addition all children had reading difficulties, though precise quantitative standardised reading scores were not quoted. Eye movements recorded by an infrared reflection technique during fixation and reading indicated abnormalities in normal fixations, saccades, regressions and return sweeps. Also during reading the children made head movements in a saccadic fashion in an effort to assist their reading ability. Downie *et al.*<sup>78</sup> made comparisons between the reading difficulties occurring in dyslexia and those occurring in preterm children. Given the magnocellular theory of dyslexia<sup>79</sup> (see also Judge *et al.*<sup>80</sup>) and the fact that LBW children with periventricular brain injury have visual dysfunction that may be due to damage of the magnocellular pathway,<sup>81,82</sup> the authors investigated a group of VLBW (very low birth weight,  $\leq 1500$  g) children for the presence of magnocellular deficits (in the area of motion processing) and any association with reading or spelling problems. The VLBW group (both with and without periventricular brain injury identified on ultrasound) scored very poorly on the motion processing task and their performance was significantly different from that of full-term controls. However, there was no relationship found between motion processing ability and reading ability in the VLBW children. This is an area that requires further research.

### Other measures of ophthalmic outcome

Given the known links between strabismus, development of refractive errors and vision, it might be expected that accommodation would be abnormal in the LBW population. Only one study was found which included an assessment of accommodation, and no deficit was found.<sup>83</sup> However, this was in a cohort of neurologically normal preterm children.

Standard clinical tests may not be sufficient to fully evaluate the visual deficits occurring in preterm children that affect their functional ability. Dutton<sup>84</sup> has proposed the inclusion of a series of questions in the ophthalmic assessment covering aspects of visuospatial function and perception, such as navigating across different floor surfaces, as he has demonstrated deficits even when stereo-acuity is normal. An additional example is difficulty in seeing objects in the distance, or distinguishing target objects from distractors despite having good acuity.

### Academic ability

Many studies have shown that, even without cerebral palsy, preterm children have a higher prevalence of impairment in visuospatial, perceptuomotor, attention-executive and gross motor function at early school age.<sup>44-50</sup> The tasks used in these studies require a certain level of visual function and these tend not to be formally measured or reported. This is potentially problematic given that it is possible a deficit in visual function contributes to higher cognitive or visuospatial impairments. In some cases deficits, such as poor reading ability, reduce with increasing age, indicating a delay in the development of LBW children, while other deficits may appear to be permanent.<sup>1,85</sup>

Another measure of cognitive performance found to be reduced in preterm children is their recall memory.<sup>86,87</sup> When evaluating simple spatial localisation tasks, such as targets on a computer monitor, we found that the only significant difference between preterm and full-term children was related not to the visual aspect of the task but the memory component.<sup>88</sup>

### School attainment

Preterm children have slightly reduced IQ scores, require longer to complete tasks,<sup>3</sup> have increased cognitive problems and increased ophthalmic defects, but it is not known whether these subtle deficits are significant enough to affect attainment. When evaluating the examination performance of VLBW children, Pharoah *et al.*<sup>89</sup> showed that while VLBW children generally sat the same number of subjects at GCSE level as full-term children, they gained lower grades compared with the controls, with a 6% reduction in the number of children achieving 5 or more subjects at grade C. In addition, performance varied by subject with the VLBW children, who demonstrated poorer performance in maths, statistics, general science, English language and literature. This impact on educational attainment also extends beyond age 16, with VLBW children less likely to continue with education after secondary school.<sup>90</sup>

Although there are a multitude of factors that



influence educational attainment, a link has been demonstrated with an adverse ophthalmic outcome irrespective of prematurity within a cohort of children whose birth weight was <1701 g.<sup>91</sup> One important finding from this study was the significant association between adverse ophthalmic outcomes and receiving additional help at school. This may indicate that if a learning disorder is suspected or found, an ophthalmic assessment should be undertaken.

### Impact on long-term ophthalmic care

While it has been established that preterm children are at increased risk of ophthalmic problems, in the UK there is no standardised provision of ophthalmic care after complete vascularisation of the retina has occurred.<sup>92</sup> The recommendations of the Hall report<sup>93</sup> are that all children should be screened between the ages of 4 and 5 years by an orthoptist, but it also states that in preterm children 'the increased risk of other eye problems including myopia, squint and cortical visual impairment should be remembered'. Therefore the question remains: Do low birth weight children require additional ophthalmic care?

The current recommended screening age was identified as the optimal age for effectively identifying and treating deficits. Testing at an earlier age would reduce the efficacy of the tests in detecting the target conditions. It has been postulated that amblyopia therapy has a poorer success rate in preterm infants<sup>53</sup> because of subtle retinal distortions from ROP, which are undetectable on routine ophthalmic examination. In addition, the developmental problems affecting LBW children can make compliance with conventional treatment methods, such as glasses and patching, difficult. Therefore should children be screened earlier? In a Scandinavian report they found that screening at the age of 2 years was not necessary, as during the child's first year of life they were checked regularly at local level and were referred for specialist treatment if necessary.<sup>94</sup> In the UK, Health Visitors refer babies to the hospital if there are any parental concerns but no standardised testing is undertaken.

The discussion regarding follow-up care of the LBW child focuses not only on the timing of the assessment, but the type of assessment. For example, given the links between hypermetropia and reading ability, should a cycloplegic refraction be incorporated into the screening protocol?

At present no further eye screening is recommended after the age of 5 years; however, based on the evidence of increased prevalence of myopia and the ability to carry out more sensitive testing (e.g. visual field analysis) at a later age, further assessment of the LBW population could be potentially useful.

### Conclusion

The increased ophthalmic deficits found in the low birth weight population have been shown to be associated with many types of functional deficits which have a long-term impact on many areas, but particularly education. Although it is difficult to prove a causal link, given the many confounding factors, the evidence does

support the need for long-term ophthalmic care of these children. While optimising the child's visual outcome may not prevent the learning difficulties, it is important to maximise their potential. Currently there are no standardised guidelines on the long-term ophthalmic care of LBW children, but given the increasing survival rates the number of children requiring ophthalmic care is on the increase. It is clear that this is an issue that needs to be addressed.

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