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Best vitelliform macular dystrophy: literature review

Review Article

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Abstract: Best vitelliform macular dystrophy (BVD) is a slowly progressive form of macular dystrophy. In most cases this disease begins in childhood although sometimes it can develop in later age. The diagnosis of BVD is based on family history, clinical and electrophysiological findings. Clinical signs are variable, yet the majority of patients have a typical yellow yolk-like macular lesion in the eye fundus. Lesions are usually bilateral, but in rare cases can be unilateral. Atrophy of the macula may develop after many years. The mutations responsible for Best vitelliform macular dystrophy are found in a gene called VMD2, which encodes a transmembrane protein named bestrophin-1 (hBest1) that is a Ca^{2+}-sensitive chloride channel. Most reported cases causing the disease are in exons 2, 4, 6 and 8 in patients with BVD. In this article we discuss the etiology of Best's vitelliform macular dystrophy, clinical presentation, diagnostics, genetic and current treatment possibilities.

Keywords: *Best vitelliform macular dystrophy • Ethiology • Pathogenesis • Clinics • Genetics*

1. Introduction

Best vitelliform macular dystrophy (BVD) is also known as Best disease, named after German ophthalmologist Friedrich Best, who in 1905 has described a family with a history of early-onset macular degeneration [1]. BVD can also be named BEST, BEST1_HUMAN, BMD (Best Macular Dystrophy), vitelliform macular dystrophy 2 (Best disease, bestrophin), VMD (Vitelliform Macular Dystrophy). Although Best disease is the second most common form of juvenile macular degeneration, with an onset usually before 15 years of age, only about 1% of all cases of macular degeneration can be attributed to Best disease [2]. However, the degree of central vision impairment and the age of onset of symptoms vary widely, even among members of the same family [3-5]. Booij et al. found that median age at the onset of visual symptoms was 33 years (range: 2-78) [6]. The cumulative risk of visual acuity (VA) below 0.5 was 50% at 55 years and 75% at 66 years, and the cumulative risk of decline less than 0.3 was 50% by the age of 66 years and 75% by the age of 74 years in BVD patients [6].

The disease is known as vitelliform (shaped like an egg yolk) macular dystrophy, with reference to the yellow macular lesions associated with the condition [7]. The Best disease has many similarities with age-related macular degeneration, which is the leading cause of vision loss among the elderly population in the western world [8]. BVD is a dominantly inherited macular dystrophy with very variable expression [9]. The yellow material is gradually resorbed over the time, leaving atrophic area of the retinal pigment epithelium (RPE) and often leading to subretinal fibrosis. Patients at the beginning of disease have normal vision. Later central visual acuity decreases and metamorphopsia starts. Patients have normal peripheral vision and dark adaptation. Combination of abnormal electro-oculography (EOG) with normal classic full-field electroretinography (fERG) is a hallmark of this disease however the macular flicker or multifocal electroretinogram (mfERG) may show reduced amplitudes in the central parts even during early stages [10].

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In this article we discuss about the prevalence of Best's vitelliform macular dystrophy, its etiology, clinical presentation, diagnostics, differential diagnostic, genetic and current possibilities for treatment.

2. Prevalence

The prevalence of Best disease is yet unknown, as BVD is a rare disorder. Best disease is found in individuals of European, African, and Hispanic ancestry. Although most commonly described in Caucasians, Best's has also been described in isolated case reports of Asian population [11]. In African Americans, an association of BVD with sickle cell trait has been reported [12].

3. Etiology

The condition mainly occurs in families with a history of Best disease but sometimes sporadic cases may apppear. Best disease is an inherited disease with an autosomal dominant pattern of inheritance, whereby, a person is affected if one of the two copies of the Best gene is abnormal. The children of an affected individual have 50 percent chance of inheriting the abnormal copy of the Best disease gene. A child who inherited the normal copy of the Best disease gene will not contract the disease and cannot pass the diseased gene to his or her children. The mutations responsible for Best vitelliform macular dystrophy are found in a gene called VMD2 that is located on chromosome 11q13 [13]. The VMD2 gene encodes a transmembrane protein named bestrophin-1 (hBest1), which is a Ca^{2+}-sensitive chloride channel [14].The protein is located in basolateral plasma membrane of RPE cells [15]. Abnormal chloride conductance across the basolateral membrane of RPE may lead to accumulation of fluid and/or debris between the RPE and the Bruch membrane, leading to detachment and secondary photoreceptor degeneration [16].

