Childhood macular dystrophies

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Purpose of review

The aim of this review is to highlight recent advances in our understanding of the molecular genetic basis and phenotype of childhood onset macular dystrophies and to summarize current attempts to develop novel therapies for this group of disorders.

Recent findings

The genes associated with the major causes of childhood onset macular dystrophies have now been identified and current research efforts have been focused on understanding the function of the encoded protein, how the mutant protein leads to photoreceptor cell death and investigation of the range of retinal phenotypes that result from mutations in these genes. Assessment of the phenotype has been greatly helped by improvements in retinal imaging such as spectral domain optical coherence tomography and fundus autofluorescence imaging. The development of animal models has, despite their limitations, helped understanding of disease mechanisms and allowed assessment of new therapeutic approaches such as gene replacement therapy and pharmacological treatments.

Summary

Molecular diagnosis and improvements in retinal imaging have greatly improved the accuracy of diagnosis in paediatric macular disease and allowed better genetic counselling and information about prognosis to be given to children and their families. Advances in basic understanding of disease mechanism will lead to the development of clinical trials of novel therapies in the near future.

Keywords

dystrophy, fovea, gene therapy, macula, molecular genetics

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Introduction

Childhood macular dystrophies are a genetically heterogeneous group of disorders associated with, usually progressive, macular dysfunction. Mostly present in early teens with central visual loss but there is an uncommon group of developmental disorders of the macula which usually present in infancy. Macular abnormalities are also seen in a variety of systemic disorders; these will not be covered by this review.

Developmental macular disorders

Three broad groups of inherited developmental abnormalities of the macula have been reported: foveal hypoplasia, nanophthalmic maculopathy and the more extensive macular abnormalities seen in North Carolina macular dystrophy and associated phenotypes.

Foveal hypoplasia

The usual presentation of foveal hypoplasia is with reduced vision and nystagmus from infancy. Fundus examination reveals the lack of a foveal pit and absence of luteal pigment. These changes can be readily demonstrated using optical coherence tomography (OCT) and confocal fundus autofluorescence imaging (FAF) [1–4]. The retinal vessels often cross the putative foveal region. Provis and Hendrickson [5•] studied the retinal vasculature of human eyes from preterm infants and demonstrated that the foveal region is not vascularized during development suggesting that the abnormal vessels seen in foveal hypoplasia are not due to a failure of transient foveal vessels to regress. Foveal hypoplasia is a common finding in aniridia and in all forms of albinism but may be seen as an isolated anomaly [6]. Missense mutations in the PAX6 gene (the gene associated with aniridia) may be associated with foveal hypoplasia but complete iris architecture and the true diagnosis can easily be missed without molecular genetic testing [7•]. Spectral domain OCT has enabled high-resolution imaging of the putative foveal region and the fast acquisition time has enabled good-quality images to be obtained in young children and patients with nystagmus. Chong *et al.* [1] compared such OCT images of a normal patient and those with albinism. The patients with albinism had absence of the normal foveal pit and an area of high reflectivity across the fovea

suggesting persistence of the nerve fibre layer. OCT also demonstrated the presence of other retinal layers normally absent from the foveal region.

Pal *et al.* [8] have recently described a new phenotype of recessively inherited foveal hypoplasia and anterior segment dysgenesis which maps to chromosome 16q23.2–24.2. Van Genderen *et al.* [9] have reported a similar family. Affected individuals have evidence of chiasmal misrouting on visual evoked potential (VEP) studies and it is possible that this disorder represents a mild form of albinism.

Nanophthalmos

Absence of the foveal pit is also a feature of eyes with nanophthalmos, an uncommon developmental disorder in which the anterior and posterior segments are reduced in size but otherwise anatomically normal. In contrast to foveal hypoplasia there is no nystagmus and OCT imaging demonstrates thickening or crowding of the inner retinal layers filling the foveal pit [10]. Nanophthalmos should be differentiated from posterior microphthalmos in which the posterior segment is reduced in size in the presence of a normal anterior segment. There is usually an elevated papillomacular fold with or without cysts and with variable yellow deposits in the macular region [10–13].

