Original Article

Clinical and visual electrophysiological characteristics of vitelliform macular dystrophies in the first decade of life

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Purpose: To evaluate patterns of pediatric vitelliform macular dystrophy (PVMD). **Methods:** This is a retrospective analysis of Indian children with vitelliform macular dystrophy (VMD) presenting within the first decade of life. Records were evaluated for clinical findings, family screening, and investigative findings including optical coherence tomography (OCT), fundus autofluorescence (FAF), full-field electroretinogram (ERG) and electrooculogram (EOG). Electrophysiology was scrutinized and audited for acquisition and interpretation errors. Findings on follow-up were also recorded. **Results:** 46 eyes of 24 patients were included. Mean age at presentation was 7.17 ± 2.17 years. Mean follow-up duration was 1.55 ± 1.69 years. Best disease was the commonest type of VMD detected (21 patients), while autosomal recessive bestrophinopathy was seen in three cases. Mean logMAR BCVA was 0.364 which decreased to 0.402 on follow-up. Hyperopia was noted in 29 out of 46 eyes (mean being +3.87 D, range ebing +0.75 to +8.75 D). Four eyes of four children had choroidal neovascular membrane at presentation, while another child developed while in follow-up. Solid type subretinal deposit was the commonest OCT finding (n = 29/38) and central hyper FAF was the commonest pattern (n = 18/32). EOG was available for review in 32 eyes, but was unreliable in 11 eyes. Seven eyes demonstrated complete absence of light rise on EOG. **Conclusion:** PVMD can present in advanced forms. Progression to complications with loss of visual acuity can happen within the first decade of life. EOG shows grossly suppressed waveforms in the light phase in a large number of such children.

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The term "bestrophinopathy" includes a group of phenotypically heterogenous disorders occurring due to deficiency of the bestrophin proteins. BEST1 protein, coded by the BEST1 gene (or VMD2 on chromosome 11) is expressed in the retinal pigment epithelium (RPE). The gene codes for a calcium gated chloride channel.[1] The dysfunction of this channel is currently linked to occurrence of macular degeneration characterized as vitelliform macular dystrophy (VMD), apart from its other associations. Best VMD (BVMD) is the most well-known of all the VMDs, and is typified by deposition of lipofuscin within the retina in autosomal dominant inheritance.[2] Other less common types include autosomal recessive bestrophinopathy (ARB), autosomal dominant vitreoretinochoroidopathy (ADVIRC) and adult onset VMD (AOVMD).[3]

It is believed that onset of BVMD happens in childhood, while the disease presents later in the second decade of life as a juvenile VMD. Most available literature presents clinical features in juvenile stages or adulthood.[4,5] Efforts have been made to link the clinical stages and visual acuity in VMD with optical coherence tomography (OCT) signs, fundus autofluorescence (FAF) patterns, and electrophysiology findings.[4,5] However, despite the noted childhood onset of VMD, literature on presentations of pediatric VMD (PVMD) is very scarce and limited to case reports or series of very small number of eyes.[6–8] Recently, investigative appraisals in BVMD have suggested the need for early childhood detection.[9,10] Therefore, knowledge of phenotypes of PVMD and its natural history is necessary.

We present the largest series of PVMD till date. We characterize the investigative profile, including electrophysiology, and critically compare it to existing literature on typical adolescent or adult presentations of VMD.

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Methods

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and local Ethics Committee (LEC-XXX). Electronic medical records were searched to identify cases of "Best vitelliform dystrophy/Bestrophinopathy/vitelliform dystrophy/ADVIRC/macular dystrophy" during the study period of January 2014 to December 2019.

Consecutive patients presenting in first decade of life (<10 years of age) were included. Records where clinical and investigative findings were not sufficient were excluded after manual screening. Discord between clinical and investigative findings was also considered as an exclusion criterion. Data collection focused on age, gender, spherical equivalent of refraction, clinical presentation, previous diagnosis, if any, OCT, FAF, electrooculogram (EOG), full-field electroretinogram (ERG) characteristics and changes during follow-up.

Study definitions

Fundus image of the vitelliform disease was divided into six stages: Stage I (Previtelliform), normal or only subtle RPE changes (tiny, central honeycomb structure centrally); Stage II (Vitelliform), classic "egg-yolk" lesion; Stage III (Pseudohypopyon), layering of lipofuscin; Stage IV (Vitelleruptive), breakup of material giving "scrambled-egg" appearance; Stage V (Atrophic), central RPE and retinal atrophy; and Stage VI, choroidal neovascular membrane (CNVM).[11] Cases with multifocal and extramacular hyper autofluorescent deposits and corresponding sub-normal electrophysiology with autosomal recessive inheritance were considered as ARB.

