Original Article/นิพนธ์ต้นฉบับ

การศึกษาลักษณะทางคลินิกและการตรวจคลื่นไฟฟ้าของตาในผู้ป่วยโรค Best's disease ในประเทศไทย

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บทคัดย่อ

การศึกษาย้อนหลังในผู้ป่วยโรค Best vitelliform macular dystrophy (BVMD) ที่ได้รับการวินิจฉัยและรักษาในโรงพยาบาลศิริราชตั้งแต่เดือนมกราคม พ.ศ.2547 ถึงเดือนธันวาคม พ.ศ.2560 (13 ปี) พบผู้ป่วย BVMD ทั้งหมด 13 ราย (26 ตา) มีอายุเฉลี่ย 40.6±19.7 ปี (8-69 ปี) เป็นเพศชาย 8 ราย (ร้อยละ 61.5) มีอาการแรกเริ่มได้แก่ ตามัว 9 ราย (ร้อยละ 69.2) และตาบอดสี 1 ราย (ร้อยละ 7.7) ในขณะที่ 3 ราย (ร้อยละ 23.1) ไม่มีอาการแต่พบโดยบังเอิญจากการตรวจตาด้วยสาเหตุโรคทางกายอื่นๆ ผู้ป่วยทุกรายมีพยาธิสภาพในตาทั้งสองข้าง ซึ่งส่วนใหญ่ (11 ตา, ร้อยละ 42.3) ตรวจพบอยู่ในระยะ previtelliform และมีค่าสายตาที่ใกล้เคียงปกติในครั้งแรกที่มาพบแพทย์ ส่วนผู้ป่วยรายที่อยู่ในระยะ atrophic จะเริ่มมีการมองเห็นที่ลดลง การตรวจคลื่นไฟฟ้าของตาพบว่า electroretinogram (ERG) อยู่ในเกณฑ์ปกติ และ electrooculogram (EOG) ผิดปกติในทุกราย โดยมีค่าเฉลี่ย Arden ratio 1.35±0.29 และ 1.27±0.15 ในตาข้างขวาและซ้าย ตามลำดับ ผู้ป่วย BVMD มีการแสดงออกของโรคที่หลากหลาย การตรวจพบภาวะขัดแย้งกันของ ERG และ EOG (ERG ปกติ ในขณะที่ EOG ผิดปกติ) มีส่วนสำคัญในการช่วยวินิจฉัยโรค การศึกษาในอนาคตเรื่องการวิเคราะห์ยีนในผู้ป่วยจะสามารถรวบรวมองค์ความรู้เพิ่มเติมเกี่ยวกับ BVMD ในประเทศไทยได้ **จักษุเวชสาร 2018; มกราคม-มิถุนายน 32(1): 13-24.**

คำสำคัญ: Best vitelliform macular dystrophy; Best's disease; การตรวจคลื่นไฟฟ้าทางจักษุวิทยา; ประเทศไทย

ผู้นิพนธ์ทั้งหมดไม่มีส่วนเกี่ยวข้องหรือผลประโยชน์ใดๆ กับผลิตภัณฑ์ที่ได้กล่าวอ้างถึงในงานวิจัยนี้

ภาควิชาจักษุวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

Original Article/นิพนธ์ต้นฉบับ

Clinical Manifestations and Electrophysiologic Tests of Best's Disease in Thailand

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Abstract

Objectives: To describe the clinical manifestations and electrophysiologic findings of Best vitelliform macular dystrophy (BVMD) in Thailand.

Materials and Methods: A retrospective review included of 26 eyes of 13 patients with a diagnosis of BVMD from January 2004 to December 2017 in Siriraj hospital, Bangkok, Thailand. Demographic data, clinical manifestations, ophthalmic examination, electro-oculogram (EOG) and full-field electroretinogram (ERG) findings were described in the study.

Results: The age at the first presentation was 40.6±19.7 years (range 8 to 69 years). There were 8 males (61.5%) and 5 females (38.5%). The presenting symptoms were blurred vision in 9 patients (69.2%), asymptomatic in 3 patients (23.1%), and color blindness in 1 patient (7.7%). All patients had bilateral lesions. The majority of eyes (11 eyes, 42.3%) were in previtelliform stage at the beginning with near-normal vision. Visual impairment was found in patients with atrophic stage. All patients demonstrated normal ERG with abnormal EOG. Arden ratio was 1.35±0.29 and 1.27±0.15 in right and left eyes, respectively. During mean follow-up time of 37.4±56.4 months (range 1 to 155 months), 4 eyes were unable to record the last follow-up fundus lesion.

Conclusion: BVMD patients showed a variable clinical expression. The findings in dissociation of ERG and EOG play an important role for a definite diagnosis of BVMD. Further investigation according to genetic mutation analysis will facilitate the genetic features of BVMD in Thailand. **Thai J Ophthalmol 2018; January-June 32(1): 13-24.**

Keywords: Best vitelliform macular dystrophy; Best's disease; Electroretinogram; Electro-oculogram; Thailand.