North Carolina macular dystrophy and related phenotypes

North Carolina macular dystrophy (NCMD) is a rare dominantly inherited developmental disorder of the macula. The disorder is completely penetrant but there is wide variation in clinical expression. The disorder is nonprogressive, although vision may deteriorate if there is development of associated choroidal neovascularization. Classically there is central macular atrophy often with associated drusen-like deposits at the edge of the lesion. Mildly affected individuals may have multiple macula drusen-like deposits with normal visual acuity. The full-field electroretinogram (ERG) and electrooculogram (EOG) are normal. Small *et al.* [14] mapped the disorder to chromosome 6q in 1992 but surprisingly the gene has not yet been identified. Recently Yang *et al.* [15] have refined the locus to a 3-cm region between markers D6S1716 and D6S1671 and screened the coding regions of all 11 genes in the refined region in six families; no mutations were identified suggesting that the disorder is due to a mutation in a regulatory region or a copy number variant. Another rare autosomal dominant developmental macular disorder – progressive bifocal chorioretinal atrophy (PBCRA) [16] – maps to an overlapping locus on chromosome 6q and again the causative mutation has yet to be identified [17]. It is unclear if PBCRA and NCMD are allelic or whether there are two closely related developmental genes on chromosome 6q. Developmental macular dystrophies similar to NCMD have been mapped to chromosome 5 [18] and chromosome 14 (macular dystrophy and deafness) [19] but again the causative genes have not been identified.

Childhood onset macular dystrophies

In this section I will review recent advances in our understanding of macular dystrophies that present in later childhood.

Vitelliform macular dystrophy (Best disease)

Vitelliform dystrophy is an autosomal dominant disorder which is characterized by abnormal deposition of yellow material between sensory retina and the retinal pigment epithelium (RPE) at the macula. Histopathological studies of donor eyes from affected patients demonstrate that the RPE has high levels of lipofuscin [20–22]. The full-field ERG is normal but the EOG shows a very poor light rise in affected family members. The phenotype is highly variable even within the same family with some carriers of the genetic mutation having no symptoms and a normal retinal appearance; the EOG is, however, usually abnormal. Recent advances in retinal imaging including OCT and FAF imaging have improved diagnosis and allowed better understanding of the site of retinal disease. FAF imaging demonstrates that the yellow material in Best disease is highly auto fluorescent and there is generally good correlation between the material seen on funduscopy and the patterns of autofluorescence and OCT changes [23–25]. A recent high-resolution OCT study [26••] has identified that the earliest change is seen as a highly reflective material between the outer nuclear layer and RPE. More OCT studies are needed of patients who carry the disease mutation but have minimal or no fundus changes to elucidate the early changes seen in this disorder.

Although the visual prognosis in Best disease is reasonably good some patients develop acute visual loss in association with choroidal neovascularization which may complicate the disorder. Treatment of this complication has always been problematic with no clear evidence of whether any treatment is better than natural history. Recently Chung *et al.* [27] have reported the natural history of untreated choroidal neovascularization complicating Best disease and demonstrated that there is a relatively good prognosis There continue to be some studies of good outcome following treatment with photodynamic therapy [28,29] and the use of anti-VEGF agents such as bevacizumab [30–32] but it is difficult to judge the efficacy of these agents given the good natural history.

The gene causing Best disease – bestrophin – was identified by positional cloning in 1998 [33]. The gene is expressed in the RPE and encodes a membrane protein that functions as a chloride channel and regulator of

voltage-gated Ca^{2+} channels. It is still not clear how the abnormal channel function gives rise to the retinal phenotype [34,35••]. New mutations, predominantly missense, continue to be described but there appears to be little correlation between genotype and phenotype. The main mechanism by which missense mutations in the bestrophin gene give rise to retinal disease is by a dominant negative effect on the normal allele, although it is possible that some mutations may result in a gain of function (see Hartzell *et al.* [35••] for fuller discussion of molecular pathology).

Recently two new phenotypes have been described in association with mutations in the bestrophin gene which cause disease by a different molecular mechanism. Burgess *et al.* [36••] have described a group of patients with an unusual retinal dystrophy who were found to have biallelic mutations in the bestrophin gene. The mutations were missense or nonsense mutations and segregated in the families as an autosomal recessive trait. The heterozygous parents had a normal retinal and electrophysiological phenotype. Functional studies of the mutations showed that they were associated with very little chloride channel function and in contrast to mutations reported in AD Best disease did not impair wild-type function [36••]. This important study delineates a new AR Bestrophin disease. Affected patients had reduced visual acuity, irregular RPE with scattered white flecks which showed increased autofluorescence on FAF imaging. Retinal oedema was common. The EOG was severely abnormal but in contrast to AD Best disease the full-field ERG was also abnormal [36••]. Recently Gerth *et al.* [37] have reported the detailed electrophysiological and retinal imaging investigations of an 11-year-old child with this disorder. A naturally occurring canine model of AR bestrophinopathy has recently been reported [38]; studies in this animal model will improve understanding of disease mechanisms and may allow preclinical testing of novel therapies.

