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ARTICLE

Clinical evaluation of torpedo maculopathy in an infant population with additional genetic testing for NEXMIF mutation

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PURPOSE: To assess clinical characteristics of torpedo maculopathy (TM) lesions in an infant population with age ≤1.5 years and to investigate the role of NEXMIF mutation in the development of TM.

METHODS: Retrospective analysis of medical records of 17 consecutive infants with the diagnosis of TM between 2016 January and 2019 December were done. Fundus images and a hand-held spectral-domain optical coherence tomography (Envisu 2300, Bioptigen, Morrisville, NC, USA) were used to identify clinical characteristics of TM lesions. Additional molecular testing for mutation screening for NEXMIF gene was also carried out.

RESULTS: Totally 55334 infants were screened during the study period and 17 (0.03%) were identified as having TM. The mean age at the time of diagnosis was 3.94±5.08 months. All TM lesions showed variable degrees of hypopigmentation. Satellite lesion in one infant was nasally located to the main TM lesion. Absence, disruption, loss, degeneration and/or irregularity of the ellipsoid zone were common findings on OCT examination. No pathogenic or likely pathogenic variant of NEXMIF gene was detected.

CONCLUSION: Fundoscopic appearance and OCT findings of lesions show similarities to those already reported previously. Contrary to popular belief, a nasally located satellite lesion was observed in one of our case.

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INTRODUCTION

Torpedo maculopathy (TM) was first described by Roseman and Gass as a solitary, well demarcated, oval, placoid lesion with a wedge-shaped tail at retinal pigment epithelium (RPE) level in the macula. They considered this lesion as an asymptomatic solitary hypopigmented nevus of the RPE [1]. It is suggested that TM lesion is congenital and could be associated with the foetal temporal macular "bulge" that normally occurs at four to six months of gestation [2]. Although the pathophysiologic aspect of TM is currently not well known, several theories have been suggested mainly addressing the developmental abnormalities in RPE [2]. Later on, several case presentations have reported on clinical documentation of this disease by using optical coherence tomography (OCT) indicating disturbance within RPE, increased choroidal reflectivity and choroidal excavation [3–6]. Based on OCT findings, TM lesions have also been grouped into two types, including Type 1 lesion that shows outer retinal attenuation without outer retinal cavitation and Type 2 lesion that shows outer retinal attenuation as well as outer retinal cavitation with neurosensorial elevation [7].

No study has documented clinical and patient characteristics of TM lesions in an infant cohort so far. Only a case report has presented OCT findings in a six-month-old child which is known to be the youngest patient diagnosed with TM in the literature [8]. Furthermore, only a few case presentations have reported on the relationship between TM and a genetic abnormality. Neurite extension and migration factor (NEXMIF) and tuberous sclerosis 2 (TSC2) gene mutations have been considered to have a possible association with TM development [9, 10]. Hence, in the present study, we aimed to demonstrate patient characteristics and clinical appearance of TM lesions along with OCT findings in a series of infants aged between 1 month and 1.5 years old at a tertiary referral hospital in Turkey. Additional molecular testing for mutation screening for NEXMIF gene was also performed.

METHODS

After obtaining institutional review board approval (No. 06.05.2020 / 87), retrospective analysis of medical records of consecutive patients in ophthalmology department at a tertiary referral hospital in Turkey identified a total of 17 infants aged ≤1.5 years diagnosed as having TM between 2016 January and 2019 December. This study followed the tenets laid out in Declaration of Helsinki. Parents of each infant provided informed consent for the study that included analyses of imaging and medical records. Data regarding gender, gestational age, birth weight, age at diagnosis of TM, medical history and clinical characteristics were noted.

Fundoscopic assessment

TM diagnosis was made based upon binocular indirect ophthalmoscopic examination following administration of tropicamide 0.5% and phenylephrine 2.5% eye drops. Retinal photographs were obtained either with

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RetCam (Clarity Medical Systems Inc., Pleasanton, CA, USA) or Heine video omega 2 C binocular indirect ophthalmoscope operating with Archimed programme (Heine Optotechnik, Herrsching, Germany).

TM lesions were defined based on previous literature data as, oval, hypopigmented, or hyperpigmented lesions at the level of the RPE, with the tip of the lesion usually directed toward the macula [11–13].

