Cone and cone-rod dystrophies

The retinal dystrophies are a genetically heterogeneous group of disorders which may be seen as an isolated ocular abnormality or may be associated with other systemic disease. In most disorders the underlying disease mechanism is not known, so that classification is unsatisfactory. There is great clinical heterogeneity even among dystrophies which share a common mode of inheritance. At present, dystrophies are mostly classified according to whether they are stationary or progressive and whether there is predominantly macular or generalised retinal disease. The latter group is subdivided on the basis of whether there is involvement of rod or cone photoreceptors or both. Most disease is progressive and eventually involves both types of photoreceptors. Patients with predominantly rod disease complain of difficulties with night vision and in the early stage of the disease will have normal visual acuity and colour vision. Cone dysfunction may be suspected if there is photophobia, fine nystagmus, reduced visual acuity, and abnormal colour vision. Although in some cases the diagnosis may be made on the basis of a history and clinical examination alone, further tests of rod and cone function are often needed. All regional genetic units should have access to a specialised electrodiagnostic service where isolated cone and rod responses can be reliably recorded in both adults and young children. This is important for diagnosis but also for recognition of the carrier status in X linked dystrophies.

Stationary cone dystrophies

Cone dystrophies may be conveniently classified according to their natural history. The stationary cone dystrophies include the commoner colour vision defects in which there is abnormal colour vision but normal visual acuity, and the different forms of achromatopsia where the colour vision defect is accompanied by reduced acuity and nystagmus. Colour vision in man is trichromatic, that is, there are three classes of cone photoreceptors that contain visual pigment, maximally sensitive at 560 nm (red cones), 535 nm (green cones), and 440 nm (blue cones). The genes for the protein component (opsin) of the red and green cone pigments have been localised to adjacent regions of the long arm of the X chromosome and the blue cone opsin to chromosome 7. About 8% of men and about 0.5% of women have a defect in the red-green system and these colour vision defects are associated with abnormalities of the red and green opsin genes. Achromatopsia presents in infancy with poor vision, photophobia, and nystagmus. Fundus examination is usually normal. Two main forms are recognised. In complete achromatopsia (rod monochromatism) there are no functioning cone photoreceptors in the retina. Vision is reduced to the level of about 6/60, there is no true colour perception, and there are normal rod but absent cone responses on electroretinography. Inheritance is autosomal recessive but there may be more than one form. Incomplete achromatopsia or blue cone monochromatism is an X linked recessive disorder which presents in a similar fashion but has a better visual prognosis. Colour vision testing and electroretinography show evidence of normal rod and blue cone function but absent red and green cone responses. Female heterozygotes may show evidence of abnormal cone responses on electroretinography. In a recent study of 12 families with this uncommon disorder, found a rearrangement of the red and green cone opsin genes or deletion of an adjacent regulatory region in each case.

Progressive cone and cone-rod dystrophies

The progressive cone dystrophies usually present in adolescence or early adult life with reduced vision. Photophobia and nystagmus are common findings and, in contrast to achromatopsia, there is usually evidence of atrophy of the retinal pigment epithelium in the macular area, giving rise to a so called 'bulls eye' appearance. Colour vision is abnormal at an early stage and the defect is usually of the red-green type. Electroretinography shows absent or substantially abnormal cone responses. Many patients who present with symptoms and signs of a cone dystrophy later develop night blindness and abnormalities of the rod electroretinogram and are then said to have a cone-rod dystrophy. Cone or cone-rod dystrophy is usually seen in otherwise normal subjects but has been reported in association with the Pierre-Marie type of hereditary ataxia and amelogenesis imperfecta. There are clearly many different disorders with cone dysfunction. Some represent pure cone dystrophies but in others, perhaps the majority, there is later evidence of rod dysfunction. At present there is insufficient evidence to classify these diseases other than by their mode of inheritance. This may be autosomal recessive, autosomal dominant, or X linked recessive, but there is clinical heterogeneity within these subtypes. Many cases are sporadic but in patients with a family history autosomal dominant inheritance is most common.
Specialised electrophysiological and psychophysical tests of rod and cone function may help identify specific patterns of disease. Went et al in this issue describe a family with a dominant progressive cone dystrophy with early loss of blue cone function and a similar family has been described by Bresnick et al. No mutation of the blue cone opsin gene has been found to date. However, Reichel et al have described an X linked cone dystrophy in which there is early loss of red cone function and a deletion of the red cone opsin gene.

Similar techniques may be useful in X linked cone dystrophy in defining the status of females at risk of inheriting the abnormal gene. Female heterozygotes are usually asymptomatic and in most cases have a normal ocular examination. In this issue van Everdingen et al report the results of colour vision testing using the Nagel anomaloscope and foveal densitometry (which measures the cone pigment density) in a group of obligate heterozygotes. They were able to identify abnormalities in 87%, but these tests remain research techniques that are not routinely available even in regional ophthalmology units. Accurate genetic counselling will have to await the localisation of the abnormal genes.

Although patients may be helped symptomatically by the use of tinted lenses, miotics, and low vision aids there is no proven treatment of the underlying retinal disease. The discovery of mutations of the cone opsin genes in some forms of cone dystrophy and the more recent identification of mutations of the rod opsin gene and the peripherin-RDS gene in retinitis pigmentosa make it likely that other genes coding for proteins involved in rod and cone structure and function will be found to be abnormal in these retinal dystrophies. The emphasis of research will shift from the present attempts at defining the phenotype to the use of electrophysiology, densitometry, and psychophysics to probe the effects on visual function of specific genetic mutations. This should help our understanding of disease mechanisms and in the long term bring closer the development of an effective treatment.

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