Best disease

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Abstract
Best disease, or vitelliform macular dystrophy, is a rare bilateral macular dystrophy with autosomal dominant inheritance characterized by subretinal accumulation of yellowish material in the macular area. Penetrance and clinical expression of Best disease vary greatly from one individual to another. Onset may occur in childhood or decades later. The typical vitelliform lesion shows an egg yolk-like appearing macular cyst measuring 0.5-3.0 disc diameters in size, and often has an asymmetric presentation. However, macular findings range from a small yellow spot, multiple vitelliform or atrophic lesions to a chorioretinal scar. Patients may complain of blurred vision, poor visual acuity, or metamorphopsia. The disease is slowly progressive and eventually results in atrophy of the retinal pigment epithelium (RPE) and photoreceptors, severely impairing central vision. Generally, orientation is normal and in most cases magnifying devices enable reading. Visual acuity cannot be predicted from the appearance of the macula. In typical Best disease the electro-oculogram (EOG) is usually abnormal, even in asymptomatic patients. Fluorescein angiography, RPE autofluorescence, OCT (optical coherence technology), full-field and multifocal electroretinogram (ERG) might add information for the correct diagnosis. Mutations in the VMD2 gene, mapped to 11q13, have been associated with Best disease. To date, there is no treatment for this disorder.

Keywords
Best disease, macular dystrophy, macular cyst, VMD2 gene, electro-oculogram
juvenile macular degeneration (Stargardt disease), fundus flavimaculatus, central areolar pigment epithelium dystrophy, cone dystrophy central); Sorsby fundus dystrophy, North Carolina macular dystrophy, Malattia Levantinese, retinopathy centralis serosa, central chorioretinitis, serous RPE detachment, colobomas of the central retina, age-related macular degeneration, foveal changes in angioid streaks.

Frequency
No reliable data are currently available.

Clinical description
Best disease is named after the German ophthalmologist Friedrich Best, who published the first pedigree presenting with this disorder in 1905. Eight persons were affected in the family reported by Best, and follow-up investigations (Vossius, 1921; Jung, 1936) increased the number to 22. Penetrance and clinical expression of Best disease vary greatly from one individual to another. The age of onset of manifest visual disability ranges from very early childhood to adolescence. Characteristically, funduscopic changes precede visual impairment. A yellow mass with the appearance of an “egg yolk” (hence the name) in the macular area later becomes deeply and irregularly pigmented and a process called “scrambling the egg” by Braley (1966) takes place. The characteristic foveal “egg yolk” is rarely present at birth. Optic disc, retinal vessels and retinal periphery are nearly always normal in patients with Best disease. Patients may complain of blurred vision, poor visual acuity, or metamorphopsia. Deutmann (1971) classified the evolution of Best disease in different stages which have been modified by Mohler and Fine in 1981:

**Stage 1: Normal fundus, abnormal electrooculogram (EOG)**
Fundus appears normal and only EOG is abnormal; carriers remain in this stage.

**Stage 2: Previtelliform stage**
The earliest visible lesions appear to be a yellow subfoveal pigment disturbance (mottling of the RPE, a small yellow spot).

**Stage 3: Vitelliform stage (“sunnyside-up egg yolk”)**
Usually apparition between age 3 and age 15. The classic vitelliform lesion appears at a later stage and is characterized by a yellow-orange, round, slightly elevated structure measuring 0.5-3.0 disc diameters in size. The cyst may remain intact for many years with maintenance of good visual function. Multifocal lesions may be seen.

**Stage 4: “Scrambled egg” stage**
The vitelliform disc develops into a cyst, in which vitelliform remnants can still be observed. The cyst shows a granular lumpy appearance resembling a “scrambled egg”. There might be slight reduction of vision (20/40).

**Stage 5: Cyst stage**
At the site of disappearance of the egg yolk, atrophic pigment epithelium with the choroid shimmering through is commonly observed.

**Stage 6: “Pseudohypopyon” stage**
Layering of the subretinal material occurs and is described as “pseudohypopyon”. The cyst is partially liquefied and reabsorbed.

**Stage 7: Atrophic stage**
Eventual rupture and reabsorption of the cyst, leaving an area of RPE atrophy and loss of central vision (20/200). A subretinal neovascular membrane may develop leading to a disciform scar. The development of the disorder can skip several of these stages. Extrafoveal lesions may also be present, including drusen and/or multiple extrafoveal vitelliform cysts. Fundus findings may range from small foveal lesions, reminiscent of pattern dystrophy, choroidal sclerosis atrophic lesions (geographic atrophy) or small deposits (reminiscent of fundus flavimaculatus). Examination of relatives can be helpful to establish differential diagnosis in those cases. It is impossible to predict visual acuity from the appearance of the macula. Decrease in visual performances can be dramatic, but is often asymmetric. Reduction of visual acuity is often due to atrophic macular changes resulting in a loss of rod and cone function. Sudden visual acuity loss may occur due to subretinal membranes.