Optical coherence tomography imaging

Spectral-domain OCT on the hand-held OCT (Envisu 2300, Bioptigen, Morrisville, NC, USA) analysis was performed in all patients to detect abnormalities within the TM lesion. Both eyes of each infant were examined. In each OCT session, linear scans that included the TM lesion were performed. OCT images were considered acceptable for analysis if the series of scans were appropriately focused and aligned and of sufficient signal strength to confidently identify the structural properties of the lesions. OCT image interpretations were made by one author (M.G) with secondary review of OCT image data by another author experienced in paediatric OCT imaging (M.K.E).

Molecular analysis for mutation screening

Genetic testing was available for all subjects. Peripheral blood samples were collected from the patients after obtaining additional written informed consent from parents. Genomic DNA was extracted from EDTA-anticoagulated peripheral blood by using standard methods. DNA extraction from the blood sample was done by using a semi-automated robot as recommended by the manufacturer (Qiagen). The concentration and quality-control (260/280 nm and 260/230 nm values) of the DNA samples were determined by fluorometrically (Qubit v3.0) and UV spectrophotometry. Custom primers are designed for mutation screening for NEXMIF gene, and mutation screening is performed with Illumina MiSeq System. The library preparation for next-generation sequencing was performed using Nextera XT index Kit V2 (illumina), Nextera XT Library Prep Kit (illumina), and Miseq V2 (illumina) Reagent Kit. Variant calling and data analysis were performed by using NextGENe (Version 2.4.2.3 / SoftGenetics LLC-USA) and Geneticist Assistant (Version 1.8.1.0/SoftGenetics LLC-USA) bioinformatics analysis tools. Compatible with the 2015 American College of Medical Genetics and Genomics (ACMG) standards and guidelines, interpretation of the variants was performed and classified into 5 categories (benign, likely benign, variant of unknown significance (VUS), pathogenic, likely pathogenic) [14]. We excluded common polymorphic variants with a minor allele frequency of more than 1%. Since there are not enough genome and exome databases for the Turkish population, 1000 genome projects, dbSNP ExAC, and GnomAD data were used as the control population. Synonymous variants were also filtered out. Finally, the effects of the variants on protein function were investigated by using in-silico pathogenicity prediction tools such as SIFT, Polyphen, MutationTaster, and GERP.

RESULTS

A total of 55,334 infants were screened during the study period. Seventeen children (0.03%) were identified with TM. The mean age at the time of TM diagnosis was 3.94 ± 5.08 months (1–21 months). The mean gestational age and birth weight of the infants were 36.23 ± 4.81 weeks (25–40 weeks) and 2721.76 ± 905.21 g (730–3620 g), respectively. There were seven girls and 10 boys. TM was detected in three preterm infants (Cases 2, 6 and 7) during retinopathy of prematurity (ROP) screening. One preterm infant (Case 7) later received intravitreal bevacizumab for ROP. Another preterm infant (Case 2) showed spontaneously regressed ROP.

Table 1 summarizes the clinical characteristics of children and OCT findings of TM lesions. Figures 1, 2, 3 and 4 demonstrate the appearance of TM lesions on retinal photographs along with corresponding structural changes on OCT (Figs. 1, 2 and 3). All TM lesions in the study had the variable amount of hypopigmentation. Associated RPE hyperpigmentation was prominent in some cases (Cases 14, 15 and 17). TM lesions were characteristically located temporal to the macula except for cases 10 and 13 who had TM lesions located nasal to the fovea. Cases 13 and 17 had satellite lesions. Satellite lesion in case 13 was very close and nasally located to the main TM lesion. Satellite lesion in case 17 was about two-disc diameter temporal from the primary TM lesion. Foveal involvement of TM was observed in cases 2, 3, 5 and 17.

Two eyes of two infants were excluded from OCT analysis due to insufficient image quality. Adequate OCT data were available for 15 subjects. All lesions demonstrated disturbance in the outer retina except for those in cases 5 and 6 where OCT findings were not notable. Absence, disruption, loss, degeneration and/or irregularity of the ellipsoid zone were common findings on OCT examination. Case 1 demonstrated a large choroidal excavation. Choroidal hyperreflectivity was observed in case 17. Cases 3 and 10 showed cone outer tip elongation. Case 11 had an intact ellipsoid zone but the accumulation of vitelliform like lesion was seen between RPE and neurosensorial retina. Another common finding was disturbance in RPE, including the absence of RPE (cases 1 and 2), RPE hypertrophy (case 3), RPE thinning (case 8), RPE degeneration (cases 9 and 12) and RPE loss (cases 15 and 17).

According to the ACMG criteria [14] as described in methods section, we did not detect any pathogenic or likely pathogenic variant of NEXMIF gene in the present study.

