Cortically visually impaired children: a need for more study

In the developed world the face of childhood blindness has changed dramatically in the past two to three decades. Improved medical and ophthalmological care since the late 1950s can be credited with the decrease in the prevalence of congenital and acquired ocular blindness. For example, the prevalence of congenital cataracts has been reduced dramatically as the result of rubella immunisation programmes. Moreover, a thorough understanding of the importance of early surgery coupled with significant improvements in surgical techniques has resulted in vastly improved visual outcomes in children with congenital and developmental cataracts.

Regrettably, the reduction in ocular blindness has been more than offset by an increasing rate of neurological visual impairment. This change can be attributed to the improvement in rates of survival of very premature infants and critically ill children. For those who provide care for visually impaired children this epidemic of neurological visual impairment has brought with it a myriad of new diagnostic and rehabilitation problems. These children are usually multidisabled visually impaired whose needs are not limited to visual rehabilitation and assistance. In addition, quite often, their multiple disabilities compound the problems of clinical visual assessment as well as rehabilitation strategies.

The term cortical blindness refers to the loss of vision, secondary to injuries or maldevelopment involving the geniculostriate pathways. Clinically, it is manifested as the absence of vision and optokinetic nystagmus in the presence of a normal ocular examination and intact pupillary light responses. It most commonly occurs in children following hypoxic insults, but may also arise as a sequela of meningitis, encephalitis, head trauma, hydrocephalus, or metabolic derangements. While children with these types of injuries seldom regain normal vision, sufficient vision often returns to allow them to navigate independently and to receive a partially sighted education. While the recovery of vision may be rapid and complete, much more often it is protracted and partial. Because these children usually regain some vision, Whiting and co-workers have proposed that their visual loss be referred to as cortical visual impairment (CVI) rather than cortical blindness.

Assessment of the residual visual function in these neurologically impaired children is difficult. Standard clinical, electrophysiological, and neuroimaging techniques are usually disappointing in their inability to define precisely the nature and extent of residual visual function in these children. For example, assessment of visual fixation and “following” in these children may not reflect the degree of insult to the geniculostriate pathways but rather be a reflection of dysfunction of the pathways subserving saccadic movements. This same problem limits the usefulness of preferential looking techniques in evaluating CVI patients. Even standardised visually evoked responses have proved to be disappointing in evaluating CVI cases. Although some early reports emphasised the absence of or marked attenuation of VEP occipital responses in patients with CVI, Frank and Torres were unable to detect a significant difference between VEP responses in children with CVI and those without. Entirely normal VEP responses have been recorded in severely disabled CVI patients. Likewise, electroencephalograms of CVI children have not been useful in the assessment of visual function or prognosis. Even state of the art neuroimaging studies are limited in their ability to define the extent of visual dysfunction in patients with CVI.

Clinicians examining children with CVI must depend primarily on behavioural assessments in their attempt to define the nature of the visual insult and attempt to establish a prognosis. It is for this reason that the study of Porro and co-workers in this issue of the BJO (p 1231) is a welcome addition to the literature concerning CVI. Although the “behaviourisms” of CVI patients have been detailed in previous reports, Porro and co-workers’ use of an ethological study paradigm is provocative and thought provoking. However, at least two major problems become apparent when reading this study. These problems are intrinsically part of the difficulty in conducting meaningful clinical research studies on patients with neurological visual impairment.

First is a problem that now bedevils even the discussion of CVI. The term CVI has been broadened increasingly in its definition so that it is no longer restricted to the patient with injury to the geniculostriate pathways. It is regrettable that the term CVI now seems to be applied to any child with a neurological insult and apparent non-ocular visual dysfunction. As a result patients with saccadic paralysis, ocular motor apraxia, visual inattention, visual perceptual disorders, autism, and even seizure disorders are often given the diagnosis of CVI even in the absence of injury to the geniculostriate pathways. This is a heterogeneous group of disorders that undoubtedly have uniquely different neurovisual pathologies and each requires a uniquely different adaptation to the underlying neurological deficits. This problem can be seen in the study of Porro and
co-workers. For example, patients 2 and 4 have no evidence on neuroimaging studies of injury to the geniculostriate pathways. They do show a diffuse pattern of abnormal myelin development and, in one case, corpus callosum dysgenesis. Patient 6 has an isolated hemifield defect and would not be included in most studies of CVI. In fact, patients with congenital hemifield disorders are known to have a unique pattern of adaptation to their visual loss.\textsuperscript{18-27} Obviously, all of the different neurological insults resulting in visual impairment require careful investigation. However, it is imperative that clinical studies be undertaken on a well defined homogeneous group of patients. Even within the group of patients with injury to the geniculostriate pathways there are distinct subgroups. For example, patients with posterior periventricular leucomalacia are distinctly different from patients with infarction of the visual cortex.\textsuperscript{3} A consistent terminology for patients with different types of neurological insults and visual dysfunction needs to be established and widely accepted.