Pathology
In 1988 O’Gorman et al. described the histopathologic findings in the postmortem eyes of a 69 year old man with this disorder. Retinal pigment epithelial cells across the entire fundus had accumulated an excessive amount of lipofuscin as defined by ultrastructural appearance, autofluorescence, and staining properties. An accumulation of heterogeneous material located between Bruch membrane and the pigment epithelium in the fovea was interpreted as representing a previtelliform lesion. The material appeared to be derived from degenerating pigment epithelial cells and contained few intact lipofuscin granules. Foveal
photoreceptor loss occurred above the lesion. Other light microscopic studies in young patients have also shown diffuse RPE abnormalities with accumulation of lipofuscin-like material in and under the RPE cells. The material was most prominent in the macular area, but was also present in the periphery (Weingeist et al. 1982).

**Genetics**

In 1992, Stone et al., who studied a 5-generation family with 29 affected members, demonstrated genetic linkage of Best disease to 11q13. In 1994, Weber et al. studied 3 large pedigrees with Best disease and refined the localization of the disease gene to the pericentromeric region of chromosome 11. In 1998, Petrukhin et al. identified the novel retina-specific gene designated VMD2. Evidence was provided that mutations within the VMD2 gene were a cause of the disorder (Petrukhin et al. 1998; Marquardt et al. 1998). Petrukhin et al. found that the VMD2 gene consists of 11 exons spanning a genomic region of 14.1 kb which encodes a 585-amino acid protein containing at least 4 putative transmembrane domains. VMD2 gene expression seems to be RPE specific. The only other site of VMD2 gene expression was Sertoli cells in mouse testis. The authors proposed the name 'bestrophin' for the protein encoded by the VMD2 gene.

In 2000, Marmorstein et al. demonstrated that bestrophin is localized in the basolateral plasma membrane of RPE cells, suggesting that bestrophin may play a role in causing electrooculographic alterations in Best disease. White et al. (2000) reported that 48 different mutations had been identified in the VMD2 gene associated with Best disease. Most of these mutations, being predominantly missense mutations, affect amino acids in the first 50% of the protein, and occur in 4 distinct clusters which possibly represent regions of functional importance.

In 2002, Sun et al. showed that the human, Drosophila, and C. elegans bestrophin homologs form oligomeric chloride channels and that human bestrophin is sensitive to intracellular calcium. They demonstrated that missense mutations associated with Best disease greatly reduce or abolish the membrane current. Four of these bestrophin mutants were coexpressed with the wildtype gene, and each of the mutants dominantly inhibited the wildtype membrane current, consistent with the dominant nature of the disorder. From these results, the authors suggested that VMD is a "channelopathy".

Qu et al. (2004) could show that mutations in mouse bestrophin-2 alter the relative permeability and conductance in the pore of the channel providing strong evidence that VMD2 forms part of the novel Cl(-) conduction pathway. However, in a rat model for Best disease Marmorstein et al. (2004) found that bestrophin does not directly generate the light-peak-conductance as expected if bestrophin would be a chloride channel. In an alternative hypothesis bestrophin appears as a regulator of voltage-dependent Ca(2+) channels assuming an indirect involvement of bestrophin in the generation of the light peak (Strauss and Rosenthal 2004). Further studies on either bestrophin-deficient mice or transgenic mice will show that either one of the hypotheses is right or maybe both will be proven correct, showing bestrophin as a Cl(-) channel and Ca(2+) channel regulator.

Another study found evidence of genetic heterogeneity in Best disease. In a large pedigree with a form of atypical vitelliform macular dystrophy (VMD1) Ferrell et al. (1983) demonstrated linkage to the glutamate pyruvate transaminase (GPT1) marker on chromosome 8q24. Early signs were minimal angiographic changes in the macula and peripapillary region, and small yellow lesions in the macula and periphery. Advanced depigmented lesions of the central and peripheral retina and peripapillary region were also documented in family members. EOG was not abnormal in all cases. However, it is not certain that this phenotype is genetically distinct from typical vitelliform macular dystrophy.