DISCUSSION

Torpedo maculopathy is a rarely seen disease that has been reported mostly as an incidental pathology on fundoscopic evaluations. TM prevalence may show variability depending upon its detection rate during routine ophthalmologic examinations. A study identifying 8 children aged between 3 and 12 years old with TM has shown a TM prevalence of two per 100000 [12]. Among examined infants during our study period, we observed 17 per 55,334 (0.03%) prevalence of TM. Our TM detection rate probably depends on awareness of this condition after encountering first cases during routine screening procedures of the infants.

Several assumptions have been made regarding the developmental mechanism of TM lesions. It has been postulated that developmental abnormalities in the choroid or ciliary vasculature lead to TM occurrence [2]. Another study has stated that retinal nerve fibre layer has an impact on the development of RPE resulting in TM [13]. One observation in the present study is that 4 infants fell under low birth weight criteria where only two had birth weight above 3500 g. This may arise a possible association with the developmental explanation of TM. Relatively higher prevalence of TM in our study may also be linked to this. We believe that this finding deserves further investigation.

In TM cases, lesions are characteristically hypopigmented and have a pointed tip towards the macula with some located adjacent to the fovea and some placed outside the macula [11, 15]. Compared to the tip of TM lesions, tail of the lesions often showed variable degrees of hyperpigmentation [6]. In our study, four patients (cases 2, 3, 5 and 17) had foveal involvement of TM and in two patients (cases 10 and 13) lesions were uncharacteristically located nasal to the fovea. Although rare, nasal origination of TM lesion has previously been documented [13, 16]. Associated apparent hyperpigmentation at the tail of the lesions was also seen in some of our patients (cases 14, 15 and 17).

Satellite lesions have been reported accompanying the main TM lesion [12, 17, 18]. These lesions are usually located temporally and tend to be smaller than the main TM lesion [12]. Consistently, satellite lesions in our study (cases 13 and 17) were found to be smaller than the primary TM lesion. Interestingly, in one of our case (case 13), satellite lesion had a nasal placement relative to the main TM lesion. As far as we know, we firstly reported a nasal location of satellite lesion in our study.

Optical coherence tomography examinations of TM lesions have revealed variable findings regarding changes in outer retinal layers, RPE and/or choroid. Studies have commonly reported loss or degeneration of ellipsoid zone [7, 19], absence or thinning of outer nuclear layer [6], RPE thinning [20], excavation of choroid [11] and increased choroidal reflectivity [21]. Most common OCT

Table 1. Clinical characteristics of the study population.

Patient No.	Gender (M:Male, F: Female)	Gestational age (weeks)	Birth weight (g)	Age at TM diagnosis (months)	Eye involved (OD:Right eye, OS: left eye)	OCT findings
1	M	39	2570	21	OD	Absence of ellipsoid zone and RPE, Choroidal excavation
2[b]	F	29	1120	6	OD	Absence of ellipsoid zone and RPE
3[b]	M	40	3050	1	OD	Cone outer tip elongation, RPE hypertrophy, degeneration of ellipsoid zone
4	F	38	3150	1	OD	N/A
5[b]	F	39	3200	2	OS	Normal findings
6	F	25	730	1	OD	Normal findings
7	M	26	970	1	OD	Irregularity of ellipsoid zone, normal RPE contour
8	M	39	3620	8	OS	Thinning of ONL, loss of ellipsoid zone, thinning of RPE
9	M	40	3100	9	OS	Ellipsoid zone disruption and RPE degeneration
10	M	38	3300	2	OS	Cone outer tip elongation
11	F	38	3500	1	OD	Intact ellipsoid zone and accumulation of vitelliform like lesion between RPE and sensorial retina
12	M	37	2950	4	OS	Degeneration of ellipsoid zone and RPE
3[a]	M	38	3340	4	OS	Loss of ellipsoid zone and minimal RPE cleft
14	M	39	3260	2	OD	Irregularity of ellipsoid zone
15	F	38	2920	2	OS	Loss of ellipsoid zone and RPE
16	F	39	3140	1	OS	N/A
17[a,b]	M	34	2350	1	OD	Loss of ellipsoid zone and RPE, thinning of ONL, Choroidal hyperreflectivity

TM torpedo maculopathy, *OCT* optical coherence tomography, *RPE* retinal pigment epithelium, *ONL* outer nuclear layer, *N/A* not available.
[a]Cases with satellite lesions apart from the main TM lesion.
[b]Cases with foveal TM involvement.

