Doc Ophthalmol (2013) 127:69–78
DOI 10.1007/s10633-013-9382-1

ORIGINAL RESEARCH ARTICLE

The spectrum of cerebral visual impairment as a sequel to premature birth: an overview

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Received: 11 January 2013 / Accepted: 1 April 2013 / Published online: 10 May 2013

Abstract
Purpose In children born prematurely, impairment of vision due to damage to the brain is more common than due to retinopathy of prematurity. Yet, the diagnosis of cerebral visual impairment may be missed. The subject of cerebral visual impairment in children is reviewed in order to explain and draw attention to the types of visual deficits and behaviours that may result as a sequel to premature birth.
Methods A wide range of sources of data has been employed to assemble this overview. The principal reference source is PubMed.
Results The material presented highlights the origin and range of visual deficits that result from damage to the brain, related to premature birth. Deficits of primary visual functions, perceptual dysfunction, simultanagnostic visual disorders and impaired visual guidance of movement (optic ataxia), as well as disorders of visual attention and memory, can occur in a variety of combinations and degrees. The resulting behavioural outcomes are described.
Conclusion Identification and characterisation of impaired vision, due to prematurity associated damage to the brain, are essential. This is required so as to ensure that affected children are not inappropriately disadvantaged on account of the diagnosis being missed or inadequately acted upon, but instead, they are managed optimally, both at home and at school, so that their development is enhanced to the greatest advantage.

Keywords Prematurity · Cerebral visual impairment · Periventricular white matter · Neuroplasticity · Habilitation

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Introduction

Cerebral visual impairment (CVI) can be defined as deficient visual function as a sequel to damage or malfunction of the retrogeniculate visual pathways (optic radiations, occipital cortex, and visual association areas) and may include deficits in central oculomotor control [1–5]. CVI is a prominent sequel to premature birth, particularly when prematurity is extreme [6–8]. Although frequently associated with cerebral palsy and intellectual disability, it can also occur in isolation [9]. Considerable focus has been given to the detection and treatment of retinopathy of prematurity, but less attention tends to be given to CVI, which can, as a consequence, be overlooked.

Amongst infants born in the UK before 27 weeks completed gestation, one-quarter suffer severe to moderate neurodisability manifesting as intellectual dysfunction and/or cerebral palsy [10]. A large proportion of such children also manifest CVI [11]. Long-term

follow-up of children from the CRYO-ROP study, with threshold retinopathy of prematurity, shows that low vision, cerebral palsy, developmental disability, autism and epilepsy presage educational disadvantage [12], but in this cohort, specific evidence of CVI was not reported. However, the motor components of cerebral palsy and CVI are now recognised to comprise integral elements of the same condition [13, 14].

Literature concerning CVI tends to focus on profound visual impairment, but CVI ranges in severity from blindness to relatively minor impairments of vision and perception [5]. Perceptual visual dysfunction [4] and disorders of visual attention [15], often with only slightly reduced or normal visual acuities, are increasingly being recognised, as forms of CVI as a sequel to prematurity [9] manifesting primarily, and most commonly as patterns consistent with dorsal stream dysfunction [16]. Yet, for those children and families affected, perceptual and visual attentional dysfunction are of profound importance [17] as it has been our clinical experience that recognition, understanding and characterisation of the condition can markedly enhance habilitation and outcome. This observation requires validation. This article outlines the condition of CVI, its features, diagnosis and management.

Origin and timing of brain damage affecting the vision

White matter damage of immaturity arises at 24–34 weeks gestation and comprises four specific lesions of myelinated white matter tracts. These comprise: white matrix/intraventricular haemorrhage, periventricular haemorrhagic infarction, periventricular leucomalacia and diffuse white matter injury, which is the commonest cause of cerebral visual impairment as a sequel to premature birth [17–19]. Lesions of peritrigonal white matter are particularly characteristic. This overall pattern of encephalopathy of prematurity encompasses a complex of primary destructive pathology, with subsequent maturational and trophic disturbances [20].

Pre-term, hypoxic ischaemic injury damages the brain, and disturbs vision, in a variety of ways [21]. Damage during the first trimester causes liquefaction necrosis. Tissue resorption but without gliosis leads to brain malformation. The foetal brain is, however, plastic and adaptable and can recover from injuries to the visual pathways to variable degree, and the visual outcome may not be predictable from the findings on imaging.

By the late second, to the third trimester, the subcortex adjacent to the lateral ventricles tends to be affected, leading to white matter injury, with the potential to afflict any aspect of visual function [22].

