Case Report

Extraretinal Fibrovascular Proliferation in a Neonate Possibly Associated with an *ESAM* Gene Variant

Sadık Etka Bayramoğlu*, Nihat Sayın*, Mehmet Erdoğan*, Sümeyra Doğan**, Alper Gezdirici***, Merih Çetinkaya****

*University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
**University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Radiodiagnosis, İstanbul, Türkiye
***University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Genetics, İstanbul, Türkiye
****University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Neonatology, İstanbul, Türkiye

Abstract

A female infant born with a gestational age of 35 weeks and birth weight of 2500 g was referred for ophthalmic examination on the second postnatal day. Bilateral venous dilatation and arterial tortuosity, severe extraretinal fibrovascular proliferation, and peripheral ischemia were detected. Fluorescein angiography showed profoundly delayed arteriovenous transit and peripheral avascularity. Both eyes were treated with diode laser photocoagulation and bevacizumab injection. Cranial magnetic resonance imaging (MRI) revealed hydrocephalus, ventricular dilatation, and cerebral atrophy. Her family history revealed that the patient's brother presented to the ophthalmology outpatient clinic at postnatal 3 months with inoperable total retinal detachment and similar cranial MRI findings. No systemic or ocular findings were detected in the parents. A recent study showed that in 13 cases, including our patients, bi-allelic variants in the *ESAM* gene lead to a new neurodevelopmental disease whose main clinical features include impaired speech and language development, seizures, varying degrees of spasticity, ventriculomegaly, intracranial hemorrhage, and developmental delay/mental disability. Newborn siblings of children with serious pathological retinal findings should undergo a detailed ophthalmic examination as soon as possible after birth to prevent total retinal detachment, even without a diagnosis of specific inherited retinal vascular diseases. Further investigations performed in collaboration with an international network may reveal more candidate gene variants possibly related to retinopathy of prematurity-like ophthalmological findings such as extraretinal fibrovascular proliferation.

Cite this article as: Bayramoğlu SE, Sayın N, Erdoğan M, Doğan S, Gezdirici A, Çetinkaya M. Extraretinal Fibrovascular Proliferation in a Neonate Possibly Associated with an *ESAM* Gene Variant. Turk J Ophthalmol 2023;53:386-389

Address for Correspondence: Sadık Etka Bayramoğlu, University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: sadiketka@windowslive.com **ORCID-ID:** orcid.org/0000-0002-9502-4368
Received: 10.08.2022 **Accepted:** 25.06.2023

DOI: 10.4274/tjo.galenos.2023.72609

Keywords: *ESAM*, FEVR, incontinentia pigmenti, Norrie, retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) occurs in infants with low gestational age (GA) and low birth weight as a result of retinal hypoxia and hyperoxia. Extraretinal fibrovascular proliferation and retinal detachment may develop in infants with ROP.[1] Usually, ROP disease occurs 4-10 weeks after birth, depending on the GA of the infant and oxygen therapy method. Rare diseases such as familial exudative vitreoretinopathy (FEVR), Norrie, and incontinentia pigmenti (IP) may cause proliferation in the retina, leading to findings that can be difficult to differentiate from ROP. This report presents a case that was not compatible with ROP, FEVR, Norrie, or IP in terms of genetics and systemic findings, in which progression to retinal detachment was prevented with laser and anti-vascular endothelial growth factor treatment on the third postnatal day.

Case Report

A female infant born with a GA of 35 weeks and birth weight of 2500 g was referred for ophthalmic examination on the second postnatal day due to a family history of bilateral retinal detachment. Anterior segment examination revealed bilateral neovascularization of the iris and pupillary rigidity. Fundus examination revealed bilateral venous dilatation and arterial tortuosity. Both eyes showed severe extraretinal fibrovascular proliferation in 6-8 clock hours, peripheral ischemia in all quadrants, and vitreous hemorrhage in the left eye, which prevented visualization of the posterior pole and temporal periphery

(Figures 1, 2). Fluorescein angiography showed profoundly delayed arteriovenous transit (>90 s), incomplete venous filling, and peripheral avascularity. Both eyes were treated with diode laser photocoagulation to the peripheral ischemic retina and intravitreal injection of 0.3125 mg bevacizumab. Additional laser photocoagulation was performed on the left eye after the vitreous hemorrhage regressed at 45 weeks' postmenstrual age (Figure 2f). The disease fully regressed after treatment; no reactivation was observed during 4 years of ophthalmological follow-up. Although the retina was anatomically attached and other optical structures were normal, the patient had nystagmus and severe visual impairment.