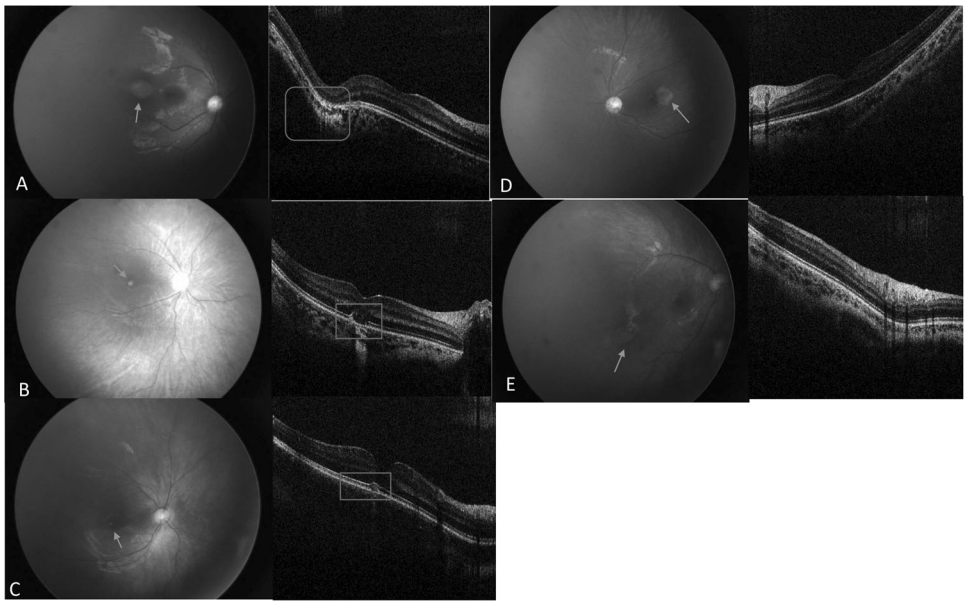

Fig. 1 Retinal photographs and OCT images for patients 1,2,3,5 and 6. Arrows show location of torpedo maculopathy (TM) lesions on each retinal photograph. Foveal involvement of TM lesions are seen in (**B**) (Patient 2), (**C**) (Patient 3) and (**D**) (Patient 5). Location of boxes demonstrate corresponding structural changes of TM lesions on OCT imaging, including (**A**). Absence of ellipsoid zone and retina pigment epithelium (RPE) with choroidal excavation (Patient 1) (**B**). Absence of ellipsoid zone and RPE (Patient 2) (**C**). Cone outer tip elongation, RPE hypertrophy and degeneration of ellipsoid zone (patient 3) (**D**) and (**E**). No visible change is seen on OCT imaging (Patient 5 and 6).

