ORIGINAL ARTICLE

Clinical Variability of Best's Disease

Streicher T., Špirková J., Tichá M.

Eye department of Bojnice Hospital, Head of Department: I. Simonidesová

First author:
Dr. Teodor Streicher
Hornoulická 9
972 01 Bojnice
Slovak Republic

SUMMARY

Clinical Variability of Best's Disease
Retrospective view of the various phenotypes 20 persons affected by classic solitary form of vitelliform macular dystrophy, in 3 pedigrees with autosomal dominant transmission and in 4 single cases. Long-term monitoring allows to observe the variability of expression, from classic course to peculiarity of the clinical expression in the disc development and their corresponding functions of the central retina.

Key words: solitary vitelliform macular dystrophy, variability of phenotypic expression, diagnostic

Čes. a slov. Oftal., 68, 2012, No. 5, p. 189–194

INTRODUCTION

62 years have elapsed since the time when Zanen and Rausin referred to the Belgian Ophthalmological Society and subsequently described an interesting lesion on the central retina. They gave it the apposite title "Kyste vitelliforme congenital de la macula" (31, 32). Its similarity to "an egg with the sunny side up" ("l'aspect d'un jaune d'oeuf sur un plat") is so typical that no doubts can arise in the differential diagnosis. It is probable that the disorder was already known previous to this article. The first description according to diagrams in a publication originates from J.E. Adams from the year 1883 (cited according to 13). However, a larger role in the discovery of this disease was played by Friedrich Best in 1905, when he described a family in which this disease occurred in 8 of 59 examined members, and identified its hereditary nature. Although Best did not regard vitelliform disc as the most characteristic lesion in the family, but only its developmental stage, he nevertheless identified the hereditary nature of the disease, as a result of which his name is rightly attributed to the condition to this day. Best's lineage was subsequently observed, referred to and illustrated by Vossius 1921, Wiesel 1922, Jung 1937 and they determined 22 members of 300 examined persons (cited according to 7). When Jaeger and Bischoff (14) examined relatives from the 3rd and 4th generations of a similar lineage, they found early stages of this hereditary disease. They determined that Best's disease and vitelliform macular dystrophy were in fact synonymous.
The term "cysta vitelliformis" became used in retinal pathology for all lesions on the retina, mainly on the macula, which had an appearance reminiscent of an egg yolk. In these contexts we understand the term "cyst" in the clinical sense, because it does not have a complete epithelium of the own cells of its wall. As a result in these cases terms such as pseudocyst, disc, or lesion were preferred. The pathological progression with reference to the etiology of the process was also incorrectly stated, and the term degeneration was confused with dystrophy. At present degeneration is understood to mean a process of deterioration, which may be the outcome of pathological conditions of various etiology (vascular, toxic, traumatic, inflammatory), but also dystrophic in the final stage of development and course of the disease. Any confusion of these terms is considered incorrect, and as a result we currently give priority to the indication "vitelliform lesion", unless we are familiar with the nature of the disease in greater detail.

OUR OWN OBSERVATIONS

Our own observations with regard to this macular dystrophy are based on monitoring of 20 patients in three lineages: no. 1 in V generations spanning 47 years (12 patients), no. 2 in III generations spanning 15 years (6 patients) and no. 3 in II generations spanning 14 years (2 patients). Another 4 patients were individual cases without previous demonstrable presence of the disease in their family. All patients had only **bilateral involvement of the macula**, mostly in various stages of development of vitelliform disc. We performed a basic ophthalmological examination on the available members (central vision, biomicroscopy, visual field, colour sensitivity, fundus, photography of fundus), and according to requirement and consent of the patients we also conducted a number of check-up examinations. We supplemented examination by fluorescent angiography of the fundus (FAG) 17 times, electrophysiological tests (ERG, EOG) 11 times, and optical coherent tomography (OCT) 6 times. In two lineages and in one individual case we recorded the bilateral stage of vitelliform disc in the patients, in the first decade in 3 cases, in the second decade in one eye in the proband (27). The original lineage no. 1 from 1967 (27) was later joined by patients in generations IV and V, and by an extramarital son III/14 (fig. 1). His ophthalmoscopic and FAG finding was bilaterally regular, but had pathological EOG. His son IV/7 at the age of eight years had an image of vitelliform disc bilaterally in the stage of resorption of a yolk-like substance in our FAG examination (fig. 2a, b). The average size of solitary vitelliform disc of the macula was within the range of 2-3 PD. The only exceptions were three members of generation II of lineage no. 2, where the disc occupied the range of almost the entire posterior pole (fig.