Investigative findings

Fundus photographs (Zeiss FF450 device) were reviewed for clinical characteristics including stage of disease and phenotypic characterization. These were reviewed by two senior retinal specialists independently to arrive at a consensus-based diagnosis. OCT was performed using high resolution spectral domain or swept source OCT (Topcon DRI-OCT triton). OCT angiography (Topcon DRI-OCT triton) was also reviewed wherever available. Fundus autofluorescence was assessed using short-wave FAF (Zeiss FF450 device). Findings were reviewed and classified as hypo-FAF, hyper-FAF, patchy FAF, spoke wheel type, and multifocal.[12] EOG and ERG (Metrovision Monpack One and LKC) were performed as per standard protocols by the International Society for Clinical Electrophysiology of Vision (ISCEV).[13,14] EOG was critically reviewed for reliability of wave forms, precise time points for calculation of light peak to dark trough ratio (Arden's ratio) and presence of light rise waves. EOG was considered as unreliable when waveforms were irregular or not square-topped. Arden's ratio was confirmed manually by reviewing time points of light peak and dark trough in all cases. This was compared to electronic readings, and in presence of a difference of 0.2 between either, the electronic readings were considered as unreliable. Arden's ratio below 1.8 was considered as subnormal.

The statistical analysis was performed using Microsoft Excel sheets and STATA v14.2 (StataCorp, College Station, TX, USA). Descriptive analysis was done with calculation of mean and frequencies. These findings have been presented in Tables 1–4.

Results

46 eyes of 24 patients with a diagnosis of vitelliform disease were recruited in the study cohort. The mean age of onset of symptoms was 7.17 ± 2.17 years (range 3–10 years, median 7.5 years, and mode 9 years), whereas the mean age at presentation to our tertiary hospital was 8.58 ± 2.20 years. The man to woman ratio was 3:1 (18 men). Bilateral presentation was noted in 22 patients. Six patients (25%) had positive family history (available up to two previous generations) of similar disease; only one patient had positive history of parental consanguinity. Detailed notes on complete family screening (excluding screening done for only the available members) were available for five patients only. Two patients exhibited associated systemic illness: one had chronic bronchitis and the other one had seizure disorder. There was no other history of developmental delays or associated systemic disease in any other patient. The main reason for presentation to our hospital was blurring of distance vision in 71% of cases (17 patients), while four patients had strabismus noticed by parents or teachers. Snellen's distant visual acuity was available in all cases. The mean logMAR best corrected visual acuity (BCVA) at baseline of the cohort was 0.364 (range 0–1.48). The mean spherical equivalent following cycloplegic refraction for the sample was +2.1 D. Interestingly, 29 eyes were hyperopic with an average hyperopia of +3.87 D (range +0.75 to +8.75 D). Only two eyes of two different patients had myopic refraction. Demography has been presented in Table 1.

Fundus image analysis

These were available in all the patients. ARB was seen in three patients [Fig. 1], while the rest had BVMD [Fig. 2]. No case of ADVIRC was noted. The differences between BVMD and ARB have been presented separately in Table 3. At presentation, majority of eyes with BVMD revealed stage 2 of disease (29 eyes); whereas stages 3 and 4 were observed in eight and three eyes respectively. CNVM was noted in four eyes of four different patients, who also had hemorrhage on fundoscopy. One eye had a full thickness trauma-related macular hole. Asymmetry of clinical stages was noted in 11 patients.

OCT analysis

OCT images of 38 eyes were available for review. Based on OCT presentation, two had type 2 CNVM while one each had type 1 or scarred CNVM. Detailed baseline OCT analysis revealed presence of specific features like subretinal hyperreflective deposits of solid type ($n = 29$), subretinal fluid ($n = 26$), elongation of photoreceptors ($n = 25$), ellipsoid zone (EZ) disruption ($n = 18$), RPE disruption ($n = 16$), and hypo-reflective spaces or cysts in inner nuclear layer (INL) ($n = 4$). CNVM or scar-like subretinal hyper reflective material was noted in four eyes after clinical correlation to fundus photograph. OCT angiography was available in three of these eyes which showed presence of a vascular network in the deep retinal capillary plexus slab [Fig. 3] [Table 2].

FAF analysis

FAF image was available in 32 eyes for review. The most common finding in FAF was central hyper-FAF surrounded by hypo-FAF ring in 18 eyes, followed by multifocal deposits (multiple, isolated increased FAF signals; $n = 8$),

Table 1: Patient profile and demography

Number of patients	24
Number of eyes	46
Man: Woman ratio	18:6
Mean age when disease noted	7.17±2.17 years (range 3-10 years, median 7.5 years and mode 9 years)
Mean age when presented to hospital	8.58±2.20 years
Laterality	Unilateral 2 patients, Bilateral 22 patients
Positive family history (parents or siblings affected)	6 patients
History of parental consanguinity	1
Any other systemic illness	Bronchitis/seizure disorder: 1/1 patient each
Mean duration of follow up	1.55±1.69 years (Range: Single visit to 6 years) <6 months of follow up: 17 eyes>6 months of follow up: 29 eyes
Chief complaint at presentation	Blurring of vision: 17 patients Squint: 4 patients (1 exotropia, 2 esotropia, hypertropia in 1 patient along with esotropia) Rubbing/itching/headache: 1/1/1 patient each
Stage of disease at presentation	Previtelliform: 0 eyes Vitelliform: 29 eyes Pseudohypopyon: 8 eyes Vitellieruptive: 3 eyes Atrophic: 0 CNVM: 4 eyes (scarred CNVM in 1 out 4 eyes) Others: 2 eyes (one had macular hole, one doubtful scarring)
Mean logMAR BCVA	0.364 (range 0-1.48)
Refractive error at presentation	Plano: 15 eyes Myopia: 2 eyes Hypermetropia: 29 eyes
Mean spherical equivalent	+ 2.1 D
Average Hyperopia	+ 3.87 D range (+0.75 to+8.75 D)