A third phenotype associated with bestrophin mutations is a rare disorder, autosomal dominant vitreochoroidopathy (ADVIRC). In this condition there is a generalized retinal dystrophy but with a characteristic 360 degree post-oral atrophy and pigmentation. Affected eyes are hyperopic and angle closure glaucoma is a feature in some families. The EOG is severely reduced and the full-field ERG is also abnormal. Screening of the bestrophin gene in families with this rare disorder has demonstrated heterozygous mutations that disrupt pre-mRNA splicing [39•,40].

Juvenile X-linked retinoschisis

Juvenile X-linked retinoschisis (XLRS) is an X-linked disorder which usually presents with reduced vision in childhood due to foveal schisis. Foveal changes are seen in the majority of affected males and about 50% have peripheral retinal schisis or other peripheral retinal changes. The full-field ERG is abnormal with reduction of the b wave in the majority of cases. Less common presentations are with large bullous schisis in infancy and spontaneous vitreous haemorrhage [41]. Imaging with OCT has greatly improved diagnosis; changes may be evident on OCT even when the fovea looks clinically normal. There have been a number of recent publications of the results of spectral-domain OCT imaging. It is evident that the schitic changes extend beyond the fovea and involve multiple retinal layers [42,43].

Apushkin and Fishman [44] reported the results of treatment with topical dorsolamide in a small group of patients with XLRS. There was a modest improvement in vision in the majority of patients and there was also a reduction in cystic change seen on OCT imaging. There was no correlation between response to treatment and class of retinoschisin mutation [45]. Ghajarnia and Gorin [46] reported a single case of a child with XLRS who had improvement in vision and resolution of foveal cystic changes with oral acetazolamide. Although these studies suggest that short-term treatment with carbonic anyhydrase inhibitors may improve foveal structure and function in XLRS further longer-term studies are needed before such treatment will gain widespread acceptance.

The gene causing XLRS, retinoschisin, was identified by positional cloning in 1997 [47] and now more than a 100 different mutations have been identified (http://www.dmd.nl/nmdb/index.php?select_db=RS1). The gene is expressed in photoreceptors and to a lesser extent in bipolar cells [48]; the encoded protein is secreted by the photoreceptor and bipolar cells and binds to the cell surface through interaction with a protein complex containing a Na/K ATPase [49]. The exact role of retinoschisin in retinal function is still unknown. The identification of the causative gene has allowed molecular diagnosis in atypical cases [50], diagnosis of the female carrier state and prenatal and preimplantation diagnosis [51]. Molecular genetic testing has also allowed confirmation of diagnosis in females with XLRS who have mutations on both X chromosomes [52]. There is disappointingly little relationship between genotype and phenotype [53]; the retinal phenotype can vary widely even within the same family. It is likely that other modifier genes may play a role in determining disease severity; one such modifier gene has been identified in genetic studies of a mouse model of XLRS [54] but no modifier genes have yet been identified in humans.

There are three published mouse models of XLRS [54–57] and the structural changes and electrophysiological phenotype are similar to the human disease. Investigation of the animal models has also highlighted

a role for retinoschisin in retinal development [58]. Gene replacement therapy in the mouse models has resulted in improvement in the ERG abnormalities and a reduction in photoreceptor cell death [57,59•,60,61]. These results are encouraging but much more work needs to be done before gene therapy can be considered in humans. Overall XLRS has a good long-term visual prognosis [62,63] and the potential risks of gene therapy currently outweigh the benefits for most patients. Patients who have the worst vision and might gain most from novel therapies have extensive structural changes which are unlikely to benefit from gene replacement therapy.