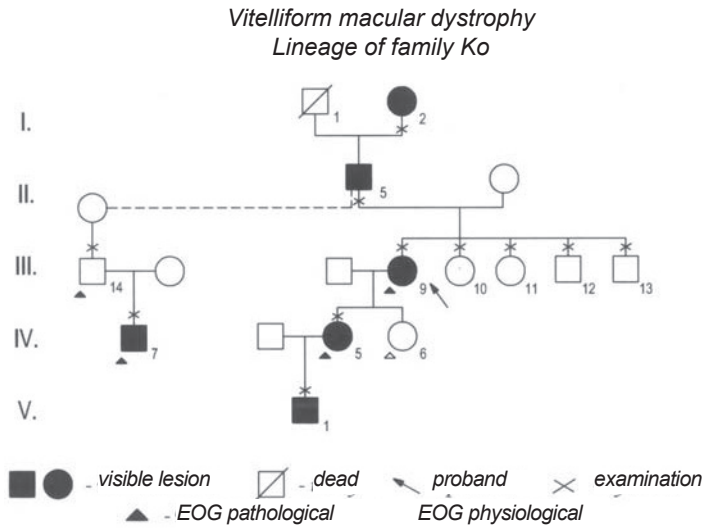


Fig. 1 Part of original lineage Ko with continuous transmission of BVMD across V generations

3a, b). In three cases we recorded haemorrhage into the disc from neovascularisation of the choriocapillaris, which represented the worst results of visual functions. In patient IV/7 in lineage no. 1 aged 27 years in the left eye (fig. 4) and on OCT (fig. 5) it is possible to see subfoveolar atrophy of the layer of retinal pigment epithelium (RPE) in the horizontal cross-section with presence of minimum residue of hyper-reflective material in front of the Bruch's membrane. Between the Bruch's membrane and the neuroretina is an optically empty hypo-reflective area. Within this range there is thinning of the outer nucleus layer. On the vertical cross-section an optically empty hypo--reflective area of the type of ablation of the neuroretina can be seen from above, in which islets of hyper-reflective material are visible. By contrast, from underneath a conspicuous accumulation of