4. Histopathology

The histopathology of BVD is not yet clear, and it may well be necessary to revise the hypothesis that photoreceptor damage may occur even earlier in the natural history of the disease, than previously believed. Indeed, in donor eyes from the BVD patients, retinal pigment epithelial and foveal photoreceptor loss were observed [17]. Frangieh et al. found fine granular deposits in the degenerating photoreceptors and in Müller cells, providing further evidence that the neural retina is an important locus of damage. Recent findings have indeed shown that cone function is impaired in the very early stage of the disease; hence, it cannot be excluded that a disease mechanism operates very early at the photoreceptor level [18].

5. Clinics

Typically, the disease starts in childhood although sometimes it may occur in adolescence. Usual onset of Best disease is between 3-15 years of age, with mean age of 6 years [19]. The onset of BVD is characterized by symptoms of metamorphopsia, blurred vision, and decrease of central vision. At the fundus a well circumscribed 0.5- to 2-disc– diameter "egg-yolk" lesion within the macula may be observed, they are located beneath the sensory retina, causing changes in the photoreceptor inner segment/outer segments [20]. The condition often is not detected until much later stage of the disease because visual acuity may remain sufficient for many years. The atrophic stage usually occurs after the age of 40. Most individuals diagnosed with Best vitelliform macular dystrophy have an affected parent, however disease can be caused by de novo mutation [14,21]. Although instances of germline mosaicism have not been reported, this still remains a possibility when the parents test negative for BVD [21,22]. Asymptomatic carriers (heterozygotes without penetrance) can be detected by the presence of an abnormal EOG, which provides a valuable tool for genetic counseling [23]. Molecular testing via blood sample for the chromosome 11q13 gene can be used within those families affected with Best's. Hyperopia, esotropia, and strabismic amblyopia are commonly encountered in this disorder [24]. There are several stages in the disease development [20,21,25]. In stage 1, fundus appears normal but EOG is abnormal. In stage 2 (previtelliform stage) there are not changes present like in the 1st stage within 10 years or subtle RPE pigment changes exists, EOG is abnormal and fluorescein angiogram shows window defects. Visual acuity remains 20/20 in 75% persons. Stage 3 (vitelliform stage) consists of circular, well circumscribeed, yellow-opaque, 0.5-5 mm, yolk-like macular lesions. The remaining part of fundus usually has normal appearance. Rare lesions may be multifocal. Fluorescein angiogram (FA) reveals marked hypofluorescence in the zone covered by lesion. VA is 20/20 to 20/50. Stage 4 (,,scrambled egg'' stage)–yellow colored vitelline substance breaks through retinal pigment epithelium and accumulates in the subretinal space and to form a cyst. The cyst is granular and lumpy resembling a ,,scrambled egg''appearance. This stage

most often is found in teenage years. FA shows partial blockage of fluorescence by vitelline material, along with superior hyperfluorescent defects. VA 20/50 or better. Stage 5 (cyst stage) At the site of disappearance of the egg yolk, atrophic pigment epithelium with the choroid shimmering through is commonly obesrved. FA shows partial blockage of hypofluorescence. VA is 20/100 or may be better. Stage 6 (pseudohypopyon stage) – the lesion develops fluid level of the yellow–colored vitelline material. FA shows inferior hypofluorescence from the blockage by the vitelline substance, along with superior hyperfluorescent defects. VA markedly reduces to 20/100. Stage 7 (atrophic stage) is characterised by the hypertrophic scar and atrophic maculopathy. This appearance is difficult to distinguish from another cases of macular degeneration. FA shows hyperfluorscece without leakage. VA markedly reduces to 20/200. Later subretinal neovascular membrane may develop leading to a disciform scar. Macula may have appearance of subretinal hemorrhage assosiated with choroidal neovascularization. The FA shows hyperfluorescence as a result of neovascularisation and leakage.