Stargardt disease

Stargardt disease is the commonest macular dystrophy of childhood. It is an autosomal recessive disorder characterized by macular atrophy usually associated with white flecks at the level of the RPE. Fluorescein angiography usually shows the dark choroid sign when the underlying choroidal fluorescence is masked by an abnormal material (likely to be lipofuscin) present in the RPE. Histopathology of donor eyes from patients with Stargardt disease shows high levels of lipofuscin in the RPE [64]. This is reflected clinically by the finding of high levels of autofluorescence seen on FAF imaging. As the disease progresses, patchy areas of loss of autofluorescence are seen and these correspond to loss of retinal sensitivity reflecting photoreceptor cell death [65].

The gene ABCA4 (ABCR) causing Stargardt disease was identified in 1997 by Allikmets *et al.* [66]. It is a retina-specific adenosine triphosphate (ATP)-binding cassette transporter that localizes to the outer segments of rod and cone photoreceptors. It is involved in removing all trans retinal from the outer segment discs. It is a large gene which is polymorphic (variable) in the normal population and this complicates identification of disease-causing variants. Mutations in ABCA4 have been implicated in Stargardt disease, fundus flavimaculatus, bulls eye maculopathy, autosomal recessive RP and autosomal recessive cone-rod dystrophy and may play a role in susceptibility to age-related macular degeneration. The clinical phenotype is dependent on the combination of ABCA4 alleles in an individual patient.

The abcr−/− knockout mouse lacks a functioning copy of ABCA4 (ABCR). The mouse shows evidence of slow dark adaptation (which is also seen in humans with Stargardt disease) and there are high levels of A2E, the major fluorophore of lipofuscin in the RPE [67]. The findings in this mouse model suggest that the photoreceptor cell loss in Stargardt disease in humans occurs secondarily to RPE cell dysfunction resulting from accumulation of A2E. Reducing serum levels of vitamin A [68] or treatment with isotretinoin (Roaccutane) [69], a drug used to treat acne, which inhibits the visual cycle reduces the accumulation of A2E in the RPE in the mouse model. Furthermore increasing vitamin A levels accelerates accumulation of A2E [70•]. This suggests that treatments aimed at slowing the visual cycle may be worth pursuing in Stargardt disease. Such treatments will result in poor night vision but may preserve photoreceptors in the longer term. Drugs less toxic than Roaccutane will need to be developed. Fenretinide – a drug which inhibits the binding of retinol to retinol-binding protein – has been suggested as a possible treatment. Marmor *et al.* [71] reported the effects of high-dose Fenretinide as a compassionate treatment in two children with advanced neuroblastoma. The drug totally abolished rod photoreceptor function whilst cone function was normal. Fenretinide which is currently being assessed in a clinical trial of atrophic age-related macular degeneration may be effective in reducing levels of A2E in Stargardt disease but needs to be formally evaluated. In the meantime it is reasonable to advise our patients with ABCA4 mutations to protect their eyes from bright light and to avoid taking supplemental vitamin A.

Other potential approaches to the treatment of Stargardt disease include gene replacement therapy and RPE cell transplantation. Recently Kong *et al.* [72••] have reported the results of treatment of the abcr−/− knockout mice with gene replacement therapy using a lentiviral vector. Efficient transduction of rod and cone photoreceptors was achieved and treated eyes showed significantly reduced accumulation of A2E in the RPE. Although more work is needed before this approach can be considered in humans the results are encouraging. In contrast the preliminary results of autologous RPE transplantation beneath the macula in Stargardt disease have been disappointing [73].

Bulls eye dystrophy

Bulls eye maculopathy (BEM) without flecks may be association with mutations in ABCA4 but there are likely to be other causes. Michaelides *et al.* [74] in a study of 49 patients with BEM found at least one likely ABCA4-causing allele in 35%. It is evident that other genes causing BEM remain to be identified. A dominant form of BEM has been mapped to chromosome 4 [75] and recently a missense mutation in the gene PROML1 has been identified as the cause [76]. The same missense mutation was found in an autosomal dominant form of Stargardt disease and in inverse RP [76]. PROML1 is expressed in photoreceptors and recessive mutations in the same gene are a rare cause of recessive retinitis pigmentosa [77].

Conclusion

Although most forms of childhood macular dystrophy are currently not amenable to treatment, recent advances in molecular genetics, cell biology and the development of

animal models of disease leads to optimism that the next decade will see the introduction of novel therapies into clinical practice.

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- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 420).

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