CNVM: Choroidal neovascular membrane, BCVA: Best corrected visual acuity

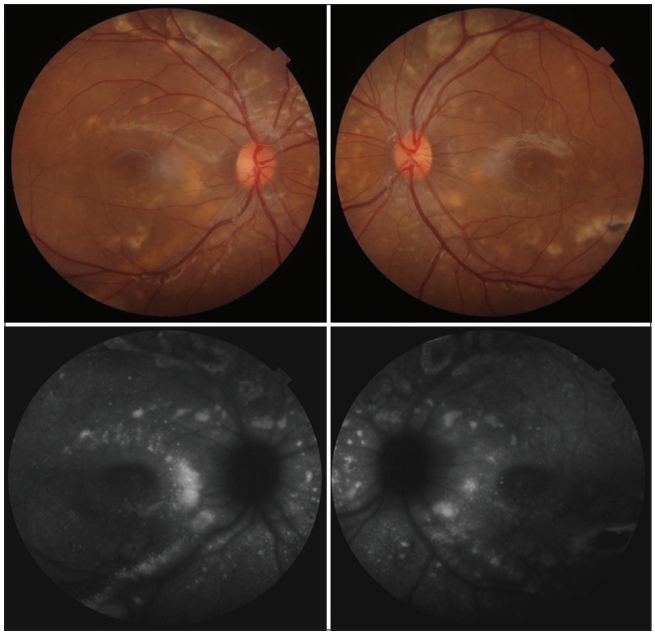

Figure 1: Image representative of case of autosomal recessive bestrophinopathy in a 4-year-old child. Note the hyper-FAF extramacular lesions seen as multifocal deposits in both eyes

central hypo-FAF surrounded by hyper-FAF ($n = 4$), and patchy FAF (combined reduced and increased FAF signal; $n = 2$). Other types of FAF signals were not seen.

Electrophysiology

Full-field ERG was available for assessment in 29 eyes. Seven of these were considered unreliable due to presence of irregular waveforms. 29 had normal ERG waves. Both eyes of one patient showed reduction of both scotopic and photopic responses with preserved oscillatory potentials. We analyzed EOG features of 32 eyes. Among them, we found the waveforms to be unreliable in 11 eyes (34.38%) [Fig. 4]. The mean Arden's ratio of the cohort was 1.4 ± 0.29. Arden's ratio was <1.5 in 11 eyes (mean value of 1.16 ± 0.17), while the ratio was between 1.5 and 1.8 in 10 eyes (mean 1.66 ± 0.11). In addition, 7 eyes (26.9%) of 5 patients showed a complete absence of light rise on EOG. EOG was poorly recorded in four eyes precluding analysis [Table 2]. In the two children labelled to have unilateral disease, there were no clinical signs in the fellow eye, and fellow eye EOG was normal in one and unreliable in the other.

Follow-up analysis

The mean duration of follow-up from initial presentation was 1.55 ± 1.69 years. Detailed presentation of distribution of follow-up data has been done in Table 4. Progression of disease or visual decline was noted in five eyes in a mean follow-up of 9.7 ± 3.12 months. Most eyes lost vision in the second year of follow up (3/5). OCT images were available for a follow-up review in 13 eyes by 6 months, and 4 eyes each by 7–12 months and 13–24 months. Subretinal deposits on OCT were seen to change in follow up; five eyes showed a reduction in subretinal deposits (flattening of solid deposits in