6. Ophthalmological evaluation

Visual aquity and visual field primarily are tested. Pacients have good visual acuity but later visual fields may show subtle central sensitity losses, while peripheral visual field is normal [26,27]. Jarc-Vidmar M et al. evaluated mapping of central visual function by microperimetry (MP) and autofluorescence in patients with Best's vitelliform dystrophy [28]. High correlation (R=0.75, -0.76, -0.48) was found between static perimetry (MS, MD and CLV indices) and MP [28]. Results showed that microperimetry enabled a highly sensitive topographic monitoring of retinal function, showing central or pericentral fixation in the early stages, until loss of central function, in the eyes with visual acuity 0.2 or less has caused evident shift of fixation to preferential retinal locus (PRL) [28]. PRL was never situated inside the central uniform hypofluorescent area, but corresponded with the hyperfluorescent ring seen by the autofluorescence imaging [28]. Progression of BVD, indicated with deterioration of VA and more dense central scotomas were detected with static perimetry, which showed a high correlation with MP results [28].

Use of other test, like fluorescein angiography, RPE autofluorescence, optical coherence tomography, full-field and multifocal electroretinogram, could hel to add additional information for the correct diagnosis of BVD. Many individuals with Best disease initially are asymptomatic, with fundus lesions noted upon examination. Sometimes during the first visit to the doctor the appearance of bilateral macular abnormalities is similar to the phenotype of patients with other macular dystrophies, e.g. Stargardt or cone dystrophies. Visual symptoms can include decreased acuity (blurring) and metamorphopsia. These symptoms may worsen if the disease progresses to the atrophic stage [20,29,30]. Since visual acuity remains normal for a long time, the atrophy starts only in the fifth decade of life, hence the BVD is commonly diagnosed late [20]. Best disease diagnosis is based on electro-oculogram abnormalities, with complete absence of light-induced rise (abnormalities present even in asymptomic patients).The EOG measures the electrical potentials across the RPE showing diffuse dysfunction of the retinal pigment epithelium (Deutmann 1971) [16,31]. The Arden ratio represents the ratio of the light peak divided by the dark trough and is redused in Best disease. A normal light peak/dark ratio (Arden ratio) is greater than >1.8. In individuals with Best disease the EOG is abnormal, with Arden ratio less than <1.5, most often 1.0 and 1.3 [21,31-33]. Most patients carrying mutation in the VMD2 gene (11p13) have an abnormal EOG, although they do not present with clinical complaints, and their macular appearance may be normal [15]. The EOG is markedly depressed, a finding that may precede any ophthalmoscopic or clinical evidence of abnormality [10,33]. This indicates that the degenerative process is not confined to the macula, but probably includes more widespread involvement of the retinal pigment epithelium, Bruch's membrane, or the potential space between these two layers [10]. EOG might also be helpful in preclinical detection or in asymptomatic carriers of Best gene [27]. Another test for Best disease is the electroretinogram (ERG), which measures the electrical responses of the rods and cones in the retina as well as ganglion cells. In patients with Best disease this test is usually normal. Slight reduction in wave amplitudes may be seen. The full-field elecroretinogram is normal. Foveal ERG or multifocal ERG reveals reduced central amplitudes [32]. Scaning laser ophthalmoscope-evoked multifocal ERG (SLO-mfERG), reveals significantly reduced amplitudes in the macula (SLO-mfERG used for topographic mapping of retinal function in individuals with BVD) [34]. There are some ancillary tests like dark adaptation and color contrast sensitivity. Dark adaptometry is almost normal, while color defects may be noted and they are proportional to the degree of visual loss. A significant proportion of individuals have anomalous color discrimination paticulary in the protan axis. But changes in color vision are non-specific and non-diagnostic [5]. Optical coherence tomography (OCT) findings for example change depending on the stage of the disease. OCT has

defined normal retinal architecture or subtle changes in the outer retina in previtelliform clinical stages, splitting and elevation at the outer retina-retinal pigment epithelium complex in intermediate clinical stages, and thinning of the retina and retinal pigment epithelium in the atrophic clinical stage [5]. Spectral-domain optical coherence tomography makes it possible to detect defects in the layers of cones and the pigment epithelium [35]. Late stages of the disorder, associated with retinal pigment epithelium degeneration, may be difficult to differentiate from other types of macular degeneration. Fundus fluorescein angiography – blockage effect by vitelliform material on fluorescein angiography in early stage of BVD, and hyperfluorescence with or without leakage in the late stage of disease [21]. Maruko et al. described the results of indocyanine green angiography in 8 patients with BVD [36], that were also compared with findings from ophthalmoscopy and fluorescein angiography [36]. These results demonstrated a number of hyperfluorescent spots in all eight eyes, and the spots were observed in the midperiphery and the periphery in the areas without visible presence of abnormality, using ophthalmoscopy or fluorescein angiography [36]. Fundus autofluorescence – widespread BVD lesions with accumulation of lipofuscin in RPE were hyperfluorescent and the intensity of fundus autofluorescence has paralleled the amount and distribution of lipofuscin [14].