Pre-term infants nearing term as well as term infants are more likely to develop focal brain ischaemic damage in the area of the parasagittal watershed zones. This causes lesions in the parasagittal and parieto-occipital cortices. The latter area is a triple watershed zone and is thus predisposed to injury that causes a range of degrees of lower visual field impairment commonly accompanied by the behavioural features of dorsal stream dysfunction [23]. Greater degrees of damage culminate in sub-cortical and cortical encephalomalacia [24] often associated with spastic quadraplegia, microcephaly and seizures. Maturation of the microstructure of the visual pathways during the late preterm period is required for normal visual function, and this can be disrupted during the third trimester, as evidenced by diffusion tensor imaging studies in infants born prematurely [25]. Involvement of the posterior corpus callosum has been shown to be associated with reduced visual acuity [26]. Whether this is a consequence or is an epiphenomenon remains to be elucidated. Additional thalamic atrophy is associated with persistent more severe visual impairment [27], probably because the thalamus underpins the capacity to accord visual attention [28].

Intraventricular haemorrhage is associated with the development of optic atrophy, with a reported incidence, when severe of over 30 % for grades 3 or 4 [29]. Hydrocephalus as a sequel to intra-ventricular haemorrhage can damage periventricular white matter, affecting the geniculostriate white matter pathways, (degrading visual acuities and constraining visual fields) as well as the higher visual pathways (the dorsal and ventral streams), impairing visual recognition, visual search and visual guidance of movement in a variety of combinations in over 50 % of cases [30, 31].

Diffusion tensor imaging studies of white matter of adolescents of very low birthweight who have associated visual, motor and visual perceptual deficits have demonstrated low fractional anisotropy

measurements in the external capsule, the posterior part of the internal capsule and the inferior fasciculus [32], providing evidence of the long-term nature of CVI that may well be related to the persisting clinical findings of reduced visual acuities and stereo acuities [33], visual field [34] and perceptual disturbances [17] found in analogous populations.

Epidemiology of cerebral visual impairment in relation to prematurity

The success of paediatric intensive care has contributed to CVI emerging as the commonest cause of impaired vision in children in developed countries [17, 35]. By the early 1990s in Scandinavia, cerebral visual impairment and secondary optic atrophy were found (at 45 % of 304 children) to be the most frequent causes of visual impairment, while retinopathy of prematurity had dropped from third (10 %) to seventh place at 4 % [36]. A recent follow-up study of the vision of 262 extremely pre-term children in Denmark has concluded that 'cerebral damage and ROP are independent risk factors for visual impairment in such children and that cerebral damage may be the primary risk factor' [37]. In a separate study, an abnormal pre- or perinatal medical history was found to be the most important risk factor for CVI [38], while in one small Swedish regional population based survey of the causes of visual impairment related to prematurity, 18 children had cerebral visual impairment and 10 of whom had periventricular leukomalacia; yet, no child had visually impairing retinopathy of prematurity [39].

Between one-quarter and one-third of children with evident CVI have prematurity as a contributory factor [40, 41].

Extreme prematurity is a major risk factor for neurodevelopmental disability including CVI [42], and those who develop intraventricular haemorrhage and hydrocephalus are particularly at risk of visual dysfunction [43]. It is possible that boys are at greater risk than girls [44]. A recent population based follow-up study of visual function of extremely premature (under 27 weeks gestation) 6–7 year olds found that none was blind, but 46 % had subnormal acuities [44]. However, evidence of perceptual visual dysfunction was not reported for this group.

Eye and oculomotor conditions associated with prematurity and cerebral visual impairment

Eye disorders, including refractive error and impaired accommodation [46], commonly accompany CVI. Children born before 32 weeks gestation are more likely than typical children to need spectacle correction [47]. In those with cerebral visual impairment, refractive error is thought to be associated with disordered emmetropisation because the wide normal distribution pattern of refractive error in cohorts of affected children closely resembles that of children during their first year of life [45]. Accommodative dysfunction is seen in over 50 % of children with cerebral palsy [48] and is a frequent complication of transdermal hysocine treatment for excessive salivation [49, 50] in children with profound cerebral palsy. Lack of the near pupil response is an effective marker [51].

Retinopathy of prematurity can coexist with CVI in a variety of combinations in prematurely born children [22]. Optic nerve hypoplasia particularly in the form of optic disc cupping may be a sequel to transynaptic degeneration secondary to occipital periventricular white matter damage [22].