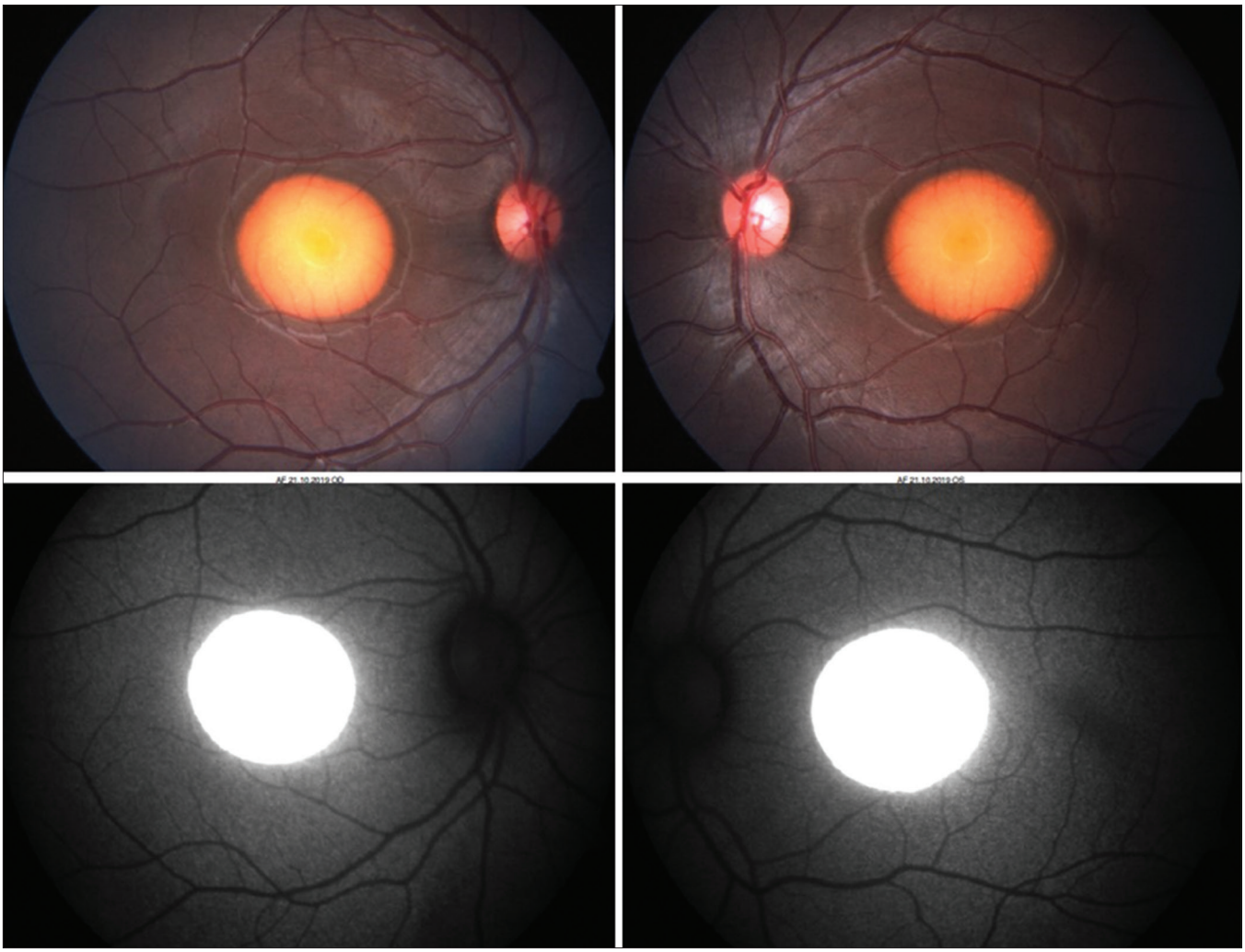

Figure 2: Image representative of Best Vitelliform macular dystrophy in a 7-year-old child. The disease is in stage 2 with noticeable corresponding hyper-FAF lesions

three cases), with one eye displaying an increase in subretinal hyperreflectivity. Reduction in SRF was noted in both eyes of one patient. Progression of stage of disease was noted in three eyes [Table 4]. The OCT changes did not correlate to change in visual acuity on follow up. FAF images were available in follow up for eight eyes only, while EOG was not repeated for any patient. One eye developed CNVM on follow up, which was noted in second year of follow up, while two eyes previously treated for CNVM showed evidence of scarring.

Discussion

We have collated the largest dataset on PVMD yet. In our series of 24 patients, we found BVMD and ARB to be the prevalent forms, the former outnumbering the latter by 7 times. This difference could be due to an actual higher prevalence of BVMD in the study population, or due to underestimation of ARB in relation to identification bias. PVMD has been reported even before the age of three years (youngest of our sample), the earliest being in a ten-month-old male infant.[6–8] BVMD was detected in that child due to family screening and was evident due to presence of clinical lesions. Thus, PVMD can be present clinically very early in life, and soon after birth too. Rishi *et al.*,[15] in their study of CNVM in children and adolescents, noted nine cases (25%) to be due to BVMD, the least age being eight years. Borman *et al.*[16] described a series of six patients with ARB (aged 1–6 years). Casalino *et al.*[17] described three patients of ARB presenting below 10 years of age, the youngest child being four years old. Apart from typical clinical features, most of the children in both these series had severely depressed EOG light rise. Other notable reports on PVMD have been summarized in Table 5. Thus, it is evident that this disorder can present very early in life with both clinical and investigative features, sometimes in severity that is enough to result in low vision. As gene therapy for monogenetic disorders like BVMD and ARB is likely to develop in future,[9,10] knowledge of clinical patterns of PVMD becomes very important, as also earliest possible clinical and genetic screening of babies born in such families with pre-conceptional genetic counselling. Lack of knowledge of such early presentations led to multiple wrong diagnosis for the children in our series before they presented to us, including macular scar, toxoplasmosis, Coats's disease, central serous chorioretinopathy and retinal tumors. Patients with PVMD analyzed in the current study were marked by a variable stage, including those of scars and CNVM, indicating a rapidly progressive form of disease. Family screening, though limited,