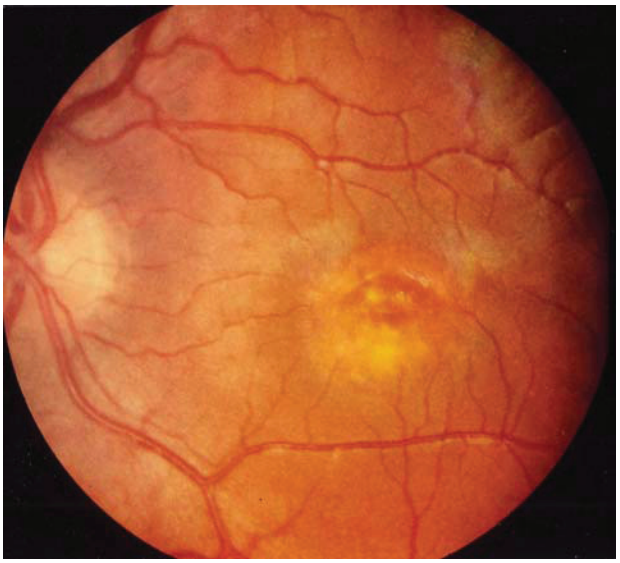


Fig. 2a Solitary vitelliform disc of left eye of 8-year old patient IV/7

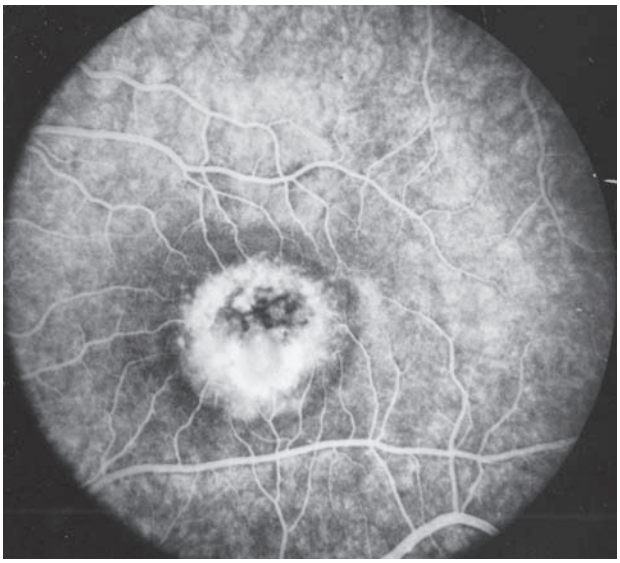


Fig. 2b FAG of left eye of 8-year old patient IV/7

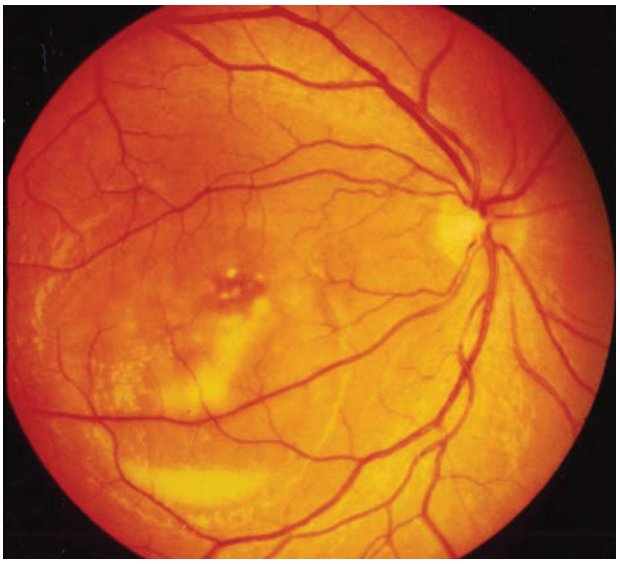
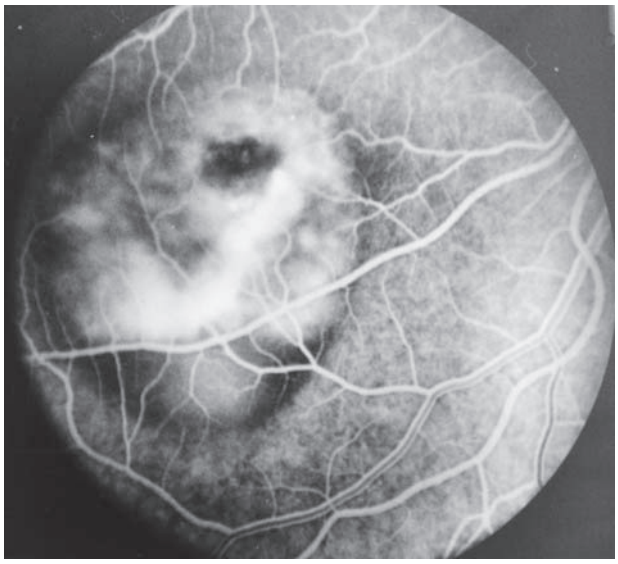