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Introduction

Best vitelliform macular dystrophy (BVMD), or Best's disease, is a rare autosomal dominant disorder which was firstly described by Dr. Friedrich Best in 1905 in a German family with a presentation of yellowish yolk-like lesion in the macula in childhood. The disease is caused by mutations in BEST1 or VMD2 gene on chromosome 11q13, resulting in dysfunction of retinal pigment epithelium (RPE)'s transmembrane protein called bestrophin-1.[1-3] Abnormal ion transportation occurs and leads to lipofuscin accumulation within retinal pigment epithelium (RPE) cells and sub-RPE space.[4] Almost all patients remain asymptomatic until late complications develop such as the vitelliform lesion breakup, RPE atrophy and choroidal neovascularization. The diagnosis is confirmed by a distinctive fundus lesion and a dissociation of low Arden ratio of electro-oculogram (EOG) with a normal electroretinogram (ERG). To date, there have been more than 200 of BEST1 mutations reported worldwide with a variable clinical features and course of disease.[5]

Best vitelliform macular dystrophy has been increasingly diagnosed in Siriraj hospital, a tertiary care center in Bangkok, Thailand. This publication describes clinical manifestations and electrophysiologic findings of Best vitelliform macular dystrophy in Siriraj hospital, Bangkok, Thailand from January 2004 to December 2017 (13 years) to gain more information of this rare disease in Thai patients with a literature review.

Methods

This study was approved by the Committee for the Protection of Human Participants in Research at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand [COA no. Si 743/2017], and followed the principles of the Declaration of Helsinki and its amendments. Written informed consent was obtained from all patients.

Thirteen patients with a diagnosis of BVMD were recruited in the study. This was a retrospective review in Department of Ophthalmology, Siriraj hospital from January 2004 to December 2017. The diagnosis was confirmed by the characteristic vitelliform lesion in the fundus and low Arden ratio from the EOG with normal ERG. Patients with uncertain diagnosis according to questionable fundus appearances and electrophysiologic findings were excluded from the study. All patients underwent complete ophthalmic examinations included best-corrected visual acuity (BCVA) and fundus examination. Full-field ERG and EOG were performed by using VERIS™ Science software version 6.0.3 (Electro-Diagnostic Imaging, Inc., CA, USA). The decreased or low Arden ratio was defined as a number less than 1.6 from the EOG.[5]

The BCVA was converted to a logarithm of the minimum angle of resolution (logMAR) equivalent. The grading of five stages of fundus appearance was based on Mohler and Fine classification; pre-vitelliform, vitelliform, psuedohypopyon, vitelliruptive, and atrophic stage.[6]

Statistical data were calculated by using Statistical Package for the Social Sciences software, version 23.0 (SPSS Inc., Chicago, Illinois). Demographic data, history of the disease, fundus appearances and results from electrophysiologic tests were retrospectively reviewed and shown as number and percentage or mean with standard deviation.

Table 1 Clinical findings of patients with Best vitelliform macular dystrophy

Patient	Eye	Sex	Age (years)	Presenting symptoms	Baseline BCVA (LogMAR)	Last BCVA (LogMAR)	Stage at baseline visit	Stage at last visit	ERG	Arden ratio	F/U time (months)
1	R	F	8	asymptomatic	0.50	0.10	previtelliform	atrophic	normal	1.19	123
	L				0.20	0.40	previtelliform	atrophic		1.20	
2	R	M	69	blurred vision	0.50	0.40	previtelliform	previtelliform	normal	1.05	155
	L				0.80	2.60	previtelliform	atrophic		1.20	
3[a,b]	R	M	26	blurred vision	0.20	0.20	atrophic	atrophic	normal	1.22	9
	L				0.20	0.50	vitelliform	atrophic		1.23	
4[a,b]	R	F	29	asymptomatic	0.00	0.00	previtelliform	previtelliform	normal	1.17	9
	L				0.00	0.00	previtelliform	previtelliform		1.20	
5	R	F	54	asymptomatic	0.20	0.20	previtelliform	NA[c]	normal	1.38	2
	L				0.20	0.20	previtelliform	NA[c]		1.35	
6	R	M	39	color blindness	0.30	1.50	atrophic	atrophic	normal	2.12	126
	L				0.30	1.00	previtelliform	atrophic		1.48	
7[b]	R	M	58	blurred vision	0.60	0.50	vitelliform	vitelliform	normal	1.50	10
	L				0.20	0.50	vitelliform	vitelliform		1.30	
8	R	F	52	blurred vision	0.50	0.60	atrophic	atrophic	normal	1.55	6
	L				1.00	1.00	atrophic	atrophic		1.54	
9	R	M	69	blurred vision	0.10	0.10	previtelliform	previtelliform	normal	1.32	6
	L				0.10	0.10	previtelliform	previtelliform		1.29	
10	R	F	31	blurred vision	0.10	0.00	vitelliruptive	atrophic	normal	1.00	8
	L				0.40	0.60	atrophic	atrophic		1.00	
11	R	M	9	blurred vision	0.00	0.10	vitelliform	pseudohypopyon	normal	1.28	30
	L				0.50	0.10	vitelliruptive	atrophic		1.25	
12	R	M	35	blurred vision	0.40	0.30	atrophic	atrophic	normal	1.54	1
	L				0.30	0.30	vitelliruptive	vitelliruptive		1.36	
13	R	M	49	blurred vision	0.40	0.30	atrophic	NA[c]	normal	1.21	1
	L				0.10	0.10	atrophic	NA[c]		1.06	

R = right; L = left; F = female; M = male; BCVA = best-corrected visual acuity; ERG = electroretinogram; EOG = electro-oculogram; F/U = follow up.