Table 2: Investigative profile of study population

Parameters	Number of Eyes
Optical coherence tomography (OCT)	
OCT available	38
Mean CMT (microns)	397.97±133.93
Subretinal hyperreflective deposits	29
Hypo spaces in INL	4
CNVM (corroborated clinically)	4
Subretinal fluid like finding	26
Elongation of photoreceptors	25
EZ disrupted	18
RPE disruption	16
Fundus autofluorescence	
FAF available	32
Central hyper surrounded by hypo AF	18
Central hypo surrounded by hyper AF	4
Multifocal (multiple, isolated increased FAF signals)	8
Patchy AF (combined reduced and increased FAF signal)	2
Electroretinogram (ERG)	
ERG available	29
Not reliable	7
Normal ERG	20
Subnormal scotopic and photopic	2 (same patient)
Electrooculogram (EOG)	
EOG available	32
Not reliable	11
Subnormal Arden ratio (<1.8)	21 eyes (<1.5 in 11 eyes, 1.5 to 1.8 in 10 eyes)
Mean Arden ratio	1.4±0.29
Absent of light rise	7 eyes (5 patients)

CMT: Central macular thickness, INL: Inner nuclear layer, CNVM: Choroidal neovascular membrane, EZ: Ellipsoid zone, RPE: Retinal pigment epithelium, FAF: Fundus autofluorescence

Table 3: The difference between BVMD and ARB

Characteristics	BVMD (*n*=40 eyes/21 patients)	ARB (*n*=6 eyes/3 patients)
Mean age at presentation	8.5 years	6 years
Visual acuity	0.39 (SD=0.43, 0-1.48)	0.16 (SD=0.19, 0-0.4)
Refractive error	+3.8 D	One patient hyperopic (+0.75 DS/+1.0 DS) Rest two had no refractive error
Fundus	At presentation majority of eyes with BVMD revealed stage 2 of disease; whereas stages 3 and 4 were observed in 8 and 3 eyes, respectively	Multifocal deposits in the posterior pole and nasal to disc also
Autofluorescence imaging features	Central hyper-FAF surrounded by hypo-FAF ring,	Multifocal deposits (multiple, isolated increased FAF signals)
Macular optical coherence tomography features	Subretinal hyperreflective deposits of solid type, subretinal fluid, elongation of photoreceptors, ellipsoid zone (EZ) disruption, RPE disruption and hypo-reflective spaces/cysts in INL	Available in 4 eyes Subretinal hyperreflective dots of solid type with SRF in all eyes, elongation of photoreceptors in 2 eyes of same patient
Electrooculogram (light rise)	7 eyes of 5 patients showed a complete absence of light rise	Only available in 1 patient Both eyes reveal light rise with Arden ratio of 1.06 and 1.53 in OD and OS respectively
CNVM at baseline	4 eyes	None
Visual decline on follow up	Progression of disease or visual decline was noted in 5 eyes	Vision remained the same, no visual decline at 6 months of follow up
Complications	One eye developed choroidal neovascular membrane on follow up	None reported

BVMD: Best Vitelliform macular dystrophy, ARB: Autosomal Bestrophinopathy, FAF: Fundus autofluorescence, CNVM: Choroidal neovascular membrane

Table 4: Follow-up data

Follow-up duration overall	Decline in visual acuity	Progression of stage in BVMD	OCT/ OCT-A	Stage progression on OCT	FAF	Progression of FAF changes	Development of complications
n=24 patients	*n*=46 eyes	*n*=40 eyes	*n*=38 eyes	-	*n*=32 eyes	-	-
6 months (10)	0	0	13	0	8	0	0
7-≤12 months (5)	1	1	4	1	3	0	2 (scarring post treatment for CNVM)
13-≤24 months (5)	3	2	4	2	0	Not available	1 (new CNVM)
>24 months (4)	1	0	0	Not available	0	Not available	0

BVMD: Best vitelliform macular dystrophy, OCT-A: Optical coherence tomography angiography, FAF: Fundus auto fluorescence, CNVM: Choroidal neovascular membrane

Table 5: Review of literature for similar cases as current study population

Author (Year, country)	Number of PVMD (<10 years)	Type (BVMD/ ARB)	Minimum age	Reason for presentation	Follow up and progression	Main conclusion or remarks by the authors	EOG
Boon *et al.*, 2009[1]	7	BVMD	2 years	Blurring of vision in 2 eyes; Routine check-up in 5 eyes	NA	Broad phenotypic variability despite similar genotype	NA
Borman *et al.*, 2011[16]	6	ARB	1 years	Squint: 2; Reduction in central vision: 1; Headache: 1; Leukocoria: 1; Asymptomatic: 1	NA	Visual loss was less in first decade of life unless subretinal neovascular membrane develops	Light rise undetected in all cases
Kinnick *et al.*, 2011[19]	1	ARB	3 years	NA	NA	Detected in a large cohort being assessed for genotypes	NA
Chhablani *et al.*, 2012[20]	1	BVMD	6 years	Blurring of vision; active CNVM	9 months follow up; one injection of anti-VEGF, Scarring noted at last visit	Intravitreal bevacizumab is useful	Subnormal EOG
Rishi *et al.*, 2013[15]	2	BVMD	8 years	Blurring of vision Involuted subfoveal CNVM stage	Observed no recurrence at the last visit	BVMD was the second-most common cause of CNVM in their cohort	NA
Griffith *et al.*, 2014[6]	2	BVMD	10 months	Asymptomatic, routine eye check up	NA	Screening pediatric patients with a family history of Best's disease	Could not be done
Padhi *et al.*, 2018[21]	Number of PVMD not mentioned, but patient <18 years: 14	BVMD	NA	NA	NA	BVMD was the most common cause of CNV in cohort (age range 1.3-18)	NA
Casalino *et al.*, 2021[17]	3	ARB	4 years	Reduced central vision	Average years of follow up of these 3 patients is 7.3 years	Need for genetic database	Severe reduction in the electro-oculogram light peak-to-dark trough ratio was detected in all cases