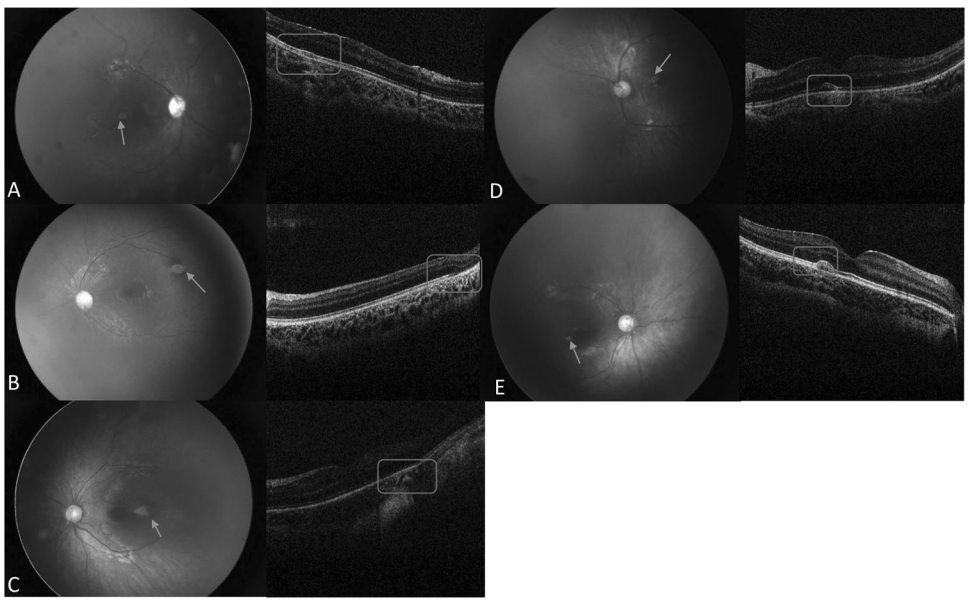

Fig. 2 Retinal photographs and OCT images for patients 7,8,9,10 and 11. Arrows show location of torpedo lesions on each retinal photograph. Location of boxes demonstrate corresponding structural changes of TM lesions on OCT imaging, including (**A**). Irregularity of ellipsoid zone with a normal RPE contour (Patient 7) (**B**). Thinning of outer nuclear layer, loss of ellipsoid zone and thinning of RPE (Patient 8) (**C**). Ellipsoid zone disruption and RPE degeneration (Patient 9) (**D**). Cone outer tip elongation (Patient 10) (**E**). Intact ellipsoid zone and accumulation of vitelliform like lesion between RPE and sensorial retina (Patient 11).

findings in the present study were disturbances in the ellipsoid zone and RPE. These findings were absence, degeneration or irregularity of the ellipsoid zone and/or RPE and RPE hypertrophy. We also observed cone outer tip elongation revealed by the elevation of the ellipsoid zone in two cases (cases 3 and 10). Furthermore, based on the previous definition by Wong et al. [7], we identified one patient (case 1) with type 1 TM lesion who presented with choroidal excavation.

OCT signs in satellite and main TM lesions have been shown to be similar. Shirley et al. [12] have demonstrated localised broadening and attenuation of the interdigitation zone with elevation of the external limiting membrane and ellipsoid zone along with preservation of the inner retina of the satellite lesion which was similar to those seen in the main TM lesion. Identically, loss of ellipsoid zone in the satellite lesion in case 13 in our study showed resemblance to that in the primary TM.

Based on the colour fundus photographic appearance and OCT findings, we can state that different heterogenetic phenotypes were observed in the present series of infants with TM. So, it may be assumed that apart from its classical descriptive terminology,

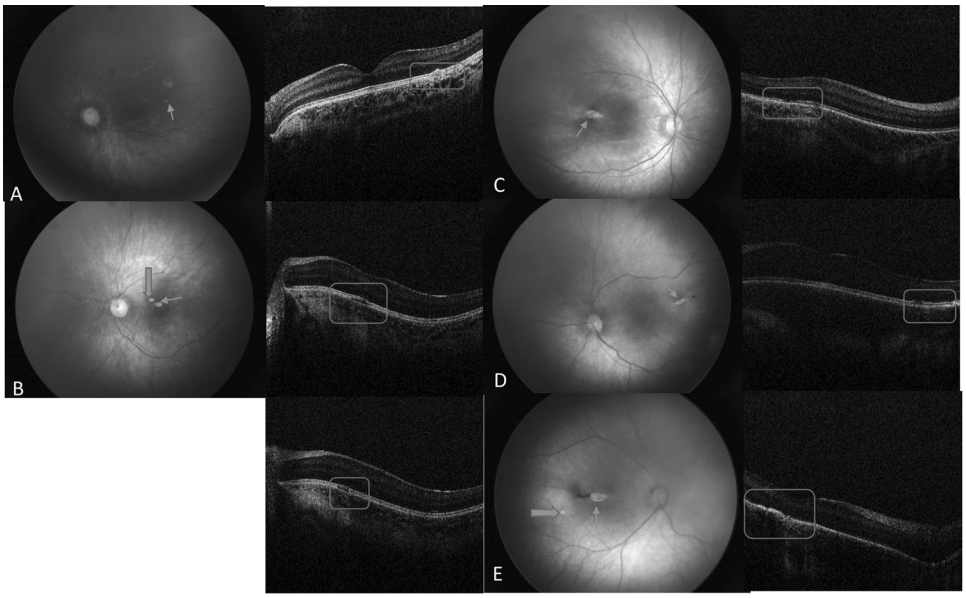

Fig. 3 Retinal photographs and OCT images for patients 12,13,14,15 and 17. Arrows show location of torpedo lesions on each retinal photograph. Foveal involvement of TM lesion is seen in **E** (Patient 17). Bold arrows show satellite lesions in B (Patient 13) and E (Patient 17). Location of boxes demonstrate corresponding structural changes of TM lesions on OCT imaging, including (**A**). Degeneration of ellipsoid zone and RPE (Patient 12) (**B**). Loss of ellipsoid zone and minimal RPE cleft in both main torpedo lesion (above) and satellite lesion (below) (Patient 13) (**C**). Irregularity of ellipsoid zone (Patient 14) (**D**). Loss of ellipsoid zone and RPE (Patient 15) (**E**). Loss of ellipsoid zone and RPE, thinning of ONL and choroidal hyperreflectivity (Patient 17).