Eye movement disorders are common in children with CVI. Premature birth, low Apgar scores and low birth weight in children with infantile esotropia are indicators of possible associated cerebral dysfunction. Strabismus, most commonly convergent, is frequent [52], but sometimes it is divergent or intermittent [53]. Long-term follow-up of untreated children not infrequently reveals convergent strabismus spontaneously evolving into divergence. This augurs in favour of deferring strabismus surgery until the angle is stable, and then performing a lesser amount of surgery than for typical children to minimise the likelihood of subsequent over-correction [54], which may relate to a greater degree of impairment of fusional vergence on account of CVI.

Abnormalities of smooth pursuit, anticipatory saccades, eye alignment [55, 56] and fixation shift [27] have been identified, and may be directly due to the degree of periventricular white matter injury [57] and inversely to the volume of the occipital region estimated by MR imaging [56]. The relationship of these findings to visual prognosis has yet to be elucidated.

Disorders of vision and visual processing due to damage to the brain

The classical visual pathways

Visual acuities, contrast sensitivities and visual fields can be impaired to any degree, depending upon the extent and severity of involvement of the visual pathways and occipital territory. Profound visual impairment results from severe brain pathology and is often accompanied by cerebral palsy. Reflex vision or 'blindsight' may, however, be evident and is worth identifying and employing optimally [58]. Low visual acuities associated with impaired contrast sensitivity and lower and/or hemianopic visual field defects [17] in some cases leading to a single intact upper quadrant of visual field is not uncommonly seen in our practice. At the other end of the spectrum, children born before 32 weeks, without major neurodevelopmental sequelae, have an increased prevalence of low visual acuity and reduced stereopsis, but contrast sensitivity tends to be spared in less severe cases [47]. The cause may relate to generalised abnormality of cortical development rather than perinatally acquired focal lesions of the brain [47].

White matter damage of immaturity associated with birth between 28 and 34 weeks gestation, when it affects vision, typically leads to lower visual field deficits [22] due to damage to the superior optic radiations in the posterior parietal white matter. These are characterised by peripheral absence of visual function, along with impaired visual sensitivity (and therefore lack of resolution), in the more central intact area of the lower visual field function [34]. Some children who trip when negotiating pavements or stairs, and who probe the ground ahead with their foot, or even walk round patterns in carpet as if they were obstacles, may not have a demonstrable visual field deficit on formal testing. Yet, in our experience, when asked to stand supported and look straight ahead, they are commonly unable to see their foot until it is raised by 30 degrees from the vertical or more. For typical children, this angle is $<20°$. This clinical observation may be explained by the fact that visual field testing rarely extends out so peripherally, but this requires further objective study.

Hemianopic visual field deficits due to unilateral visual pathway or occipital damage need to be distinguished from hemianopic deficits of visual attention, related to unilateral posterior parietal damage. Unilateral visual inattention tends to be most severe when the right parietal lobe is affected, leading to inattention to the left [59]. The key clinical feature is that hemianopic visual field impairment moves with and is compensated for by movement of the head and eyes, whereas hemianopic lack of visual attention tends to relate to the position of the body, which needs to be turned into the field of impaired awareness to afford attention, but is not compensated for by head and eye movement, unless the clinical picture is mixed [57]. This observation can be used to guide educational and mobility habilitation strategies.

The pathways serving perception of motion

Visual perception of motion is served by the middle temporal lobes, which are connected to the other visual areas. Disability seeing moving targets (dyskinetopsia) is common in children with periventricular white matter disorders affecting higher cortical areas and has been demonstrated with visual evoked potentials to global motion [60] and motion onset [61].

Impaired perception of motion is remarkably common, being identified in all of 26 children in a cohort born at less than 34 weeks. Thirteen had manifest brain pathology on MRI imaging, and they had greater impairment of perception of movement than the thirteen who did not [62]. These findings again indicate that the dorsal stream higher visual pathway is particularly at risk in premature children.

The perception of biological movement requires an ability to identify the pattern of movement when only a small number of moving elements that represent the movement of, for example, a walking man, are shown. This ability tends to be impaired in association with prematurity-related periventricular white matter lesions in the area of the parieto-occipital complex, where the extent of MRI scanned cerebral pathology relates to the degree of disability [63].

From a clinical perspective, affected children can have difficulty seeing moving traffic and identifying friends running on the playground. They prefer to watch television programmes in which movement is slow or limited, and it is our experience that when they are asked what happens to a ball that has been kicked, the answer is commonly 'it disappears to begin with of course', as affected children 'know' that their vision is 'normal' [9].