7. Genetics

BVD is inherited in an autosomal dominant manner. Mutations in the BVD gene named BEST1 (formerly VMD2; MIM 153700) is mapped to a region on longer arm of chromosome 11 q12-q13, that was identified in 1998 [15]. BEST1 codes for a 585 amino acid transmembrane peptide with size of 68 kDa, named bestrophin1 and is required for normal ocular development [37,38]. BEST1 mRNA is expressed mainly in the retina, especially in the basolateral plasma membrane of retinal pigment epithelial cells although some expression has also been detected in the kidney, brain, spinal cord, and testis [39]. The protein product of VMD2, bestrophin, has been localized to the basolateral plasma membrane of the RPE where it forms a component of chloride channel responsible for maintaining chloride conductance across the basolateral membrane of the RPE. Mutations in BEST1 gene alter the function of bestrophin and ion transport by the RPE, resulting in the accumulation of fluid and/or debris between RPE and photoreceptors, and between RPE and Bruch's membrane, thus leading to detachment and secondary photoreceptor degeneration [40, 41]. At least 253 mutations of this gene have been described (VMD2_database), very large majority of which are missense mutations [42]. The clinical features in patients with mutations in BEST1 comprise of four major categories: Best vitelliform macular dystrophy or Best disease (BVMD, OMIM 153700)), adult-onset vitelliform macular dystrophy (OMIM 608161), autosomal dominant vitreoretinochoroidopathy (OMIM 193220) and autosomal recessive bestretinopathy (ARB, OMIM 611809) [41]. Recently, missense mutations of BEST1 have been implicated in retinitis pigmentosa [41]. Most reported cases presented BEST1 gene with missense mutations causing the disease in exons 2, 4, 6 and 8. The variable expression of Best disease remains unexplained and other genes in addition to VMD2, and/or environmental factors may be at play.

8. Differential diagnosis

Best disease should be differentiated from the other types of dystrophy, like dystrophy of the central part of retina and choroid (Table 1), central chorioretinitis, serous retinal pigment epithelium detachment, colobomas of the central retina, age-related macular degeneration or foveal changes in angioid steaks [16].

9. Treatment

There is not a causal treatment of Best vitelliform macular dystrophy. Anti-VEGF (vascular endothelial growth factor) agents such as bevacizumab are used increasingly to treat individuals with choroidal neovascularization (CNV) [63]. Intravitreal bevacizumab appears to be a promising and cost-effective modality of treatment in CNV associated with BVD with good visual recovery [63]. Long-term follow-up of these patients is unknown. There are not as yet clinical trials to demonstrate the effectiveness of anti-VEGF agents on CNV in Best vitelliform macular dystrophy. Although the pharmacokinetics of anti-VEGF agents have been studied in the adult population, not as much is known in the pediatric population [64]. These medications can inhibit normal retinal vasculogenesis, revascularization, and organogenesis [64]. These are important considerations when treating children. We must consider both the local and systemic risks and benefits of any treatment prior to its use [64]. Only A few select case reports have been published discussing positive results using intravitreal anti-VEGF agents in the treatment of choroidal neovascularization secondary to Best disease in children [64]. Frennesson et al. performed photodynamic therapy using verteporfin for subfoveal choroidal neovascularization in a single