[a]Patient 4 was patient 3's elder sister.

[b]Patient 3, 4, and 7 were previously described by Atchaneeyasakul and co-workers.[26]

[c]NA = Data was not available because patients were lost to follow-up.

Results

A total of 13 patients with BVMD were included in the study (table 1). There were 8 males (61.5%) and 5 females (38.5%). The age at the first visit ranged from 8 to 69 years with a mean age of 40.6±19.7 years. Presenting symptoms were blurred vision in 9 patients (69.2%) and color blindness in 1 patient (7.7%). Three patients (23.1%) were asymptomatic. Patient 2 and 5 were accidentally diagnosed during routine eye screening for deferoxamine and hydroxychloroquine, respectively. Patient 4 had a positive family history of BVMD (Patient 3). Mean follow-up time was 37.4±56.4 months (range 1-155 months).

All patients had bilateral lesions. The mean BCVA at baseline visit was 0.31±0.25 (0.00-1.00) and decreased to 0.45±0.57 (0.00-2.60) at the last visit. The fundus appearance showed various stages of lesion. Of 26 eyes, 11 eyes (42.3%) presented with previtelliform lesion characterized by a normal macula or minimal RPE changes. At the last visit, 5 of 11 eyes (45.5%) remained in the same stage with a mean BCVA from 0.14±0.21 to 0.12±0.16 LogMAR. Four of 11 eyes (36.4%) progressed to atrophic stage with a decreased BCVA from 0.45±0.26 to 1.03±1.11 LogMAR. Two of 11 eyes (18.2%) were unable to record the last follow-up fundus lesion.

Four of 26 eyes (15.4%) showed vitelliform lesion or a typical yolk-like lesion at the beginning (Figure 1). At the last visit, 2 of 4 eyes (50%)

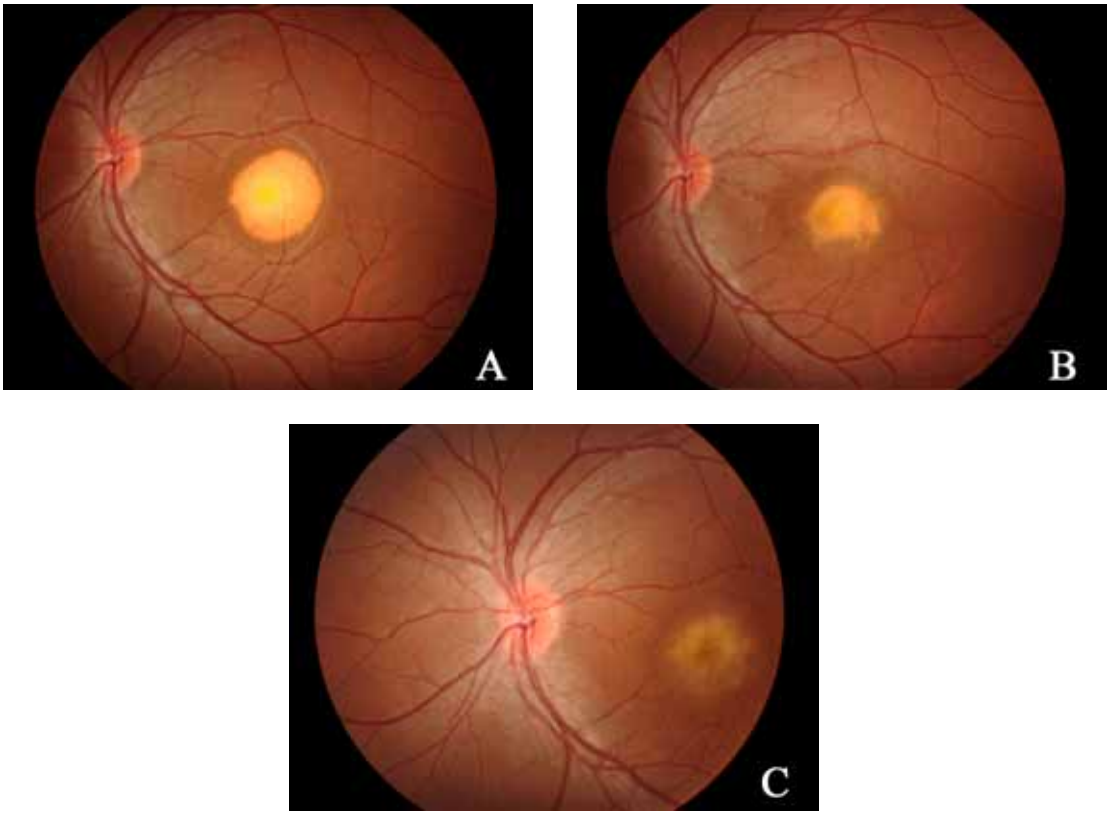

Figure 1 *Fundus photographs of the left eye of patient 3 show a vitelliform stage with a yolk-like lesion at the first visit (A), a vitelliruptive stage in a following month (B), and a scar stage with fibrotic changes in the next 4 months (C) (Colored figures are on page 45)*