Finally, other genes, e.g. the peripherin/RDS gene (Wells et al. 1993), may cause a similar vitelliform dystrophy phenotype. Another retinal candidate gene at 11q13, the rod outer membrane protein-1 gene (ROM-1), has been excluded as a disease-causing gene for Best disease by a number of studies (Graff et al. 1994, Stohr et al. 1995).

**Diagnostic methods**

In patients with Best disease, or vitelliform macular dystrophy, the EOG is distinctly abnormal, with complete absence of a light-induced rise. The EOG measures the electrical potentials across the RPE showing diffuse dysfunction of the pigment epithelium (Deutmann 1971). The Arden ratio represents the ratio of the light peak divided by the darktrough and is reduced in Best disease. The EOG might also be helpful in preclinical detection or in asymptomatic carriers of the Best gene. Furthermore, examination of relatives is essential to diagnosis in advanced or atypical cases. However, in some cases presenting with vitelliform lesions, like in "pseudovitelliform macular dystrophy" or "adult onset Best disease", EOG may be normal (Gass 1974,

Fluorescein angiography, RPE autofluorescence, OCT (optical coherence technology), full-field and multifocal electoretinogram (ERG) might add information for the correct diagnosis.

Visual fields may show subtle central sensitivity losses, but the peripheral visual field is normal. Colour vision might be affected along the blue-yellow axis. Depending on disease stage fluorescence angiography may reveal defects (e.g. window defects, blockage).

Dark adaptation and electoretinography, including oscillatory potentials, are usually normal. In some patients the pattern or multifocal ERG was found to be abnormal (Power et al. 1990, Scholl et al. 2002). Massof and co-workers reported abnormal flicker fusion threshold intensities in Best patients (Massof et al. 1977). These studies indicate that Best disease affects the inner retina in the foveal region even at a stage when visual acuity is still normal or almost normal.

Management including treatment
To date, there is no causal treatment for this disorder. Management may include genetic counselling, as well as support concerning school or professional activities of patients. In case of visual acuity loss, magnifying low vision aids should be carefully and individually applied for optimal use of the remaining visual functions. Furthermore, clinical and/or genetic examination of other family members might be individually considered.

Genetic counseling
Best disease is transmitted in an autosomal dominant pattern. Consequently, an affected person is at 50% risk of transmitting the disease to his/her progeny.

Rarely, a "new mutation" might arise in an affected person. Typically, in such a case there is no other affected person known in the family, or clinical examination (e.g. EOG) is normal in all other family members. Concerning the next generation, the affected person will transmit the disorder in an autosomal dominant fashion.

There is an intrafamilial variation in disease severity. Sometimes, due to variable expression and reduced penetrance, Best disease manifestations may be so mild in affected members that there are no, or very few, symptoms. The age at onset of Best disease symptoms may also vary within the same family: some members can experience symptoms early in life, possibly in childhood, whereas other affected members may not develop symptoms until middle age.

Unresolved questions
The underlying biochemical defect in Best disease and the functional properties of VMD2 remain to be elucidated for developing therapeutic approaches.

References
Graff, C; Forsman, K; Larsson, C; Nordstrom, S; Lind, L; Johansson, K; Sandgren, O; Weissenbach, J; Holmgren, G; Gustavson, KH; Wadellius, C. Fine mapping of Best’s macular dystrophy localizes the gene in close proximity to but distinct from the D11S480/ROM1 loci. Genomics 24: 425-434, 1994.
Marmorstein, AD; Marmorstein, LY; Rayborn, M; Wang, X; Hollyfield, JG; Petrukhin, K; Bestrophin, the product of the Best vitelliform macular dystrophy gene (VMD2), localizes to the basolateral plasma membrane of the retinal pigment epithelium. Proc. Nat. Acad. Sci. 97: 12758-12763, 2000.
Marquardt, A; Stohr, H; Passmore, LA; Kramer, F; Rivera, A; Weber, BHF. Mutations in a novel


Petrukhin, K; Koisti, MJ; Bakall, B; Li, W; Xie, G; Marknell, T; Sandgren, O; Forsman, K; Holmgren, G; Andreasson, S; Vujic, M; Bergen, AAB; McGarty-Dugan, V; Figueroa, D; Austin, CP; Metzker, ML; Caskey, CT; Wadelius, C. Identification of the gene responsible for Best macular dystrophy. Nature Genet. 19: 241-247, 1998.


White, K; Marquardt, A; Weber, BHF. VMD2 mutations in vitelliform macular dystrophy (Best disease) and other maculopathies. Hum. Mutat. 15: 301-308, 2000.