Fig. 3a Unusually large vitelliform disc of right eye



Fib. 3b FAG of large vitelliform disc in "scrambled egg" stage

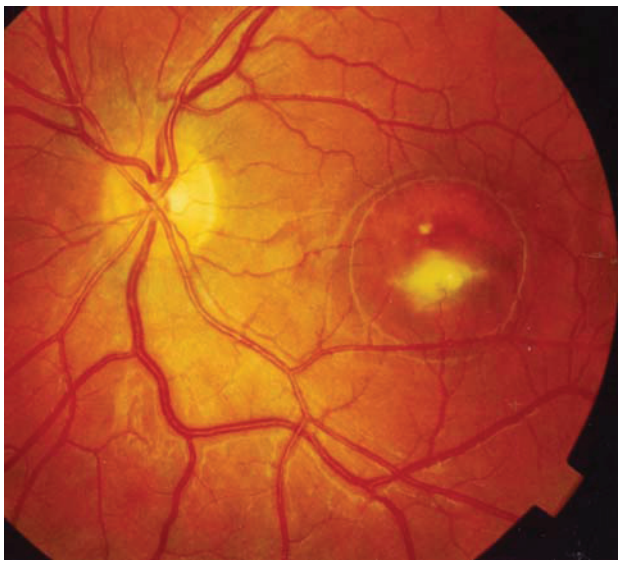


Fig. 4 Final stage of left eye of 27-year old patient IV/7

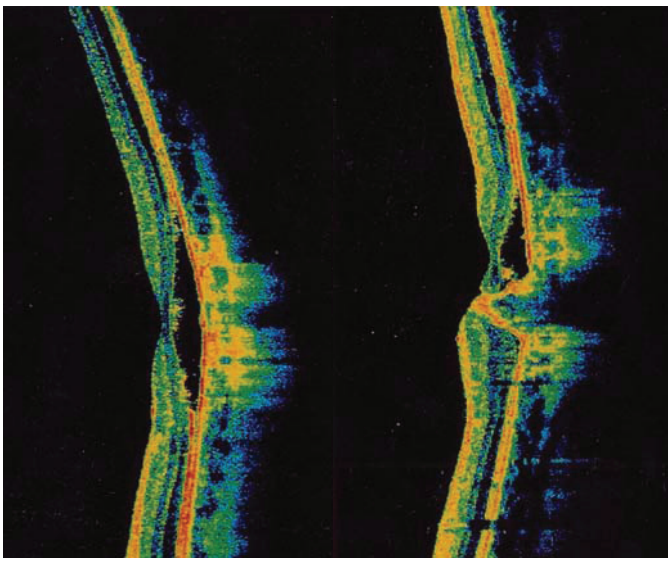


Fig. 5 OCT of left eye of patient IV/7

hyper-reflective material is visible in the form of a cone, which encroaches into the inner layers of the neuroretina to the membrana limitans interna.

We recorded re-secretion of the yolk--like content of the pseudocyst in two cases. In one case this concerned an independent finding in a girl in the first decade, in the second case it concerned an adult male from the original lineage no. 1 from 1967 (27) II/4 aged 43 years, with change of the level of the content of yolky-like substance by the position of the head.

DISCUSSION

Best's vitelliform macular dystrophy (BVMD) is a relatively common hereditary disorder of the central retina. It has a number of standard morphological, electrophysiological, angiographic, genetic and functional manifestations. Amongst the most characteristic symptoms of the disease are:

1. Autosomal dominant hereditary modus,
2. Pathological gene VMD2 on 11th chromosome, responsible for disease and transmission,
3. Vitelliform solitary disc of the macula,
4. Pathological EOG,
5. Low alteration of central vision in initial stages,
6. Large pleomorphy of expressivity during development amongst other hereditary macular disorders,
7. No other ocular or systemic disorder,
8. Variable age of initial manifestation of disease,
9. Large variability of manifestation in intra and interfamilial families,
10. Frequent hypermetropia with or without astigmatism.

Autosomal dominant hereditary type with incomplete penetration and variable expressivity is generally accepted. If we however allow the possibility that incomplete penetration may be influenced also by pathological EOG, the hitherto used concept of incomplete penetration may change. The pathological gene was discovered in 1992 (8, 26) and indicated as VMD2, mapped on the long arm of the 11th chromosome in the area of 11q12--q13.3. In 1998 mutations in the VMD2 gene were first recorded in patients with morbus Best. This gene codes the transmembrane protein bestrophin, which is exprimated in RPE and is found specifically in its basolateral plasmatic membrane and partially in apical peaks. This is created by a complex of chloride cha-