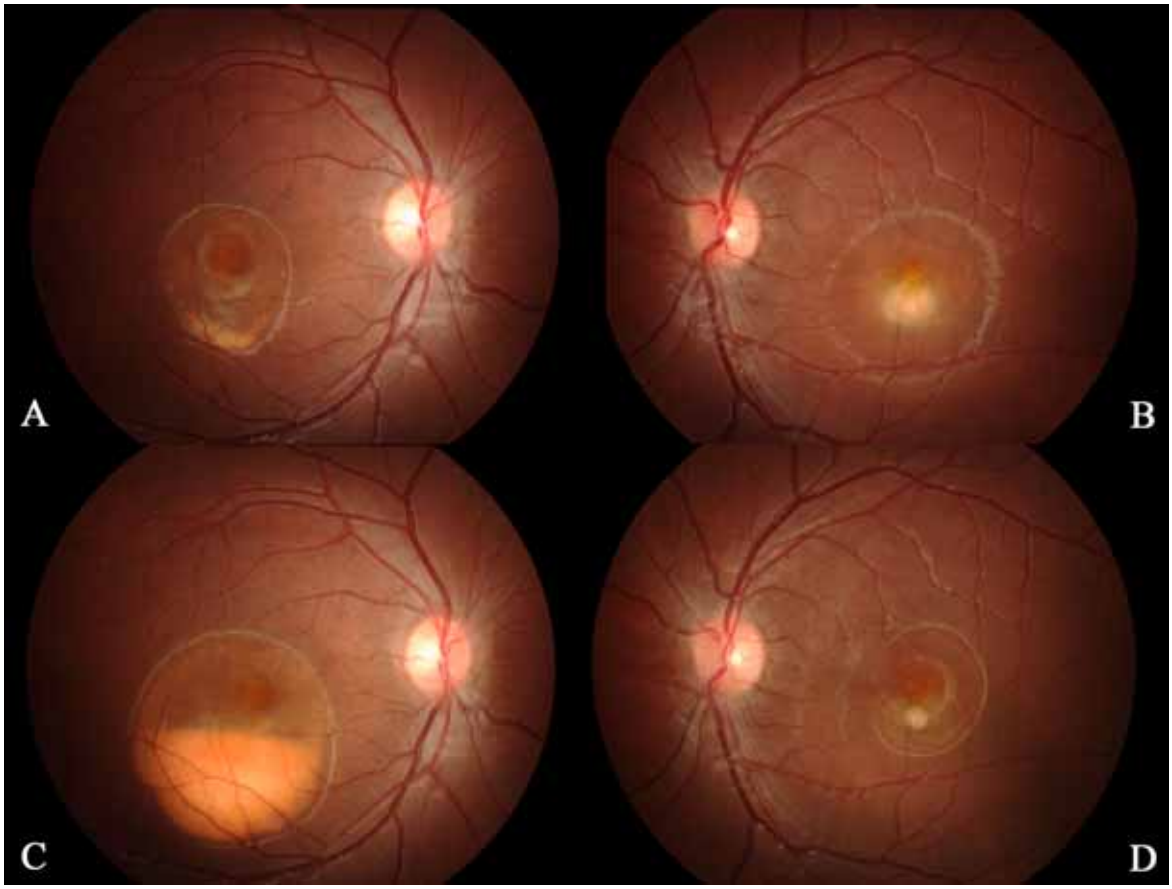

Figure 2 *Fundus photographs of patient 11 show a vitelliform stage in the right eye (A) and a vitelliruptive stage in the left eye (B) at the first visit. After 30 months, the lesions progressed to pseudohypopyon stage in the right eye (C) and an atrophic stage in the left eye (B). (Colored figures are on page 46)*

remained in vitelliform with a BCVA from 0.40±0.28 to 0.50 LogMAR. One of 4 eyes (25%) became a psuedohypopyon lesion (Figure 2) with a BCVA from 0.00 to 0.10 LogMAR. One of 4 eyes (25%) progressed to atrophic stage with a BCVA from 0.20 to 0.50 LogMAR.

Three of 26 eyes (11.5%) presented with vitelliruptive lesion, characterized by a breakup of the vitelliform lesion or scrambled-egg lesion, without atrophic changes. One of 3 eyes (33.3%) was in the same stage with a mean BCVA of 0.30 LogMAR, and the others changed to atrophic lesion with a mean BCVA from 0.30±0.28 to 0.05±0.07 LogMAR.

Eight of 26 eyes (30.8%) showed atrophic lesion at the first visit, which 6 of 8 eyes (75%) remained in atrophic stage with a decreased mean BCVA from 0.47±0.28 to 0.70±0.48 LogMAR. Two of 8 eyes (25%) had unavailable records of last fundus examination.

All patients had a decreased Arden ratio from the EOG in bilateral eyes except patient 6 who had a normal EOG in one eye and an abnormal EOG in the other. All of them had normal full-field ERG findings. The mean Arden ratio was 1.35±0.29 and 1.27±0.15 in right and left eyes, respectively.