PVMD: Pediatric vitelliform macular dystrophy, BVMD: Best vitelliform macular dystrophy, ARB: Autosomal recessive bestrophinopathy, EOG: Electroretinogram, CNVM: Choroidal neovascular membrane

revealed a positive association of similar disease on fundus evaluation in 25% cases overall, but EOG had not been done uniformly for all the family members. It is known that BVMD can occur without preceding family history, and the sensitivity of genetic sequencing is also lower in such cases. The absence of a known family history and negative fundus examination of

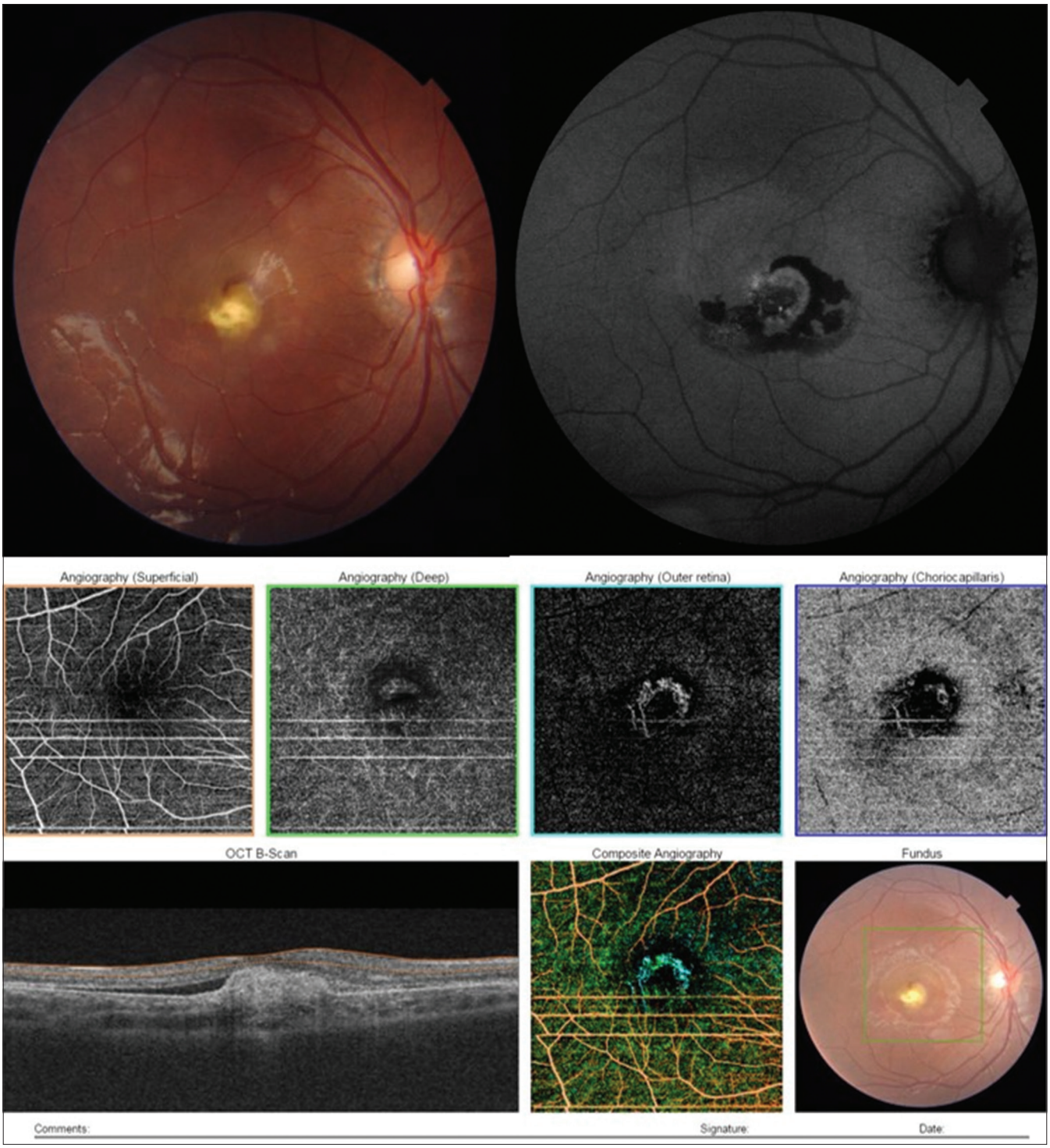

Figure 3: Image representative of Best disease in a 10-year-old child with CNVM in right eye. OCT angiography proved useful in showing a type 2 vascular network in deep retinal as well as outer retinal complex

parents does not exclude the diagnosis of BVMD in children, and the index of suspicion needs to be high.[18]