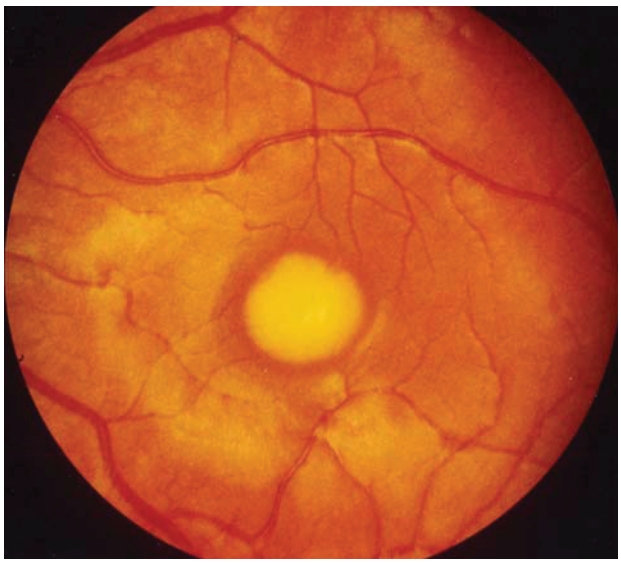


Fig. 6a Vitelliform disc of left eye of 6-year old patient IV/5

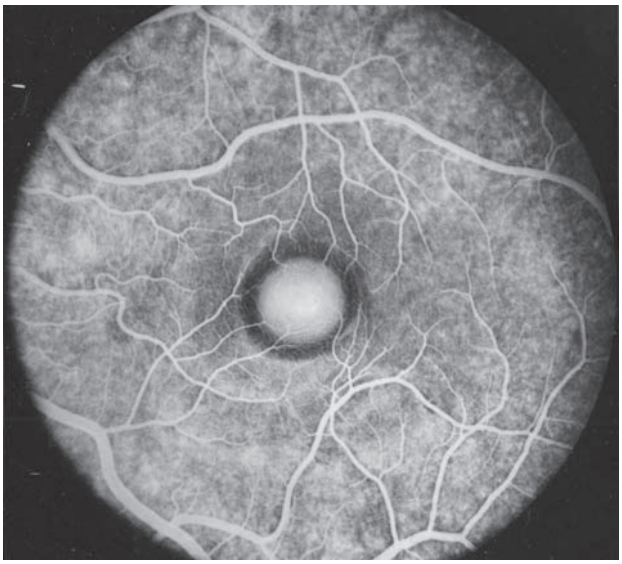


Fig. 6b FAG of left eye of 6-year old patient IV/5

nnels, which are responsible for regulating the transport of fluids via the RPE. It is assumed that dysfunction of bestrofin results in abnormal transport of fluids and ions via the RPE, which subsequently causes an accumulation of fluids and debris in the weakened space between the RPE and photoreceptors, or between the RPE and Bruch's membrane. To date over 100 various mutuations of morbus Best have been described. To a large degree this concerns "missense mutuations", which lead to defined exchanges of amino-acids in the protein sequence. In the case of a positive family anamnesis with pathological EOG, mutuations in the VMD2 gene were found in practically all cases. Further progress towards a clarification of the pathogenesis is expected from genetic studies and in the observation of the complex relationships of the structures on the level of cellular pathology (12, 33).

Stage of development of vitelliform disc

Best's disease is a progressive disorder, which never ceases at the level of vitelliform disc. In this stage it remains in a variable condition, which cannot be temporally delimited, because we do not know when it began. It would be necessary to examine risk cases within the framework of the afflicted family at short time intervals, which is practically impossible. From the aspect of the macromorphology of development, certain characteristic stages have been accepted (2, 11, 13, 18, 28).

Stage I – pre-vitelliform. This has only highly uncharacteristic or no ophthalmoscopic manifestations whatsoever and without observation of EOG and the occurrence of the disease in the family we would have great difficulty in classifying any patient as a potential candidate for a vitelliform disc.

Stage II – vitelliform. The solitary vitelliform disc, into which the macular is embedded, remains the most common manifestation of Best's disease. The colour of the yolk is a fundamental variable, and even with other shades in the coloration of the disc is always the basic colouring. The content of the yellow substance is accumulated yellow-orange pigment of lipofuscin in RPE cells within the scope of the central fovea. Lipofuscin is generally considered to be a pigment of ageing. In RPE it is derived from fats of the outer segments of the neurosensoric epithelium in the process of degradation and renewal of the outer segments, including damage by means of absorption of light and oxidation. Lipofuscin is found at an early age in RPE cells of the entire fundus, but is clinically most pronounced in the case of dystrophic macular disorders such as morbus Best. The mechanism by which this substance is accumulated is thus far unknown. Its specific properties include participation in autofluorescence of macular and extramacular deposits and the blockage of fluorescence upon FAG of the vitelliform disc of the macula (20, 25). Each finding of such a manifestation on the macula must oblige us to perform routine screening and genealogical examination of all possible and available members of the family. This decides as to whether the disease is hereditary or whether it concerns an independent case, the first mutation of this disease. In the stage of vitelliform disc, central vision is surprisingly only slightly altered or not altered whatsoever. This has been demonstrated by examinations of the functions bound on the foveola (distance and close-up vision, colour sensitivity, Haidinger's brushes, macular ERG). This indirectly indicates also the primary location of affliction and the primary undamaged photoreceptors of the macula. There is frequently conspicuous presence of hypermetropia with or without astigmatism, which we can also confirm in our patients. In further studies of the development of the disc, the values of visual acuity are very different and a deficit of functions is present in every case.

BMVD is not linked with any ocular or systemic disease or any abnormality with disorders in the biochemical or haematological spectrum. Vitelliform disc occurs within the period of the first or second decade, approximately between the 5th and 15th year of life, but in isolated cases also in later decades. The fact of whether vitelliform disc is congenitally present was considered from the first publications (3, 23). It is difficult to confirm such a presence, and this would require examination of every newborn baby from the afflicted family.

Stage III – pseudohypopon. The content of the yolk-like mass after the end of production is subject to the resorption process via liquefaction, in which it settles with a horizontal surface in the potential space depending on gravitation, which we indicate as a pseudocyst. According to the degree of liquefaction the content may overflow with the change of position of the head in various time relations. In our case this was after 30 minutes. Together with resorption of the content, RPE lesions are revealed and on FAG zones of hyperfluorescence from transmission of colour. In rare cases the content of the pseudocyst may again be filled by a yolky substance, as observed by certain authors (11, 17, 23). We also observed this rare phenomenon in two cases.