Discussion

BVMD is inherited in an autosomal dominant pattern. Because of the rarity, the prevalence is still unknown. This slowly progressive disease has an early onset in the 1st decade of life which begins typically in a child from 3 to 15 years old.[5] Several studies have reported a late onset BVMD which extends through 6th decade of life.[7,8] Initially, the patients are asymptomatic and then progress to blurred vision, decreased central vision and metamorphopsia in later stage.[5,9] The disease usually affects bilaterally and symmetrically.

Based on fundus findings, BVMD can be categorized into 5 stages by Mohler and Fine classification.[6] In stage 1 (previtelliform stage), the fundus shows normal macula or minimal RPE alterations. The vision appears normal. In stage 2 (vitelliform stage), there is a yellowish, well-circumscribed, homogenous material within the macula, sometimes multifocal. The size of this yolk-like lesion can range from 0.5 to 3 mm with central elevation at the fovea. VA remains normal or minimally decreased to 20/50. In stage 3 (psudohypopyon stage), the vitelliform substance breaks and accumulates within sub-RPE space. The fundus shows horizontal fluid-level with yellowish material collecting at the inferior part of the lesion. In stage 4 (vitelliruptive stage), a partial reabsorption of the vitelliform lesion occurs, resulting in less homogenous, scrambled-egg lesion. VA can reduce to 20/100 at this stage. In stage 5 (atrophic stage), fibrosis and scar develop at the macula.[9-11] Choroidal neovascularization and subretinal hemorrhage can occur in this stage and are associated with markedly decreased VA.[12]

In this study, the onset of disease was variable, ranging from 1st to 7th decade of life. Haft of our patients were diagnosed in their young adulthood, while the rest of them were in their middle to late adulthood. The patients may experience no symptoms until the disease progressed to later stage and this diminution of vision brought them to the hospital. The most common presenting symptom in our patients was blurred vision and almost all of them already had developed more than vitelliform lesion at the first visit. Asymptomatic patients were in their previtelliform stage which were accidental findings and their BCVA appeared normal or mildly decreased. The visual impairment was found in patients with atrophic stage.

The dissociation of a normal full-field ERG with an abnormal EOG is a hallmark of the disease.[5] In all stages, the full-field ERG usually appears normal. EOG reveals decreased to absent light rise and abnormal Arden ratio, commonly between 1.0-1.3. In our study, electrophysiological findings played an important role to detect asymptomatic BVMD patients and carriers. However, Renner *et al.* reported a BVMD patient with a normal EOG.[8] Wabbels *et al.* identified a normal EOG in 2 young patients and 1 carrier with Ile295del mutation.[13] Testa *et al.* described a Phe305Leu mutation in 3 members in an Italian family and all of them had a normal EOG.[14] One patient in this study also had an abnormal EOG in only one eye, therefore, further genetic study could gain more information according to these findings.

Several studies have reported the association between BEST1 gene mutations and late-onset BVMD[7, 8] and a spectrum of retinal diseases; best

vitelliform macular dystrophy, adult onset vitelliform macular dystrophy, autosomal recessive bestrophinopathy, autosomal dominant vitreoretinochoroidopathy, and retinitis pigmentosa.[5,11,15,16] Since the disease can be misdiagnosed as other macular disorders, apart from fundus examination, electrophysiological findings can distinguish BVMD at even very early stages. Other diagnostic modalities such as optical coherence tomography (OCT), fundus fluorescein angiography (FFA), and fundus autofluorescence (FAF) can be performed.[5] Genetic testing is an important tool to confirm a diagnosis of BVMD, especially in uncertain cases. It can detect BEST1 gene mutations in approximately 96% of people with positive family history, and 50-70% of people with no family history of BVMD.[17]

Genetic analysis

BVMD is an autosomal dominant disease caused by mutations in the gene on chromosome 11q13 region named BEST1 gene, or previously named VMD2 gene.[18,19] In 1998, Petrukhin *et al.* proposed that the BEST1 gene encoded a protein called bestrophin, therefore, BEST1 gene mutations could alter the bestrophin protein function and are associated with a spectrum of retinal diseases.[3] Supporting evidences from northern blot analysis from Marquardt *et al.* confirmed that BEST1 gene exclusively expressed in the RPE.[2] In 2000, by using biochemical and immunocytochemical data, Marmorstein *et al.* discovered that the bestrophin protein was located on the basolateral plasma membrane of RPE cells.[1] Since then, several studies have gained more information about the localization and function of bestrophin protein.[11]

Bestrophin protein consists of 585 amino acids with an approximate size of 68 kDa.[1] It works as a Ca^{2+}-activated chloride channel to regulate intracellular calcium signaling and anion transportation to maintain the retinal homeostasis.[11,20] Mutations in BEST1 gene makes changes to bestrophin protein function and ion transportation, leading to abnormal accumulation of fluid within the RPE cells and sub-RPE space. There have been more than 200 of BEST1 mutations reported and the majority of them are missense mutations. These mutations can be associated with a spectrum of degenerative retinal diseases.[5,11,16,21]