The dorsal and ventral stream pathways

The visual cortex and adjacent areas of the occipital lobes serve the primary visual functions of visual acuity, visual fields and the perception of contrast and colour, while higher visual function is served by myriad pathways and locations in the brain. However, there is considerable evidence that there are two higher visual pathways and regions that serve discreet elements of visual function [64].

The ventral stream links the occipital lobes with the temporal lobes, where conscious and cognate visual function is served. The temporal lobes provide the repository of visual memories that facilitate recognition and understanding of what is seen. If the incoming visual data match with memory, recognition takes place, if not the data are stored for subsequent recall [64]. Focal damage to the temporal lobes gives rise to impairment of recognition. For example, the fusiform gyrus of the temporal lobes serves face recognition and route finding, and damage impairs either or both of these functions [64]. The white matter of the ventral stream on each side is related to the inferior horns of the lateral ventricles. Expansion due to hydrocephalus as a sequel to intraventricular haemorrhage can lead to impaired visual recognition despite requisite visual acuities [30, 31]. Inability to recognise faces, as well as the language conveyed by facial expression, is particularly disabling.

The dorsal stream links the occipital lobes with the posterior parietal territory, the area particularly susceptible to damage as a sequel to premature birth. As well as conducting the passage of fibres that serve the lower visual field, this territory effectively accords an internal template that mirrors the external world, facilitating 'on-line' immediate and unconscious visual guidance of movement [16]. This area can be anatomically subdivided into the dorso-dorsal stream (d-d stream) and the ventro-dorsal stream (v-d stream). The d-d stream links to the superior parietal lobe and provides fast online processing, for visual guidance of movement. The v-d stream links to the inferior parietal lobe, a flexible dynamic area that serves goal-dependent updating and execution of action [65] and mediates high-level visual control of movement [66]. The posterior parietal cortex also mediates and maps visual and tactile spatial working memory, processing spatial information irrespective of the modality of input [67, 68]. A third extension of the dorsal stream, the parieto-medial pathway, identified by neuroimaging and lesion studies serves navigation [69].

Damage to the dorsal stream culminates in a diminished capacity to perceive as many entities as normal in surrounding visual space, culminating in simultanagnostic visual dysfunction, accompanied by inaccuracy of visual guidance of movement, or optic ataxia. In its severe form, this clinical picture resembles Balint's syndrome [70], while in its less severe form, the condition has become known as dorsal stream dysfunction [17]. The accuracy of visually guided movement [71, 72], visual search [9], object recognition and visual memory are typically impaired in affected children born before 34 weeks, even where parietal and temporal white matter appears spared on conventional brain MRI [4, 5]. On the other hand, face and letter recognition and non-verbal intelligence are separate and distinct functions [73] and are less likely to be affected [4].

Children adapt or react to what they 'know' to be their normal visual perception, and they show sets of typical behaviours that can, at present, best be elucidated by structured history taking of parents and carers [17, 74] for features outlined in Table 1 Children born before 32 weeks gestation may exhibit such behaviours that are not identified by standard psychological testing. Moreover, current tests, for example of global form and motion coherence, are often normal in symptomatic children. Novel investigations with greater sensitivity are needed. In a recently completed study in our department, of 46 children born before 32 weeks gestation, 15 were identified by cluster analysis of the results of structured history taking, to show sets of behavioural features typical of dorsal stream dysfunction (Table 1).

Visual attention is inevitably diminished by reduced visual acuity and contrast sensitivity, visual field impairment and perceptual visual dysfunction, because visual information that is not perceived cannot be accorded attention. Moreover, disorder of the multisensory mapping accorded by the dorsal stream [67, 68] may well be the reason why children with significant bi-parietal pathology are commonly described as being unable to see so well, when focussing their attention on what is being said. For example, such children commonly bump into obstacles when walking along when engaged in conversation. They also tend not to look at faces when in

Table 1 Clinical features indicative of dorsal and ventral stream dysfunction in children (Modified from Dutton et al. 2006)