Stage IV – (scrambled egg). Here residues of the mass organise themselves cicatricially and upon FAG their colouring increases by imbibition into newly formed tissue in the later phase. RPE atrophies together with the tissue, by reactive hyperplasia and accumulation of pigment.

Stage V – atrophy and neovascularisation. In this final stage, the development takes place predominantly in two ways. More frequently it concerns complete atrophy of the retinal and choroid structures with reactive hyperplasia of the RPE. In rarer cases there is haemorrhage from the defects in the Bruch's membrane and subsequent neovascularisation with choriocapillaris and the formation of a submacular neovascular membrane and a disciform scar (19, 30).

Electrophysiological examinations

The variable expressivity of Best's disease, in particular in the later stages and at a later age, represents large diagnostic problems and classification of this disease. If we do not record a vitelliform disc in one member of an affected family, it is absolutely essential for us to conduct an electrophysiological examination. In the results of eletroretinography (ERG), no fundamental changes were determined with the exception of macular (pattern) ERG. The most frequent pathological findings were however recorded in EOG examinations (5). These are expressed in the light/dark (L/D) ratio or Arden's quotient, and represent an index of the functional capacity of the RPE. Deutman (6) stipulated that an L/D ratio of above 185% is normal, up to 165% probably normal, up to 145 probably subnormal, less than 145% subnormal and around 100% unequivocally pathological. However EOG is not the only specific test in the case of BMVD and cannot be evaluated on the basis of a single sporadic case.

Fluoroangiographic examination

In our patients FAG was a routine examination for all those afflicted. The individual findings corresponded to the stages in which we identified them at the time of the first examination either by chance in the case of visual problems of the patient or within the framework of a genealogical examination of the family. The characteristic image of a disc filled with a yolk-like material upon FAG presents an image of blockage of

background fluorescence (7, 11). Such an image can be identified only in rare cases. We were however surprised by the FAG finding in the left eye of a 6 year old patient IV/5 from lineage no. 1, with a bilaterally homogenous disc (fig. 6a, b), in which the disc area became coloured from the beginning of the venous phase by hyperfluorescence. This area was lined by a narrow zone of hyperfluorescence of the thickened RPE. Colouring of the disc in the interior of the pigment ring could be explained in various manners without a claim for an explanation: 1. Either the content of the disc is watery and the RPE altered in such a way that it does not block but reveals choroid fluorescence, whilst it is not yet in the stage of complete pseudohypopyon with gravitation in the lower segments. 2. The disc is coloured by an accumulation of colour in its content via disruption of the Bruch's membrane with choriocapillaris. Identification of a thick pigmented lining around the hyperfluorescent disc, through which perifoveolar capillaries penetrate, was evident in the colour and orthochromatic images in the pre-injection phase. We found this in the literature by other authors (2, 7, 10, 24) without separate attention and explanation. In further stages of development of the disc this phenomenon tails off, and we did not record this in the further three patients.

Histopathology

In 1982 two histopathological studies of BVMD were published in parallel, in which eyes were examined by light and electron microscopy. Both findings related to a member of a family evidently affected by BVMD. According to our knowledge, the article of Weingeist et al. (29) is a demonstration of the youngest patient affected by this disease. The object of the histopathological study was a 28 year old man, who was first clinically examined at the age of 15. He is from the second generation of a lineage, the youngest of four male siblings. Over the course of 12 years of observation he did not suffer from any more serious visual complaints. He was examined angiographically, he had pathological EOG, an acquired colour sensitivity defect in the spectrum of the red-green degree of measurement, and in the ophthalmoscopic image had changes in the development of a vitelliform lesion. At the time of the histological processing, the eyes were in the stage of resorption of the yolky-like mass with detachment of the neurosensoric retina. The results of the examination by the authors of this study indicated a diffuse RPE disorder with an accumulation of lipofuscin granules, with the largest number in the macula as responsible for the material of the yolk-like lesion. The conclusion of the study was a finding of primary malfunction in the RPE and the role of accumulation of lipofuscin in the potential space between the sensoric retina and the RPE.

The group of authors centred around Frangie et al. (9) arrived at different results of the histopathological examination. The object of their examination was the eyes of an 80 year old woman with well documented BVMD from a lineage with 6 affected persons in three generations. During the course of her life she first encountered complaints around the age of 50 years, when she was first ophthalmoscopically examined. The finding revealed bilateral cicatricial changes and FAG determined neovascularisation in both maculas. The findings of two relatives aged 8 and 14 years from the 3rd generation documented earlier stages of development of a lesion and abnormal EOG. In the histological examination the authors determined diffuse depositing of abnormal lipofuscin in the RPE within the scope of the macular area, but extramacular diffuse changes were not evident. A prominent finding was also PAS positive electron-dense granular material in the internal segments of the degenerative photoreceptors and Mueller cells. The authors concluded that the primary area of the malfunction may be the sensoric retina.