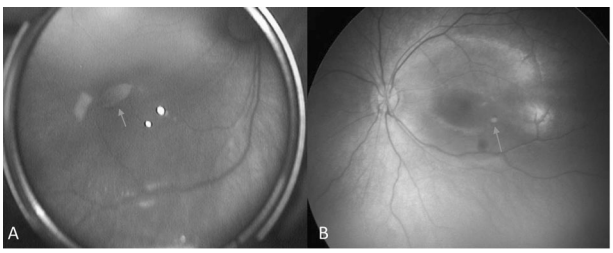

Fig. 4 Retinal photographs for patients 4 and 16. Retinal photographs for patient 4 (**A**) and patient 16 (**B**) where OCT imaging was not available for these cases due to insufficient image quality. Arrows show location of torpedo lesions on each retinal photograph.

TM development might be associated with different pathogenetic mechanisms including different genetic pathways resulting in different phenotypic clinical pictures.

Although TM lesions have been reported to be benign lesions without further clinical progression, some authors have demonstrated choroidal neovascular membrane formation accompanying the main TM lesion [17]. Besides, choroidal neovascular membrane has been shown even in a 15-year old female adolescent patient in another study [12]. It has been suggested that structural alterations in outer retina have a chance to induce development of choroidal neovascular membrane in TM patients [17]. We did not identify such additional pathology at least in the current series. This might depend on very early examination of our cohort. But, it is reasonable to think that these patients need to be carefully examined periodically in order to detect a possible presence of choroidal neovascular membrane in the future.

It is important to differentiate TM lesions especially those lying outside the macula from other RPE lesions and congenital hypertrophy of the RPE (CHRPE). CHRPE is classically either nonpigmented or pigmented lesion and frequently located in the mid-peripheral fundus [22]. Additionally, CHRPE lesions can be associated with familial adenomatous polyposis and in this situation, these lesions tend to be bilateral, occur in multiple quadrants, have a pisiform shape with irregular margins [23]. Based on these findings, we did not find any concordance in clinical definition between TM lesions in our study and CHRPE.

Association of TM with a genetic abnormality remains scarce in the literature. In a case report, Alarcon-Martinez et al. [9] have documented constellation of findings in a 32-months old boy with pathogenic NEXMIF mutation, including mild motor delay, language delay, autistic features, strabismus and TM. Another relationship between TM and TSC2 mutation has been shown in a 12-year old boy with tuberous sclerosis who had astrocytic hamartomas and TM [10].

Mutations in NEXMIF gene have been shown together with ophthalmologic abnormalities. Strabismus was the common condition with pathogenic NEXMIF variant [24]; in addition, keratoconus was also seen in another patient [25]. No pathogenic or likely pathogenic variant of NEXMIF gene was observed in the present cohort. To the best of our knowledge, our study is the first presenting a genetic analysis in a series of infants with TM. Based on our results, we believe that TM was incidentally detected in previous patients with pathogenic variant of NEXMIF gene.

In conclusion, we exhibited clinical characteristics of TM in an infant cohort aged between one month and 1.5 years. This is the first infant series of TM estimating a prevalence of 17 per 55334. OCT findings of TM lesions in our study seemed to be identical to those already reported in the literature. Contrary to popular belief, we showed a nasally placed satellite lesion of TM in one of our case. This may arise a phenotypic variance in TM lesions as proposed previously [12]. In addition, we did not identify a possible genetic association of TM development with NEXMIF mutation.

Summary

What was known before

- Torpedo maculopathy is a benign and rare lesion of the retinal pigment epithelium. Only one published paediatric case series of torpedo maculopathy exists in the literature. Few numbers

of studies suggested an association between NEXMIF mutation and torpedo maculopathy development.

What this study adds

- First infant cohort of torpedo maculopathy exhibiting an incidence of 17 per 55334 over four years. We reported nasal location of a satellite lesion due to torpedo maculopathy. No pathogenic or likely pathogenic variant of NEXMIF gene was observed.

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AUTHOR CONTRIBUTIONS

GC, MG and OK conceived and designed the presented study. GC, AV, OK and YKD performed the data collection. GC, MG, AV and MKE performed the analysis and wrote the manuscript. MG and MKE provided critical review of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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