Table 1. Differential diagnosis of Best vitelliform macular dystrophy

Disorder	Inheritance	Gene associated with disorder	ERG	EOG	Dark adaptation
Best disease (Best vitelliform macular dystrophy) [7,16,43]	AD	VMD2(11p13)	N	A	N
Dominant progressive foveal dystrophy (autosomal dominant Stargardt) [16,44]	AD	ELOVL4(6q14) PROML1(4p)	N	N	N
Stargardt macular dystrophy and fundus flavimaculatus [16,45,46]	AR	ABCA4(1p21-p13), CNGB3(8q21-q22)	N/S	N	N
Adult-onset vitelliform macular dystrophy [16,47]	AD	Peripherin/RDS (6p)	N	N	-
Pattern dystrophy: 1. Butterfly-shaped pigment dystrophy of the fovea [16,48]	AD	Peripherin/RDS (6p)	N	A	N
2.Reticular-like dystrophy of the RPE [16,48]	AD /AR		N	A	N/A
3. Macroreticular dystrophy of the RPE [16,48]	AD /AR		N	A	-
Doyne honeycomb retinal dystrophy [49,50,51]	AD	EFEMP1(2p)	A	N/A (6:2)	A
Autosomal dominant drusen and macular degeneration [52]	AD	6q14	N	N	N
North Carolina macular dystrophy [53,54]	AD	6q16	N	N	-
Progressive bifocal chorioretinal atrophy [16,55]	AD	6q14-q16.2	A	A	-
Sorsby fundus dystrophy [56-59]	AD	TIMP3(22q)	N	N	N
Central areolar choroidal dystrophy [16,60]	AD	Peripherin/RDS	N	N	N
Dominant cystoid macular dystrophy [16,61]	AD	7p15-p21	N	A	-
X linked inheritance [16,62]	Linked with X chromosome	XLRS1(Xp22.2)	A, ↓ b wave	N	N

Disorder	Prevalence	Visual acuity (VA)	Color vision disturbancies	Visual field
Best disease (Best vitelliform macular dystrophy) [7,16,43]	Prevalence not known	VA remains without disturbancies for a long time	Protanopic color vision disturbancies	Relative central scotomas early in the disease, with more dense scotomas being noted after degeneration and organization of the macular lesions.
Dominant progressive foveal dystrophy (autosomal dominant Stargardt) [16,44]	Rare	Decreased central vision. VA 20/20 to 20/400	Mild defective color vision	Central scotoma
Stargardt macular dystrophy and fundus flavimaculatus [16,45,46]	1:8000 - 1:15000	VA 20/200 to 20/400	Moderately defective red and green color vision	Central scotoma
Adult-onset vitelliform macular dystrophy [16,47]	Prevalence not known	Usually normal central vision in early stages. VA 20/30 to 20/60 (may be worse if neovascolaristion occurs)	Mild tritan defect	Small central scotoma
Pattern dystrophy: 1. Butterfly-shaped pigment dystrophy of the fovea [16,48]	Prevalence not known	VA 20/25 to20/40	Not disturbed	Relative central scotoma with normal peripheral fields
2.Reticular-like dystrophy of the RPE [16,48]		Normal VA, loss of vision may occur later	Not disturbed	Normal visual field
3. Macroreticular dystrophy of the RPE [16,48]		VA 20/30 to 20/70		Relative central scotoma with normal peripheral fields

CONTINUED **Table 1.** Differential diagnosis of Best vitelliform macular dystrophy

Doyne honeycomb retinal dystrophy [49,50,51]	Rare	VA is maintained through the fifth decade, but patients usually become legally blind by the seventh decade	From mild to severe defective color vision	
Autosomal dominant drusen and macular degeneration [52]	Prevalence not known	VA 20/30 to20/100 or 20/200	Not disturbed	Central scotoma
North Carolina macular dystrophy [53,54]	Rare	Central vision disturbancies starts in fifth – sixth decade	Not disturbed	Small central or paracentral scotomas
Progressive bifocal chorioretinal atrophy [16,55]	Rare	VA ≤ 20/200	Moderately defective yellow and blue color vision	Paracentral scotomas and peripherical visual field defects
Sorsby fundus dystrophy [56-59]	1:100000	VA ≤ 20/200	Tritanopic color vision disturbancies	Normal; (central scotoma if macular lesions)
Central areolar choroidal dystrophy [16,60]	1-9:100000	VA 20/25 to 20/200	Moderately protan-deutan defective or not disturbed color vision	Large central scotoma
Dominant cystoid macular dystrophy [16,61]	Rare	VA 20/200	Moderately defective blue and yellow color vision	Relative-to-absolute central scotoma
X linked inheritance [16,62]	1:5000, 1:25000	VA20/40 to 20/100	Mild defective red and green color vision	Relative central scotoma, absolute visual field defects corresponding to zones of peripheral retinoschisis are present