We established a preponderance of hypermetropia in 63.04% of eyes (29/46 eyes) with an average hyperopia of +3.87 D (range +0.75 to +8.75 D); 16/29 eyes had hyperopia of >3D. The refractive error analysis in our study is in accordance with the previously done study by Coussa *et al*.[22] where the authors reported hyperopia in 69.9% cases with a mean SE of +1.73 D in patients aged <18 years (16 eyes). In general, hyperopia is consistent across all decades of life in patients with VMD, displaying a greater prevalence with increasing age and independent of vitelliform deposit height, as measured using OCT. For these reasons, the BEST1 gene has been linked to ocular growth, and remarkably has also been implicated in diseases that cause severe stunting of eye growth. Our study

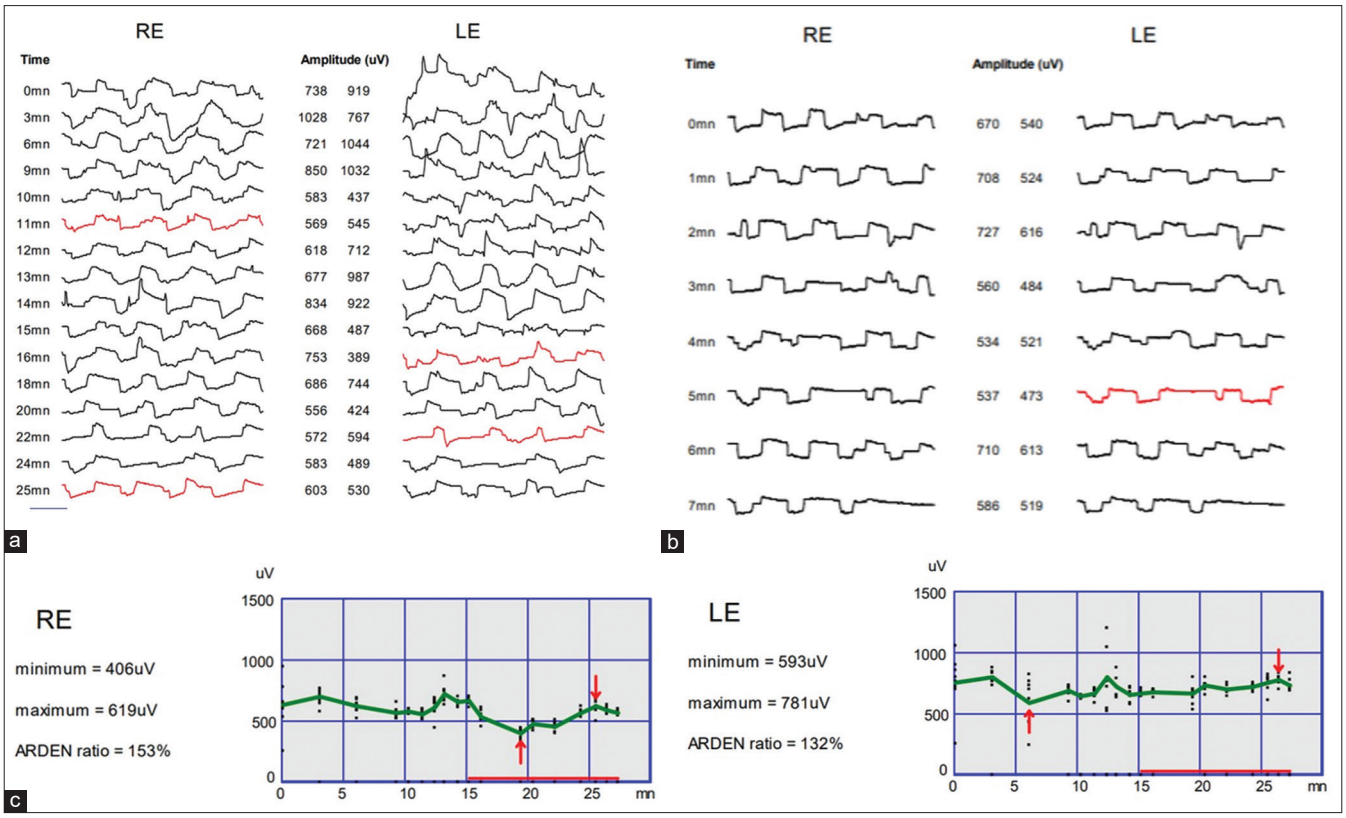

Figure 4: Acquiring electrooculogram (EOG) is challenging in children and must be scrutinized for reliability, specifically for regularity of the wave forms and time points of measurements. (a) Image shows the irregular waveforms filled with noise throughout the EOG study of a 9-year-old boy with Best disease. (b) Image shows smoother and more regular square wave forms during EOG of a 5-year-old child with Best disease during dark phase. (c) Automated calculation of Arden's ratio in a 9-year-old child. Though the ratio as reported a low in both eyes, right eye image shows the automated measuring point for "dark trough" has been erroneously picked during the light phase at 19 minutes. The time points are correct for the left eye

demonstrates a tremendously high prevalence of hyperopia in PVMD, in comparison to the population-based prevalence of hyperopia in only 4% of Indian children aged 0–15 years.[23] Thus children with VMD, must be carefully assessed for hyperopia due to its obvious implications in this age group. Despite the high incidence of hyperopia, we did not notice angle closure glaucoma or rise in IOP in any of the patients.

