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Adult-onset foveomacular vitelliform dystrophy: A fresh perspective

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ABSTRACT

Adult-onset foveomacular vitelliform dystrophy (AFVD) was first described by Gass four decades ago. AFVD is characterized by subretinal vitelliform macular lesions and is usually diagnosed after the age of 40. The lesions gradually increase and then decrease in size over the years, leaving an area of atrophic outer retina and retinal pigment epithelium. This process is accompanied by a loss of visual acuity. Vitelliform lesions are hyperautofluorescent and initially have a dome-shaped appearance on optical coherence tomography. The electro-oculogram and full-field electroretinogram are typically normal, indicating localized retinal pathology. Phenocopies are also associated with other ocular disorders, such as vitreomacular traction, age-related macular degeneration, pseudodrusen, and central serous chorioretinopathy. A minority of AFVD patients have a mutation in the *PRPH2*, *BEST1*, *IMPG1*, or *IMPG2* genes. A single-nucleotide polymorphism in the *HTRA1* gene has also been associated with this phenotype. Accordingly, the phenotype can arise from alterations in the photoreceptors, retinal pigment epithelium, and/or interphotoreceptor matrix depending on the underlying gene defect. Excess photoreceptor outer segment production and/or impaired outer segment uptake due to impaired phagocytosis are likely underlying mechanisms. At present, no cure is available for AFVD. Thus, the current challenges in the field include identifying the underlying cause in the majority of AFVD cases and the development of effective therapeutic approaches.

Contents

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1. Introduction

Adult-onset foveomacular vitelliform dystrophy (AFVD) is one of the most prevalent forms of macular degeneration. When first described by Gass in 1974, this phenotype was initially called “peculiar foveomacular dystrophy” (Gass, 1974). It was later renamed adult-onset foveomacular vitelliform dystrophy (AFVD), and has since been classified as one of several forms of pattern dystrophy (PD) (Gass, 1997). Following Gass' initial description, several groups have reported patients with a similar phenotype. Thus, the nature of the underlying pathology, the potential role of genetics in the etiology, and the composition and location of the vitelliform lesion has become the subject of intense interest and debate.

AFVD has traditionally been included in the heterogeneous group of PDs which also includes the phenotypes of butterfly-shaped pigment dystrophy (BPD), reticular dystrophy of the retinal pigment epithelium, pseudo-Stargardt pattern dystrophy (multifocal pattern dystrophy simulating Stargardt disease/fundus flavimaculatus), and fundus pulverulentus. The term PD itself was suggested by Marmor and by Hsieh to describe dystrophies affecting the retinal pigment epithelium (RPE) (Marmor and Byers, 1977; Hsieh et al., 1977). However, some of the aforementioned PDs, including AFVD, pseudo-Stargardt pattern dystrophy, and butterfly-shaped pigment dystrophy have been associated with mutations in the same gene, *PRPH2*, which encodes the photoreceptor (and not RPE) protein peripherin-2, which has an important structural role in the photoreceptor outer segments (Boon et al., 2007b, 2008a). Typically, eyes affected by PDs show various patterns of progressive RPE alterations often accompanied by deposition of yellow-dark subretinal material involving the macula and posterior pole.

The age at onset in PDs is highly variable, but, patients tend to remain asymptomatic until the 5th decade, or may even remain asymptomatic throughout life. The course of PDs is relatively benign, although severe vision loss occurs in up to 50% of the affected individuals after the age of 70, as a result of chorioretinal atrophy and/or the development of choroidal neovascularization (Yang et al., 2003; Francis et al., 2005). Patients may show different subtypes of PD in each eye, or PD forms which do not fit one specific subtype, suggesting clinical and pathogenetic overlap of the PDs, in particular by AFVD and BPD (Sections 2.3 and 4).

Unfortunately, several different terms have been used over the years when describing AFVD. These terms include adult macular vitelliform degeneration (Glacet-Bernard et al., 1990), adult vitelliform macular degeneration (Epstein and Rabb, 1980; Greaves et al., 1990; Theischen et al., 1997), pseudovitelliform macular degeneration (Sabates et al., 1982), adult-onset foveomacular pigment epithelial dystrophy (Vine and Schatz, 1980), adult foveomacular vitelliform dystrophy (Burgess et al., 1987; Benhamou et al., 2003), and adult vitelliform macular dystrophy (Brecher and Bird, 1990; Renner et al., 2004). The generic term adult vitelliform lesion was also used to describe vitelliform lesions in adults that do not necessarily have genetic origin. This wide diversity in nomenclature has led to considerable confusion among clinicians, researchers, and patients, and it might account—at least in part—for this condition's high misdiagnosis rate (Renner et al., 2004). This variable terminology reflects the lack of consensus with respect to the diagnostic criteria and pathogenesis of AFVD.

In this review, Gass' term adult-onset foveomacular vitelliform dystrophy will be used exclusively to describe the phenotype, regardless of the underlying specific genetic cause, family history, and/or age of onset (provided the onset occurred in adulthood). This original term, AFVD, describes the phenotype appropriately with regard to its age at onset, clinical aspect, and its genetic component. For phenocopies which are assumed not to be with a genetic cause (central serous chorioretinopathy, vitreomacular traction, etc.; Section 2.3) the term “acquired vitelliform lesion” may be more appropriate as it does not commit to genetic predisposition (Freund et al., 2011). However, while Gass' terminology suggests that AFVD is a dystrophy, a significant fraction of cases may in fact not be monogenic and could thus be better described with the term degeneration which will be discussed further in Section 6. Furthermore, any precise definition of the AFVD phenotype should take into consideration the fact that vitelliform lesions can be associated with a wide variety of underlying diseases. Because these associations were not recognized fully by Gass when AFVD was originally described, the definition of AFVD should be revisited (see Section 6).

The review summarizes the knowledge and insights regarding AFVD obtained in the 40 years since its original description. We will discuss the clinical, histological, genetic, imaging, and functional characteristics of AFVD, and we will conclude with a comprehensive overview of our current understanding of AFVD and its putative causes.

2. Clinical characteristics of adult-onset foveomacular vitelliform dystrophy

2.1. The adult-onset foveomacular vitelliform dystrophy phenotype

In his original description of nine cases, Gass suggested that AFVD typically manifests between 30 and 50 years of age, presenting with bilateral subfoveal yellowish deposits covering approximately one-third of the disc area, with a central pigmented spot (Fig. 1). Over time, the lesion's pigmentation may become