Disorder	Fundus presentation	Fluorescein angiography (FA)
Best disease (Best vitelliform macular dystrophy) [7,16,43]	Yellow – orange, circular, yolk-like, subretinal macular lesions.Later may develop subretinal neovascularisation ans scarring. Fundus appearance may be normal in early stages.	Hypofluorescence of the vitelliform lesion due to blockage of dye transmission the vitelline material in early stage.Depending on disease stage FA may reveal defects (window defects, blockage, in later stages leakage as result of neovascularisation)
Dominant progressive foveal dystrophy(autosomal dominant Stargardt) [16,44]	Fundus view and flecks as in fundus flavimaculatus.	Irregular PRE transmision within fovea; occasional „bull-eye" pattern of tranminssion; nonperfusion of choriocapillaris in advance cases
Stargardt macular dystrophy and fundus flavimaculatus [16,45,46]	Typical macular atrophy with white RPE spots (flecks).	Generalized decreased choroidal fluorescence (dark choroid); flecks demonstrate early blockage and late fluorescent staining. Irregular PRE transmision within fovea; occasional „bull-eye" pattern of tranminssion
Adult-onset vitelliform macular dystrophy [16,47]	Yellow circular, wellcircumscribe, symetrical 0.5-5mm yolk like macular lesion.	Small, irregular ring of hyperfluorescence surrounding a central hypofluorescent spot; no evidence of perifoveal fluorescein dye leakage
Pattern dystrophy: 1. Butterfly-shaped pigment dystrophy of the fovea[16,48]	Bilateral symetrical yellow-orange deposits at the macula in various distributions. FAG shows RPE pigmentary disturbance.	Reticular hypofluorescent pattern corresponding to areas of hyperpigmentation
2.Reticular-like dystrophy of the RPE [16,48]		Net-like hypofluorescent pattern corresponding to reticular hyperpigmentation
3. Macroreticular dystrophy of the RPE [16,48]		Reticular hypofluorescent pattern corresponding to areas of hyperpigmentation
Doyne honeycomb retinal dystrophy [49,50,51]	Multiple, small, round yellow-white drusen-like deposits under the RPE, distributed at the macula and around the optic disc.	Early blockage of transmission of possilbe late staining; irregular dye trasmission and leakage depending on degree of associated degenerative change

CONTINUED **Table 1.** Differential diagnosis of Best vitelliform macular dystrophy

Autosomal dominant drusen and macular degeneration [52]	Bilateral symmetrical drusen at the macula or congenital atrophic maculopathy. Early onset in children or young adults.	Early blockage of transmission of possilbe late staining
North Carolina macular dystrophy [53,54]	Bilateral, symmetrical, from a few small yellow drusen-like lesions to large confluent lesions or colobomatous lesions in central macula.	PRE transmission defects and late staining if drusen-like lesions. Later nonperfusion of choriocapillaris
Progressive bifocal chorioretinal atrophy [16,55]	Progressive macular and nasal retinal atrophic lesions, accompanied by myopia and nystagmus.	FA shows a large circumscribed area of macular choroidal atrophy with staining of deposits in the peripheral retina
Sorsby fundus dystrophy [56-59]	Yellow-white deposits (which are not drusen) in macula extends on nasal optic disc side, are associated with atrophic macular degeneration. Later subretinal haemorrhage may occur as complication of choroidal neovascularisation.	Window defect on FA and leakage if choroidal neovascularisation occurs
Central areolar choroidal dystrophy [16,60]	Pigmentary disturbance and subtle mottling in early stages, later progresses to atrophy of the RPE and choriocapillaris.	FA shows faint areas of hyperfluorescence within the fovea corresponding to RPE transmission defects. Later sharp demarcated zone of chorioretinal atrophy with no choroidal fluorescence
Dominant cystoid macular dystrophy [16,61]	Cystoid macular oedema with leakage on fluorescein angiography.	Fluorescein angiography reveals leakage from perifoveal capillaries with dye pooling in a cystoid pattern. Later in the disease, transmission defects are seen in areas of RPE atrophy
X linked inheritance [16,62]	Fundus abnormalities varies from a cystic spokewheel-like maculopathy to bilateral schisis cavities, vascular closure, inner retinal sheen, and pigmentary retinopathy. Macular lesions may change appearance later.	Most often appears normal posterior pole on FA