Features	Recommendations
Dorsal stream dysfunction	
Impaired ability to handle complex visual scenes can cause difficulties with*:	
Finding a toy in a toy box	Store toys separately
Finding an object on a patterned background	Use plain carpets, bedspreads and decoration
Finding an item of clothing in a pile of clothes	Store clothes separately in clear compartments
Seeing a distant object (despite adequate acuity)	Get close. Share a zoom video/digital camera view
Identifying someone in a group	Identify through waving and speaking
Tendency to get lost in crowded locations	Training in seeking and identifying landmarks
Distress in busy shops and crowded places	Visit shops when they are quiet
Reading	Determine whether double spacing, or masking of surrounding text improves reading ability
Impaired visually guided movement (optic ataxia)	
Upper limbs: Inaccurate visually guided reach that may be compensated for by reaching beyond an object then gathering it up	Occupational therapy/mobility training
Lower limbs: Feeling with the foot for the height of the ground ahead at floor boundaries. Difficulty walking over uneven surfaces (Despite full visual field and looking down.)	Provision of tactile guides to the height of the ground ahead. For example, pushing a toy pram or holding on to the belt pocket or elbow of an accompanying person
Impaired attention	
Difficulty 'seeing' when talking at the same time, which may cause a child to trip or bump into obstacles	Limit conversation when walking
Marked frustration at being distracted	Limit distraction by reducing background clutter and background activity
	(Performance may be enhanced at the 'quiet table' at school.)
Ventral stream dysfunction	
Impaired recognition	
Difficulty recognising people and photographs	Family and friends introduce themselves and wear consistent identifiers
	Training to identify and recognise identifiers
Difficulty recognising shapes and objects	Training in tactile recognition as well as visual
Impaired orientation	
Tendency to easily get lost in known locations	Training in orientation

conversation, perhaps because the dual processing of visual and auditory data is problematic.

Impairment of visual memory

Compared to children born at full term, those born very pre-term who have manifest cerebral pathology show poorer visuospatial and verbal memory performance [72]. The impaired verbal memory may be associated with the decreased hippocampal grey matter volume that has been identified in children born prematurely [75].

Identifying and managing affected children

Children with profound damage to the brain leading to manifest visual and motor dysfunction are easily identified. It is important to recognise that notwithstanding, vision may be a major strength in these children, and they need to be refracted to identify refractive and accommodative dysfunction, and where appropriate, they need the required spectacle correction. It goes without saying that a child can best learn from material that is comfortably visible. It is therefore essential that educational

material and materials at home are matched to the child's level of functional vision (assessed to determine the characteristics of imagery, print and other materials that are easily and quickly assimilated with both eyes open, even when tired). One needs to cater for all aspects of visual dysfunction, including low acuity and contrast sensitivity, visual field impairment, simultanagnostic visual dysfunction, optic ataxia and impaired recognition, as well as disorders of visual attention and visual memory. This is best orchestrated through a team approach, led for example by community paediatric services [17].

It is very important to identify children whose principal visual disability is visuo-perceptual in nature. It has been our experience that before the diagnosis is made, children with lower visual field impairment can be thought to be misbehaving when they refuse to jump off a low bench (because they cannot see the ground) or jump into a swimming pool. Those with optic ataxia can be considered clumsy, and those with simultanagnostic and attentional problems can be deemed to be careless, because they miss what they do not see, and this leads to 'careless mistakes'. They also can become distressed in crowded situations and react with 'bad behaviour'. Moreover, children who cannot interpret facial expressions (due to low acuity, low-contrast sensitivity, dyskinetopsia, prosopagnosia, or a combination), and those whose attentional difficulties may mean that they cannot look at a face and listen at the same time, can be labelled as having atypical autistic spectrum disorder, on account of their failure to engage socially. The children who cannot identify their friends in the playground tend to play alone and can be thought of as being aloof, and this may compound the impression of autistic behaviour. While autistic spectrum disorder is a well-recognised complication of premature birth, atypical presentations warrant re-evaluation for evidence of such visual dysfunctions [76].

Identification of these visual difficulties and explanation of the resultant adaptive behaviours (whether compensatory or reactive), to all those looking after affected children, in our experience, fundamentally change the social dynamics. No longer are the children criticised. They are understood, action is taken to deal with the difficulties, and praise is given when milestones are achieved. Newly diagnosed children often become one's best friends because their lives have been revolutionised for the better. At present, in some countries, perceptual visual impairment has yet to be recognised as a major cause of disability, as it has yet to be recognised by International Classifications of Disease, and care is devolved to parents. This unfortunate situation is one that needs to be addressed with some urgency, owing to increasing prevalence of dorsal and ventral stream dysfunction in the community.

Conflict of interest None.

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Addendum

The term cortical visual impairment has not been applied in this article as it tends to be conceptually constrained to damage to the primary visual pathways only, referring to significant reduction of visual acuity in the absence of ocular pathology.