Both controversial findings and opinions on the location of the primary malfunction were commented upon by Cavender (4), who focused the attention of another study in connection with BVMD on three questions: 1. What is the yellow material? 2. Where is this material located in relation to the RPE during the vitelliform stage of BVMD? 3. Where does this yellow material originate?

A third histopathological study was conducted by O'Gorman et al. (22) in 1988. The object of the examination was the eyes of a 69 year old man with BVMD and a clinical picture of the early stage in one eye and the later stage in the second eye. The authors confirmed the findings of the previous two studies, that the RPE cells accumulated an excessive quantity of lipofuscin and melanolipofuscin, and a loss of cells in the foveal and parafoveal area beneath the RPE. In a background of the determined findings, they outlined a hypothesis close to the findings conducted by Wiegeist et al., i.e. that the yolky mass forms on the RPE, and is deposited on the RPE and between the RPE and the Bruch's membrane. Disruption of the considerably thinned RPE filled with lipofuscin and an inability to degrade material of the external segments of the photoreceptors in the area of the macular causes the mass to penetrate into the subretinal area, commencing further destruction of the sensoric retina.

Clinical experience confirmed by a number of authors, as well as by an examination on 4 our eyes in the stage of vitelliform disc, unequivocally points to a minimal deficit of visual functions linked to the foveola. From this it ensues that in this stage the primary location of the pathology of BVMD shall not be the photoreceptors, but that damage thereto shall be secondary.

CONCLUSION

The large degree of polymorphy of the developmental stages of vitelliform macular dystrophy requires a standard procedure in the differential diagnosis of this macular disorder. The most reliable evidence is the finding of vitelliform disc and its assessment with reference to age. There follows examination of all the available members of the family in order to determine whether the disease is the first mutation or has a definitive hereditary nature. There follow functional and illustrative examinations with an aspect on determination of the morphological stage as evidence of unaffected persons who are carriers of the pathological gene, as well as the expected natural course of the disease. After obtaining an unequivocal conclusion it is possible to talk of all fundamental aspects of the disease within the framework of consultancy. This includes explanation of the nature of the disease, its course, influence on occupation and the circumstances of regular life, the possibility of inheritance and the risks thereof, and everything that can be provided at the current time of the disease in order to improve the quality of vision.

Causal treatment of vitelliform macular dystrophy does not yet exist. Our endeavour focuses on the optimum correction of refractive errors, the preservation of the clarity of optic media and on adaptation to the light conditions of the surroundings. Only in certain situations and entirely exceptionally in the case of sub- and parafoveal neovascularisations is the method of choice laser treatment.