person with Best vitelliform macular dystrophy [65]. VA decreased during follow-up from 0.5 (20/40) to 0.08 (20/250) due to a subfovealneovascularization with haemorrhage, and after treatment the haemorrhage resolved within 2 months, and VA had increased to 0.25 (20/80). One year later, acuity had improved to 0.5 (20/40), and this result was stable throughout the 7 years of the follow-up. PDT seemed to be beneficial also in a long-term follow-up [65]. Resolution of subretinal hemorrhage and regression of CNV as well as exudative manifestations occurred after PDT. Photodynamic therapy may be a viable treatment for subfoveal neovascular macular lessions in Best vitelliform macular dystrophy. Individuals with BVD should be regularly monitored by an ophthalmologist, who will also assess vision and the need for visual aids. Visual habilitation and rehabilitation should be carried out in cooperation with an ophthalmologist and a vision resource centre. Interventions should be planned out to meet the needs of the individual affected by the BDV. Pedagogical, technical, psychological and social support are typically equally adapted to the age and lifestyle of affected persone. Therea re visual aids, such as magnifiers, special eye wear for close-up work, enhanced-vision TV systems and computers, that are available and may be provided for training the affected individuals. Compensating techniques such as braille and using a cane to facilitate mobility should be considered. It is important to offer psychological support to the patient, both at the time of diagnosis and later. In additio, children and young people should be offered psychological support, adapted to their individual needs.

Gene therapy is a promisisng therapy for treating inherited macular dystrophies and other types of genetic diseases. As an example, in March 2010 the FDA the Food and Drug Administration granted orphan drug status to Advanced Cell Technology (Worcester, Mass) to test the human embryonic stem cells as a treatment for the Stargardt's form of macular dystrophy, with the idea of regenerating damaged cells to support function of photoreceptors. Human clinical trials are expected to begin in the near future, and some clinical trials of gene therapy for retinal diseases are in phase I or III of clinical study. The eye, in particular, is an attractive target for gene therapy for several reasons. The eye is one of the few immunologically privileged sites in the body, so the gene vectors used are unlikely to cause a systemic immune response [66]. Given the defined volume of the

eye, small amounts of viral vectors may be all that are necessary to achieve therapeutic effects – likely to be a positive for reducing the risk of toxicity and increasing the likelihood of being able to manufacture quantities of vector sufficient to treat the retina [66]. The eye also allows for localized treatment without intravenous delivery, thus decreasing the chance of systemic absorption and toxicity, and the effects of localized ocular treatments can be easily observed and monitored for efficacy and safety, something that cannot be readily done with systemic conditions [66]. With these advantages in using the eye as a target for gene therapy, and the continued understanding of gene mutations and their role in retinal diseases, investigators are actively determining the potential for gene therapy in different conditions.

Kachi et al. (2005) in the study explored the use of electroporation or media that promote lipoplex formation for nonviral gene transfer in the eye [67]. was no detectable staining for LacZ after subretinal, intravitreous, or periocular injection of a plasmid containing a Cytomegalovirus (CMV) promoter expression cassette for LacZ, but when plasmid injection in each of the three sites was combined with electroporation, there was efficient transduction [67]. These data suggest that electroporation or lipofection can be used as experimental tools for ocular gene transfer to evaluate tissue-specific promoter fragments or to evaluate the effects of transgene expression in the retina, also, with additional optimization, nonviral gene transfer may prove to be a valuable approach for the treatment of retinal and choroidal diseases [67]. In the later studies Kachi et al. (2009) proved that equine infectious anemia viral vector-mediated codelivery of endostatin and angiostatin driven by retinal pigmented epithelium-specific VMD2 promoter inhibits choroidal neovascularization [68]. Equine infectious anemia virus (EIAV) is a nonprimate lentivirus that does not cause human disease. Subretinal injection into mice of a recombinant EIAV lentiviral vector in which lacZ is driven by a CMV promoter (EIAV CMV LacZ) resulted in rapid and strong expression of LacZ in retinal pigmented epithelial (RPE) cells and some other cells including ganglion cells, resulting in the presence of 5-bromo-4-chloro-3-indolyl-beta-D-galactopyranoside within the optic nerve [68]. Substitution of the RPE-specific promoter from the vitelliform macular dystrophy (VMD2) gene for the CMV promoter resulted in prolonged (at least 1 year) expression of LacZ that was restricted to RPE cells, albeit reduced 6- to 10-fold compared with the CMV promoter. Compared with murine eyes treated with a control EIAV vector, subretinal injection of EIAV vectors expressing murine endostatin alone or in combination with angiostatin driven by either the CMV or VMD2 promoter caused significant suppression of CNV at laser-induced rupture sites in Bruch's membrane [68]. These data support proceeding toward clinical studies with EIAV-based gene therapy for choroidal NV, using the VMD2 promoter to selectively drive expression of a combination of endostatin and angiostatin in RPE cells [68].