Once the behaviours of the various types of neurological insults affecting vision have been catalogued the real problem begins. Understanding why these children behave as they do is of fundamental importance if better strategies of rehabilitation and education are to be designed. Yet our knowledge is wanting in this area and in most cases the best we can do is speculate. For example, it is well known that children with CVI often prefer to turn their head and eyes away from the target of fixation.\textsuperscript{6-17} Why do they do this? Porro and co-workers suggested they may be using intact peripheral field when the central field is damaged. An extremely eccentric position of fixation might even suggest they are using the temporal crescent as the authors suggest. However, equally plausible is the notion that they may be using their extrageniculostriate system as a replacement for the injured geniculostriate system.\textsuperscript{28-30} This might even come about as the result of rewiring of neural pathways not ordinarily intended to have visual function.\textsuperscript{31,32} Yet, much more simple explanations may prove to be correct. For example, it may be that this “aversive” to the target is simply a way to reduce the amount of visual information to be processed. We need new tools to explore these theses in order to understand this important group of visually impaired children. Perhaps more discriminating functional neuroimaging techniques or improved electrophysiological and psychophysiological techniques will become available soon and provide us with more details on how children adapt to neurovisual insults to the visual pathway. Certainly appropriate laboratory models of neonatal visual cortex damage continue to provide vital data concerning this clinical problem.\textsuperscript{33-35} In the meantime, careful, well designed clinical studies of the recovery patterns of these children provide fundamental information about the problems of neurologically damaged visually impaired. It is hoped that the study of Porro and co-workers is the first of many that will address the needs of this large group of understudied and poorly served visually impaired children.

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Towards a more accurate assessment of the malignant potential in conjunctival melanosis

It is not uncommon in clinical practice for an ophthalmologist to identify, during routine examination, unilateral or bilateral areas of flat stippled pigmentation in the bulbar or palpebral conjunctiva in middle aged or elderly patients. The pigmentation can have been unrecognised for many years and be static but in a minority of cases the process may progress to malignant melanoma. Thus, any pigmented lesion which is increasing in size should be given serious consideration and tissues should be submitted to an experienced pathologist in the form of an excision biopsy.

The simplest form of conjunctival pigmentation is the result of hypertrophy and hyperplasia of the basal cell layer of the epithelium which becomes packed with melanosomes. In this histological pattern, the nuclei of the melanocytes do not show variations in size and shape and do not possess obvious nucleoli: this pathology is classified as primary acquired melanosis without atypia (or benign acquired melanosis).1–3 Primary acquired melanosis without atypia does not carry the risk of progression to malignancy.4

A more sinister type of melanocytic proliferation (within the basal and wing cell layers of the epithelium) is characterised by variation in size and shape of the nuclei, the presence of prominent nucleoli, and migration of these cells towards the surface of the epithelium. This histological pattern is graded as mild/moderate or severe primary acquired melanosis with atypia.5 The problem for the pathologist is that assessment of the degree of “atypia” is subjective and atypia does not necessarily signify neoplasia because, as a reactionary process, it is seen after cryotherapy or irradiation. An added pathobiological complication is that melanocytic proliferation in areas of primary acquired melanosis with atypia can be very variable within a large area of pigmentation: this could be regarded as a field change with multifocal neoplasia or alternatively as superficial spreading of neoplastic melanocytes within the epithelium. In some individuals primary acquired melanosis with severe atypia progresses to full thickness infiltration of the epithelium by neoplastic melanocytic cells (melanocarcinoma in situ) and there is no doubt that this carries an increased risk of invasion of the basement membrane and frank malignant melanoma.6–9 In attempts to simplify and strengthen the subclassifications of melanocytic proliferation pathologists have used immunohistochemistry to identify melanocytic cells.

Initially reports were optimistic that the immunohistochemical marker HMB-45 would differentiate malignant melanocytes from reactionary benign cells5 but subsequent studies showed that this marker simply identifies active melanocytes. The antibody NK1C3 was regarded as more reliable as a marker for malignancy but again the distinction between benign reactionary proliferations is not made clear by this marker. Neither is S100 a useful marker except in the situation where the proliferating melanocytes do not contain melanosomes as in primary acquired melanosis sine pigmento.4 These markers are advantageous in one regard in that they clearly demonstrate the extent of melanocytic infiltration within a conjunctival biopsy and as time goes by there is cause for optimism that the specificity of immunohistochemical markers for malignant melanocytes will improve.

The study of cell proliferation has advanced considerably owing to identification of non-histone nuclear proteins such as Ki 67 and proliferating cell nuclear antigen (PCNA) within the nuclei of dividing cells. In paraffin sections Ki 67 can be labelled with MIB-1 antibody and PCNA by PC10 antibody using conventional immunohistochemical techniques. The proliferating cells are identified by a red label which immunostains the nuclei. In the current issue of the BJ O Chowers et al (p 1316) have shown the value of this approach and have stressed the lack of interobserver variation, thus substantiating an earlier study by Seregard.7 By these techniques it is possible to identify those melanocytic proliferations which carry a high risk of progression to malignant melanoma. These advances in histopathology are relevant to changes in protocols for the treatment of precancerous melanosis which has traditionally been based on excision and cryotherapy.8 Recent reports9 10 indicate that topical mitomycin C chemotherapy may be an appropriate treatment for primary acquired melanosis with atypia so that accurate pretreatment diagnosis is essential for correct management.

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