LITERATURE

1. Benson, W.E., Kolker, A.E., Enoch, J.M. et al.: Best`s vitelliform makular dystrophy. Am J Ophthalmol, 79; 1975, 1: 59–66.
2. Blodi, CH.F., Stone, E.M.: Best`s vitelliform dystrophy. Opthalmic Paediatrics and Genetics, 11; 1990, 1: 49–59.
3. Braley, A.E., Spivey, B.E.: Hereditary vitelline macular degeneration. Arch Ophthalmol, 72; 1964: 743–762.
4. Cavender, J.C.: Best`s macular dystrophy. Arch Ophthalmol, 100; 1982, 7:1067.
5. Cross, H.E., Bard, L.: Electro--oculography in Best`s macular dystrophy. Am J Ophthalmol, 77, 1974, 1: 46–50.
6. Deutman, A.F.: Electro-oculography in families with vitelliform dystrophy of the fovea. Arch Ophthalmol, 81, 1969, 3: 305–316.
7. Deutman, A.F.: The hereditary dystrophies of the posterior pole of the eye. Van Gorcum, Assen, 1971, s. 198–299.
8. Forsman, K., Graff, C., Nordström, S., et al.: The gene for Best`s macular dystrophy is located at 11q13 in a Swedish famili. Clin Genet, 42;1992: 156–159.
9. Frangieh, G.T., Green, R.W., Fine, S.L.: Histopathologic study of Best`s macular dystrophy. Arch Ophthalmol, 100; 1982, 7: 1115–1121.
10. Friedenwald, J.S., Maumenee, E.A.: Peculiar macular lesions with unaccountably good vision. Arch Ophthalmol, 45; 1951: 567–569.
11. Godel, V., Chaine, G., Regenbogen, L., et al.: Best`s vitelliform macular dystrophy. Acta Ophthalmol, Supplement 175; 64, 1986: 5–31.
12. Hartzell, C.H., Qu,Z., Yu, K., et al.: Molecular physiology of bestrophins: multifunctional membrane proteins linked to Best disease and other retinopathies. Physiol Rev, 88; 2008: 639–672.
13. Huismans, H.: Cysta vitelliformis – Bericht über ein seltenes heredodegeneratives Makulaleiden. Klin Mbl Augenheilk,166; 1975, 2: 252–254.
14. Jaeger, W., Bischoff, E.: Vitelliforme Makuladegeneration und Bestsche Makuladgeneration sind dasselbe Krankheitsbild. Klin Mbl Augenheilk, 170; 1977, 6: 890–899.
15. Kingham, J.D., Lochen, G.P.: Vitelliform macular degeneration. Am J Ophthalmol, 84; 1977, 4: 526–531.
16. Krämer, F.,White, K., Pauleikhoff, D. et al.: Mutations in the VMD2 gene are associated with juvenile-onset vitelliform macular dystrophy (Best disease) and adult vitelliform macular dystrophy but not age-related macular degeneration. Eur J Hum Genet, 8; 2000, 4: 286–292.
17. Kraushar, M.F., Margolis, S., Morse, P.H. et al.: Pseudohypopyon in Best`s vitelliform macular dystrophy. Am J Ophthalmol, 94; 1982, 1: 30–37.
18. Lisch, W.: Die verschiedenen Stadien der vitelliformen Makuladegeneration. Klin Mbl Augenheilk, 176; 1980, 2: 214–221.
19. Miller, S.A., Bresnick, G.H., Chandra, S.R.: Choroidal neovascular membrane in Best`s vitelliform macular dystrophy. Am J Ophthalmol, 82; 1976, 2: 252–255.
20. Miller, S.A.: Fluorescence in Best`s vitelliform dystrophy, lipofuscin, and fundus flavimaculatus. Brit J Ophthalmol, 62; 1978: 256–260.
21. Morse, P.H., MacLean, A.I.: Fluorescein fundus studies in hereditary vitelliruptive macular degeneration. Am J Ophthalmol, 66; 1968, 9: 485–494.
22. O`Gorman, S., Flaherty, W.A., Fishman, G.A. et al.: Histopathologic findings in Best`s vitelliform macular dystrophy. Arch Ophthalmol, 106; 1988, 9: 1261–1268.
23. Remky, H., Rix, J., Klier, K.F.: Dominant – autosomale Maculadegeneration (Best, Sorsby) mit zystischen und vitelliformen Stadien (Huysmans, Zanen). Klin Mbl Augenheilk, 146; 1965, 4: 473–497.
24. Schum, U.: Fluorescenzangiographie bei vitelliformer Maculadegeneration. Bericht 70, Zukunft DOG, Heidelberg, 1969: 252–257.
25. Spaide,R.: Autofluorescence from the outer retina and subretinal space: Hypothesis and review. Retina, 28; 2008, 1: 5–35.
26. Stone, E.M., Nichols, B.E., Streb, L.M. et al.: Genetic linkage of vitelliform macular degeneration (Best`s disease) to chromosome 11q13. Nat Genet, 1; 1992: 246–250.
27. Streicher, T.: Viteliformná heredodegenerácia makuly. Čs Oftal, 23; 1967, 6: 423–428.
28. Thiel,H.J., Behnke,H.: Klinik und Vererbung der vitelliformen Maculadegeneration. Klin.Mbl.Augenheilk., 158, 1971, 2: 235–246.
29. Weingeist, T.A., Kobrin, J.I., Watzke, R.C.: Histopathology of Bestęs makular dystrophy. Arch Ophthalm, 100; 1982: 1108–1114.
30. Záhlava, J., Karel, I., Lešták, J.: Bestova viteliformní dystrofie komplikovaná neovaskulární membránou a krvácením. Čes a Slov Oftal, 58; 2002, 3: 158–164.
31. Zanen, J., Rausin, G.: Kyste vitelliforme congénital de la macula. Bull Soc belge Ophthal, 96; 1950: 1–5.
32. Zanen, J., Rausin, G.: Kyste vitelliforme congénital de la macula. Bull Soc belge Ophthal, 98, 1951: 1–2.
33. Yu, K., Qu, Z., Cui, Y. et al.: Chloride channel activity of bestrophin mutants associate with mild or late-onset macular degeneration. Invest Ophthalmol Vis Sci, 48; 2007: 4694-4705.