10.Genetic counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance and implications of genetic disorders to help them make informed medical and personal decisions [69]. Each child of an individual with Best disease has a 50% chance of inheriting the mutation. The proportions of cases caused by de novo mutations is unknown. Prenatal testing is possible for families in which the disease causing mutation is known. The optimal time for determination of genetic risk and discussion of availability or prenatal testing is before pregnancy [69]. Genetic counseling and discussion of potential risks to offspring and reproductive option is recomended to young adults who are affected or at risk. Prenatal test for BVD is not common, because the condition not affect intellect or life span. However th eage onset, clinical manifestations of the disease and degree of functional impairment in an affected person cannot be predicted [69].

11.Prognosis

Prognosis usually refers to the likelihood of outcomes of BVD. The prognosis of Best vitelliform macular dystrophy may include duration and possibility of complications of the disease. Booij et al. (2010) described that age of the onset of visual symptoms varies greatly among patients with BVD [6]. All patients show a gradual decrease in VA, and most progress to visual impairment at a relatively late age [6]. Atrophy of the macula may develop after many years and most patients retaining reading vision till the fifth decade of life [6].

Over 253 different BEST1 mutations have been described in patients with Best vitelliform macular dystrophy [70]. Some authors suggest that we cannot speculate a genotype-phenotype correlation [16], some found, that genotype-phenotype correlation was limited [71], but some others suggest, that prognosis might be associated with genotype [6]. Family members with the VMD2 gene mutation and who have minimal macular abnormality or a normal fundus appearance (but abnormal EOG) in early adult life, usually retain near normal visual acuity long term [16]. There is great phenotypic

variability among patients carrying these mutations in BEST1 gene. Most individuals carrying mutations in the VMD2 gene have an abnormal EOG, but the macular appearance may be normal in some [16]. There is only one individual reported with evidence of non-penetrance, in that he is a mutant VMD2 gene carrier with a normal fundus examination and normal EOG [72]. The variable phenotype in dominant heterozygous Best VMD is highlighted in most studies [73,74]. Compound heterozygous, biallelic recessive or homozygous dominant mutations in BEST1 may confer a particulary severe phenotype, featuring retinal lesions, in additional to VMD [75]. Different mutations might cause Best disease by different mechanisms. However, there seems to be no clear pattern relating type of BEST1 mutation to severity clinical expression [43]. Booij et al. (2010) data suggest a phenotype-genotype correlation, because the Ala10Val mutation has a more rapid disease progression than other common mutations [6]. Other study found that the lesion area did not depend on the mutation (I295del and N99K) and did not correlate with visual acuity [16]. Boon CJ et al. examined 40 eyes of 20 patients with BVMD, and proved, that genotype-phenotype correlation was limited because a broad phenotypic variability may be observed in BVD, however, the p.Ala243Val seems to cause a mild and relatively invariable BVD phenotype [71]. Interestingly, a recent study described an asymptomatic 64-year-old patient with family history of Best disease with minimal ocular findings with Best disease caused by the c.653G>A mutation in BEST1 [76].

Environmental factors or unknown modifier genes could modulate the phenotype in patients with BVD. A better knowledge of the spectrum of *BEST1* sequence mutations variants help to improve molecular diagnostic approaches and select patients for future therapeutic options [77].

Conflict of interest statement

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