The genotype-phenotype correlation is extensively discussed.[13,15,22-25] Several previous studies have reported variable expressions and genotype-phenotype correlations, mostly in European and African population. In Asian countries, there have been some reported BVMD patients among Chinese, Japanese, and Thai people.[26-32] There has been only one study reported a gene analysis of BVMD in Thai families.[26] Atchaneeyasakul *et al*, described mutations in 2 unrelated Thai families with BVMD. Val-242-Met mutation showed a late onset presentation and Arg-218-Cys mutation revealed a variable expression in the same family. Several studies described BEST1 gene mutations which were consistent with autosomal recessive inheritance.[31,33,34] However, there was a study showing that the genotype-phenotype correlation was still inconclusive. Querques *et al.* reported BEST1 gene mutations which were not associated with differences in clinical manifestation and severity.[35]

Treatment

Approximately 75% of patients remain VA of 20/40 or better in at least one eye without intervention.[36] and the vision gradually deteriorates until the 4th decade of life.[37] Rare complications such as choroidal neovascularization, subretinal hemorrhage, or macula hole can lead to poor visual prognosis.[12] As the visual prognosis of BVMD is good, the recommended strategy is observation and monitoring further complications.[9]

The intervention is considered in cases with choroidal neovascularization and subretinal hemorrhage. Anti-vascular endothelial growth factor (anti-VEGF) therapy has been used and associated with the improvement of choroidal neovascularization. Two studies reported that a single dose of intravitreal bevacizumab in patients showed choroidal neovascularization regression and visual recovery after 6 and 9 months, respectively.[38,39] Rishi *et al.* performed three intravitreal injections of bevacizumab in a patient who revealed an improved vision and stable fundus after 7 months of treatment.[40] Cennamo *et al.* reported a full visual recovery after 1 month of intravitreal bevacizumab injection and a total regression of choroidal neovascularization over an 18 month-period.[41] Cakir *et al.* described a visual improvement after a single dose of combined bevacizumab and triamcinolone intravitral injection.[42] Ranibizumab injection was also reported as a successful treatment after 1-month follow-up.[43]

Photodynamic therapy has also been proposed as an effective treatment in BVMD with choroidal neovascularization. Andrade *et al.* reported a case of choroidal neovascularization regression and subretinal hemorrhage resolution after a session of photodynamic therapy with verteporfin.[44] Long-term outcome was reported by Sodi *et al.* in pediatric patients who were treated with photodynamic therapy. After an average follow-up time of 77 months, 3 patients had a visual recovery and improved choroidal neovascularization.[45] Frennesson *et al.* revealed 7-year follow-up of resolved subretinal hemorrhage and improved VA after a photodynamic therapy.[46]

An improvement of vision and macular detachment was reported in a patient with choroidal neovascular membrane who underwent argon laser photocoagulation.[47] Prevention of macular degeneration by prescribing dietary docosahexaenoic acid (DHA) was conducted by Lee *et al.* but the result cannot determine whether the effect is beneficial.[48]

However, due to the disease rarity, there is no definite medical or surgical treatment for BVMD. Genetic counseling is very important. Giving information about risk assessment and the nature of the disease to family members is recommended.

Conclusion

This paper describes a series of BVMD patients during a 13-year period in clinical manifestation and electrophysiologic aspects. The disease has a variable clinical expression and good visual prognosis but can progress from normal to impaired visual acuity in later stages. Dissociation of ERG and EOG is the hallmark of BVMD. More diagnostic investigations and genetic testing will provide more knowledge about the disease in order to diagnose and treat BVMD patients in Thailand. Due to the rarity, our study was limited by a small population size and short duration of follow-up time. Further studies should consider more diagnostic tools, such as OCT, FFA, and FAF

to give additional information about the disease and the overlap with clinical manifestations. Genetic analysis should be included to identify the genotype-phenotype correlation among BVMD patients in Thailand. Further study in genetic analysis will be performed. Genetic counseling is also important for risk assessment and disease prevention.

Conflict of interest declaration

All authors declare that they have no conflict of interest.

