Macular Dystrophies

Clinical Findings and Genetic Aspects

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Core Messages

- A clinical diagnosis in juvenile macular dystrophies is essential for genetic counselling as well as for direct molecular genetic investigations
- Stargardt disease, Best vitelliform macular dystrophy and X-linked juvenile retinoschisis are the most prevalent macular dystrophies in Western Europe
- Stargardt disease contributes to a spectrum that includes other retinal dystrophies associated with *ABCA4* gene mutations, such as autosomal recessive forms of cone-rod dystrophy and retinitis pigmentosa
- Cataract, retinal detachment and especially choroidal neovascularization are associated with some of these macular dystrophies. Since these complications may be amenable to treatment, regular follow-up of patients with macular dystrophies is important
- Pattern dystrophies may be associated with systemic abnormalities, including pseudoxanthoma elasticum and myotonic dystrophy
- Many of these so-called macular dystrophies also display abnormalities of the peripheral retina as demonstrated by ophthalmoscopy and electrophysiology

3.1 Introduction

A variety of dystrophies, principally located at the macula, can be distinguished according to fundus appearance, inheritance pattern and, in some cases, molecular genetic analysis. Although these disorders are all characterized by loss of central vision and atrophic changes in the macula and underlying retinal pigment epithelium (RPE), they are highly heterogeneous as to the clinical findings and the underlying genetic cause. The macular dystrophies are a significant cause of blindness, especially in the young. Nevertheless, surprisingly few data are available as to the exact prevalence of these disorders. For Stargardt disease and X-linked juvenile retinoschisis – with Best vitelliform macular dystrophy among the most common macular dystrophies – a prevalence of respectively 1:10,000 and 1:5,000 to 1:25,000 has been reported. Despite the term "macular dystrophies", which suggests localized pathology, many of these disorders are at a molecular level panretinal disorders, in which the macular region shows greater susceptibility to the degeneration.

The past few decades have witnessed impressive advances in molecular genetics. Also in the field of inherited macular dystrophies many genes and loci have been implicated. Only a few macular dystrophies disorders turn out to be genotypically ho-

mogeneous. More often, these disorders display a considerable genetic heterogeneity, which means that mutations in different genes result in clinically similar phenotypes.

The advent of molecular genetics in modern medicine has made it possible to analyse a disease from the "inside out". The identification of the underlying genetic defect in macular dystrophies is only the first step in understanding the fundamental causes of the disease. Hopefully, our increasing knowledge of the pathophysiologic mechanisms will enable the development of future treatment regimes.

Current classifications are still based on clinical observations, in selected cases supplemented with the underlying genetic defect. A correct clinical diagnosis remains of the utmost importance, not only to facilitate or even enable analysis of the underlying genetic abnormality, but also to provide the patient with the most accurate prognosis.

In this chapter we address the various clinical findings in the most common monogenic macular dystrophies. When possible, the underlying genetic defect and pathophysiological mechanisms will be discussed. Although age-related macular degeneration could be considered a macular dystrophy, in view of the genetic associations, this disorder will be discussed separately.

3.2 Macular Dystrophies

3.2.1 Stargardt Disease

3.2.1.1 Clinical Findings

Autosomal recessive Stargardt disease (STGD1) is arguably the most common hereditary macular dystrophy. Most patients with STGD1 experience bilateral loss of visual acuity in childhood or early adulthood. In a large study of 150 unrelated and genetically proven STGD1 patients, the mean age of onset was 15.2 years [42]. However, the age at which STGD1 patients develop visual loss may range from 4 to 65 years. Most patients experience a decrease in visual acuity to 0.05–0.1.

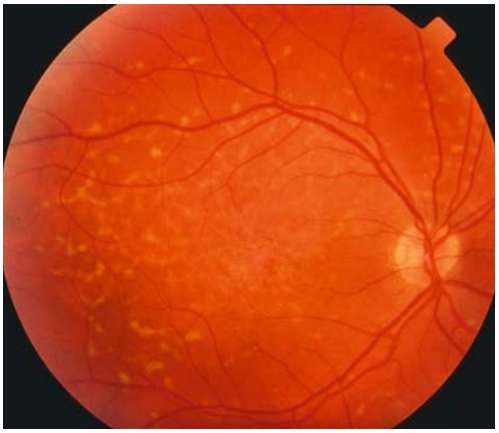

Fig. 3.1. Stargardt disease with pisciform yellow flecks and macular atrophy

Typically, pisciform yellow flecks can be observed in the posterior pole at the level of the RPE. These flecks are variable in size, shape and distribution and may extend as far as the equator (Fig. 3.1). As the disease spreads centrifugally new flecks may appear while older flecks resorb, during which time their colour changes from yellow to grey. Histological studies have shown that these flecks represent aggregates of swollen RPE cells engorged to 10 times their normal size with lipofuscin. Occasionally, the clinical findings in STGD1 may be minimal or atypical. The yellow flecks may be absent, especially in young children, or may be quite small in size and number. Some individuals demonstrate minimal fundus abnormalities with a heavily pigmented RPE that is easy to overlook ('vermillion fundus') [23]. With progression of the disease, atrophy of the RPE in