Patchy FAF pattern (combined reduced and increased FAF signals) is known to be common in adults. We found hyper-autofluorescent pattern to be commoner (56.2% eyes) in the children of our series. These patterns are known to be non-specific to clinical stage of VMD.[12] Various signs of VMD on OCT have already been evaluated, and even linked to disease prognosis.[24,25] Presence of solid type subretinal deposits, SRF-like finding, outer-retinal changes, subretinal hyperreflective material (SHRM) and CNVM noted by us in children are thus well documented in adults too. We noted photoreceptor elongation in 25 eyes, suggesting photoreceptor dysfunction beyond clinically apparent lesions.[26] Presence of SRF-like finding was noted in 26 eyes. Only four eyes had CNVM proven on OCTA. SRF-like finding can't be taken as an indicator of underlying presence or resolving CNVM, and is known to be related to changes in the subretinal deposits.[27] All the children with CNVM had hypo-reflective spaces in inner-nuclear layers [Fig. 3]. As noted by other authors, we also found OCTA to be very useful in detection and confirmation of CNVM in children, as dye-based angiography may not be an easy option in most cases.[28,29] Three out of four eyes of CNVM (except the eye with scarred CNVM at presentation) were treated with intravitreal anti-VEGF (Bevacizumab 1.25 mg/0/05 ml), and subsequently manifested scarring at 6 month follow up. The mean number of injections required was two per eye. The eye which developed CNVM on follow up (at 6 months) had pseudo hypopyon stage at presentation while fellow eye had CNV at presentation itself. OCT findings are known to change with time. This includes the amount of solid deposit, SRF, and outer-retinal changes.[30] As in adults, we were not able to correlate these findings on first visit to the disease stage or visual acuity.[31] Flattening of subretinal deposits is known to occur with disease progression.[30] We found this phenomenon to occur soon in follow up, indicating a possible progressive nature of the disease in early life.

EOG measures the standing potential of the eye indirectly, and is known to be subdued in preclinical stages of VMD in adults, while ERG is generally normal in absence of severe photoreceptor damage. The EOG may also be affected in the carriers of BVMD.[32] The Arden ratio (ratio of the light peak amplitude to dark trough amplitude) is typically reduced in adult eyes with VMD, and is also the most well-studied indication of EOG.[32] Normal values of this ratio are generally in excess of 1.8, while other studies have considered other normal ratio values (1.6–2.0).[33,34] In some adults with VMD, there is

a gradual deterioration of the Arden ratio, and normal EOG gradually becomes abnormal with disease progression.[35] We found markedly subdued EOG response noted in our sample amongst the reliable EOG studies (mean Arden ratio of 1.4). This phenomenon was also reported by Borman *et al*.[16] in their six cases of pediatric ARB where no light rise could be detected in all the cases where it was performed, including a one-year-old child. Similarly, from the graphs provided by Casalino *et al*.[17] in their study on ARB, it can be seen that the Arden ratio was one or nearly one in at least 2/3 children below 10 years of age, indicating an absence of light rise altogether. Though data on PVMD-related EOG is generally lacking, the RPE function seems to be severely affected in PVMD on EOG. This is notable in our results as well as those of other authors. In line with the previous discussion, this marks the severity of PVMD in early childhood itself. However, one should be cautious while interpreting the results of EOG in PVMD, as we found the test to be unreliable in a significant number of cases. We checked the results on EOG manually in all the cases, which has also been suggested in the ISCEV standards for performing EOG.[13] The primary faults noted by us were erroneous automated calculation of Arden ratio due to wrong choice of measurement points, followed by absence of plateau pattern of waveforms.

The major limitation of our study is the lack of genetic evidence. Family screening and history may be taken as a "soft" substitute, but is not enough especially if EOG has not been performed in family members.[36] Despite considerable emphasis and encouragement, most of the families of this series denied genetic tests, citing expenditure. Most of our cases had only OCT or OCTA performed in the follow-up, which could have limited our understanding on progression of the VMD. These limitations are partly due to retrospective nature of the analysis. However, because of the rarity of VMD, and more so PVMD, prospective data collection is difficult. A more viable way may be an ambispective approach for PVMD, where missing data points including those on genetic analysis be completed in prospect. A newborn screening protocol and prospective evaluation of the children of probands would help in determining the natural history of this disease in early life.

Conclusion

In summary, we have provided a rare dataset on PVMD. The children had all clinical and investigative findings known in adults. While some had very advanced disease, others showed progressive decline early in follow up at a very young age. EOG is useful for diagnosis of PVMD and shows markedly suppressed response, but can be unreliable in children. There is a need for studying PVMD in future for genetic linkages responsible for early presentation of advanced disease.

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Conflicts of interest

There are no conflicts of interest.

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