References

1. 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 Natl Acad Sci U S A. 2000;97(23):12758-63.
2. Marquardt A, Stohr H, Passmore LA, Kramer F, Rivera A, Weber BH. Mutations in a novel gene, VMD2, encoding a protein of unknown properties cause juvenile-onset vitelliform macular dystrophy (Best's disease). Hum Mol Genet. 1998;7(9):1517-25.
3. Petrukhin K, Koisti MJ, Bakall B, Li W, Xie G, Marknell T, et al. Identification of the gene responsible for Best macular dystrophy. Nat Genet. 1998;19(3):241-7.
4. Sun H, Tsunenari T, Yau KW, Nathans J. The vitelliform macular dystrophy protein defines a new family of chloride channels. Proc Natl Acad Sci U S A. 2002;99(6):4008-13.
5. Budiene B, Liutkeviciene R, Zaliuniene D. Best vitelliform macular dystrophy: literature review. Central European Journal of Medicine. 2014;9(6):784-95.
6. Mohler CW, Fine SL. Long-term evaluation of patients with Best's vitelliform dystrophy. Ophthalmology. 1981;88(7): 688-92.
7. Eksandh L, Bakall B, Bauer B, Wadelius C, Andreasson S. Best's vitelliform macular dystrophy caused by a new mutation (Val89Ala) in the VMD2 gene. Ophthalmic Genet. 2001; 22(2):107-15.
8. Renner AB, Tillack H, Kraus H, Kramer F, Mohr N, Weber BH, et al. Late onset is common in best macular dystrophy associated with VMD2 gene mutations. Ophthalmology. 2005; 112(4):586-92.
9. MacDonald IM, Lee T. Best Vitelliform Macular Dystrophy. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mefford HC, et al., editors. GeneReviews((R)). Seattle (WA)1993.
10. Maggon R, Parihar J, Vats DP, Mathur V. Best's Vitelliform Macular Dystrophy. Med J Armed Forces India. 2008;64(4): 379-81.
11. Johnson AA, Guziewicz KE, Lee CJ, Kalathur RC, Pulido JS, Marmorstein LY, et al. Bestrophin 1 and retinal disease. Prog Retin Eye Res. 2017;58:45-69.
12. Chung MM, Oh KT, Streb LM, Kimura AE, Stone EM. Visual outcome following subretinal hemorrhage in Best disease. Retina. 2001;21(6):575-80.
13. Wabbels B, Preising MN, Kretschmann U, Demmler A, Lorenz B. Genotype-phenotype correlation and longitudinal course in ten families with Best vitelliform macular dystrophy. Graefes Arch Clin Exp Ophthalmol. 2006;244(11):1453-66.
14. Testa F, Rossi S, Passerini I, Sodi A, Di Iorio V, Interlandi E, et al. A normal electro-oculography in a family affected by best disease with a novel spontaneous mutation of the BEST1 gene. Br J Ophthalmol. 2008;92(11):1467-70.
15. Boon CJ, Theelen T, Hoefsloot EH, van Schooneveld MJ, Keunen JE, Cremers FP, et al. Clinical and molecular genetic analysis of best vitelliform macular dystrophy. Retina. 2009; 29(6):835-47.
16. Seddon JM, Afshari MA, Sharma S, Bernstein PS, Chong S, Hutchinson A, et al. Assessment of mutations in the Best macular dystrophy (VMD2) gene in patients with adult-onset foveomacular vitelliform dystrophy, age-related maculopathy, and bull's-eye maculopathy. Ophthalmology. 2001;108(11): 2060-7.

17. Best vitelliform macular dystrophy [Internet]. Genetic and Rare Diseases Information Center (GARD). National Center for Advancing Translational Sciences (NCATS); 2016 [cited 2017 Nov18]. Available from: https://rarediseases.info.nih.gov/diseases/182/best-vitelliform-macular-dystrophy#ref__8276
18. Forsman K, Graff C, Nordstrom S, Johansson K, Westermark E, Lundgren E, et al. The gene for Best's macular dystrophy is located at 11q13 in a Swedish family. Clin Genet. 1992;42(3): 156-9.
19. Stohr H, Marquardt A, Rivera A, Cooper PR, Nowak NJ, Shows TB, et al. A gene map of the Best's vitelliform macular dystrophy region in chromosome 11q12-q13.1. Genome Res. 1998;8(1):48-56.
20. Moskova-Doumanova V, Pankov R, Lalchev Z, Doumanov J. Best1 shot through the eye-structure, functions and clinical implications of bestrophin-1 protein. Biotechnology & Biotechnological Equipment. 2013;27(1):3457-64.
21. Boon CJ, Klevering BJ, Leroy BP, Hoyng CB, Keunen JE, den Hollander AI. The spectrum of ocular phenotypes caused by mutations in the BEST1 gene. Prog Retin Eye Res. 2009;28(3): 187-205.
22. Booij JC, Boon CJ, van Schooneveld MJ, ten Brink JB, Bakker A, de Jong PT, et al. Course of visual decline in relation to the Best1 genotype in vitelliform macular dystrophy. Ophthalmology. 2010;117(7):1415-22.
23. Boon CJ, Klevering BJ, den Hollander AI, Zonneveld MN, Theelen T, Cremers FP, et al. Clinical and genetic heterogeneity in multifocal vitelliform dystrophy. Arch Ophthalmol. 2007;125(8):1100-6.
24. Cohn AC, Turnbull C, Ruddle JB, Guymer RH, Kearns LS, Staffieri S, et al. Best's macular dystrophy in Australia: phenotypic profile and identification of novel BEST1 mutations. Eye (Lond). 2011;25(2):208-17.
25. Wabbels B, Demmler A, Preising M, Lorenz B. Fundus autofluorescence in patients with genetically determined Best vitelliform macular dystrophy: Evaluation of genotype-phenotype correlation and longitudinal course. Investigative Ophthalmology & Visual Science. 2004;45(13):1762.
26. Atchaneeyasakul LO, Jinda W, Sakolsatayadorn N, Trinavarat A, Ruangvoravate N, Thanasombatskul N, et al. Mutation analysis of the VMD2 gene in thai families with best macular dystrophy. Ophthalmic Genet. 2008;29(3):139-44.
27. Katagiri S, Hayashi T, Ohkuma Y, Sekiryu T, Takeuchi T, Gekka T, et al. Mutation analysis of BEST1 in Japanese patients with Best's vitelliform macular dystrophy. Br J Ophthalmol. 2015;99(11):1577-82.
28. Ouyang YL, Zhang YJ, Xu GZ, Jiang R, Chen Q, Wang L. [Clinical manifestations and gene analysis in one Chinese family with Best vitelliform macular dystrophy]. Zhonghua Yan Ke Za Zhi. 2008;44(4):321-6.
29. Wong RL, Hou P, Choy KW, Chiang SW, Tam PO, Li H, et al. Novel and homozygous BEST1 mutations in Chinese patients with Best vitelliform macular dystrophy. Retina. 2010;30(5): 820-7.
30. Yanagi Y, Sekine H, Mori M. Identification of a novel VMD2 mutation in Japanese patients with Best disease. Ophthalmic Genet. 2002;23(2):129-33.
31. Zhao L, Grob S, Corey R, Krupa M, Luo J, Du H, et al. A novel compound heterozygous mutation in the BEST1 gene causes autosomal recessive Best vitelliform macular dystrophy. Eye (Lond). 2012;26(6):866-71.
32. Li Y, Wang G, Dong B, Sun X, Turner MJ, Kamaya S, et al. A novel mutation of the VMD2 gene in a Chinese family with best vitelliform macular dystrophy. Ann Acad Med Singapore. 2006;35(6):408-10.
33. Iannaccone A, Kerr NC, Kinnick TR, Calzada JI, Stone EM. Autosomal recessive best vitelliform macular dystrophy: report of a family and management of early-onset neovascular complications. Arch Ophthalmol. 2011;129(2):211-7.
34. Kinnick TR, Mullins RF, Dev S, Leys M, Mackey DA, Kay CN, et al. Autosomal recessive vitelliform macular dystrophy in a large cohort of vitelliform macular dystrophy patients. Retina. 2011;31(3):581-95.
35. Querques G, Zerbib J, Santacroce R, Margaglione M, Delphin N, Rozet JM, et al. Functional and clinical data of Best vitelliform macular dystrophy patients with mutations in the BEST1 gene. Mol Vis. 2009;15:2960-72.
36. Fishman GA, Baca W, Alexander KR, Derlacki DJ, Glenn AM, Viana M. Visual acuity in patients with best vitelliform macular dystrophy. Ophthalmology. 1993;100(11):1665-70.
37. Clemett R. Vitelliform dystrophy: long-term observations on New Zealand pedigrees. Aust N Z J Ophthalmol. 1991;19(3): 221-7.

38. Chhablani J, Jalali S. Intravitreal bevacizumab for choroidal neovascularization secondary to Best vitelliform macular dystrophy in a 6-year-old child. Eur J Ophthalmol. 2012;22(4): 677-9.

39. Leu J, Schrage NF, Degenring RF. Choroidal neovascularisation secondary to Best's disease in a 13-year-old boy treated by intravitreal bevacizumab. Graefes Arch Clin Exp Ophthalmol. 2007;245(11):1723-5.

40. Rishi E, Rishi P, Mahajan S. Intravitreal bevacizumab for choroidal neovascular membrane associated with Best's vitelliform dystrophy. Indian J Ophthalmol. 2010;58(2):160-2.

41. Cennamo G, Cesarano I, Vecchio EC, Reibaldi M, de Crecchio G. Functional and anatomic changes in bilateral choroidal neovascularization associated with vitelliform macular dystrophy after intravitreal bevacizumab. J Ocul Pharmacol Ther. 2012;28(6):643-6.

42. Cakir M, Cekic O, Yilmaz OF. Intravitreal bevacizumab and triamcinolone treatment for choroidal neovascularization in Best disease. J AAPOS. 2009;13(1):94-6.

43. Querques G, Bocco MC, Soubrane G, Souied EH. Intravitreal ranibizumab (Lucentis) for choroidal neovascularization associated with vitelliform macular dystrophy. Acta Ophthalmol. 2008;86(6):694-5.

44. Andrade RE, Farah ME, Costa RA. Photodynamic therapy with verteporfin for subfoveal choroidal neovascularization in best disease. Am J Ophthalmol. 2003;136(6):1179-81.

45. Sodi A, Murro V, Caporossi O, Passerini I, Bacci GM, Caputo R, et al. Long-Term Results of Photodynamic Therapy for Choroidal Neovascularization in Pediatric Patients with Best Vitelliform Macular Dystrophy. Ophthalmic Genet. 2015;36(2): 168-74.

46. Frennesson CI, Wadelius C, Nilsson SE. Best vitelliform macular dystrophy in a Swedish family: genetic analysis and a seven-year follow-up of photodynamic treatment of a young boy with choroidal neovascularization. Acta Ophthalmol. 2014;92(3): 238-42.

47. Andrade RE, Farah ME, Cardillo JA, Hofling-Lima AL, Uno F, Costa RA. Optical coherence tomography in choroidal neovascular membrane associated with Best's vitelliform dystrophy. Acta Ophthalmol Scand. 2002;80(2):216-8.

48. Lee TK, Clandinin MT, Hebert M, MacDonald IM. Effect of docosahexaenoic acid supplementation on the macular function of patients with Best vitelliform macular dystrophy: randomized clinical trial. Can J Ophthalmol. 2010;45(5):514-9.