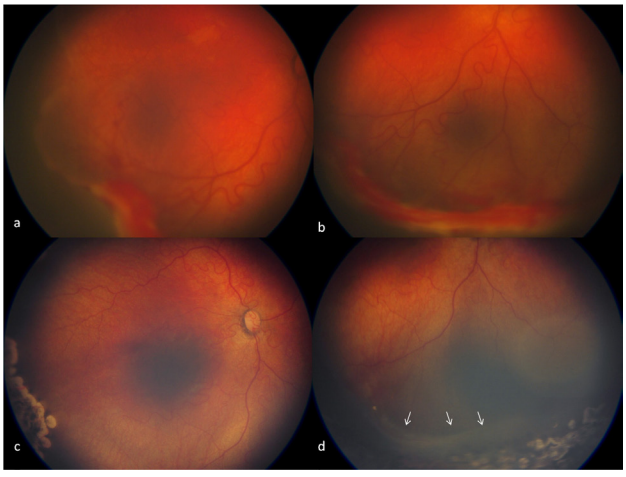

Figure 1. (a, b) Wide-field fundus photos of the right eye showing venous and arterial dilation, arterial tortuosity, and severe extraretinal fibrovascular proliferation on postnatal day 2. The eye was treated with combined laser and intravitreal 0.3125 mg bevacizumab. (c, d) At two months after treatment, the vascular dilation had regressed

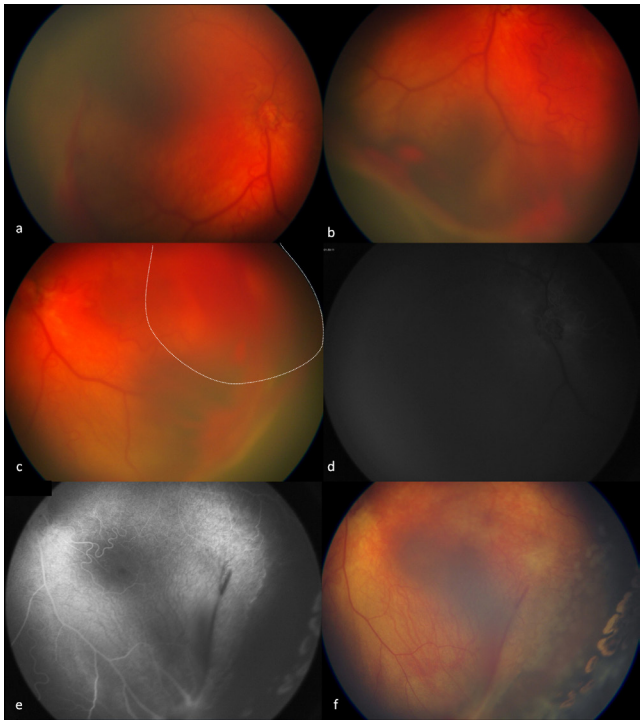

Figure 2. (a, b) Wide-field fundus photos of the left eye on postnatal day 2. (c) Vitreous hemorrhage prevents visualization of the temporal quadrant (circled area). (d) Fluorescein angiogram demonstrated profoundly delayed arteriovenous transit on postnatal day 3. The eye was treated with combined laser and intravitreal 0.3125 mg bevacizumab. (e) Fluorescein angiography performed after the vitreous hemorrhage regressed at the age of 2 months showed avascular retina between the laser scars and the normal retina. (f) Laser was applied to the residual avascular retinal area. Significant regression of the vascular dilation and fibrovascular proliferation are observed in wide-field fundus photos obtained at 2 months

On physical examination, triangular face, smooth philtrum, and prominent chin were present. Cranial magnetic resonance imaging (MRI) revealed a thin corpus callosum, diffuse calcification in the periventricular white matter, hydrocephalus, ventricular dilation, and cerebral atrophy (Figure 3). The patient had severe neuromotor retardation (severe developmental delay and intellectual disability, absence of speech and language development, hypotonia, and severe epileptic seizures). Hypertrophic cardiomyopathy was detected during follow-up.

The patient's family history revealed that her brother presented with bilateral iris coloboma and total retinal detachment at postnatal 3 months. Dysmorphic features, MRI and neurologic findings, and neuromotor development were similar between the siblings. No systemic or ocular findings were detected in the parents. Whole exome sequencing revealed the homozygous c.115del (p.Arg39Glyfs*33) frameshift variant in the *ESAM* gene in both siblings. The parents were heterozygous for the variant.

Discussion

Although our case had findings similar to severe stage 3 ROP and plus disease, we considered that the presented case may be related to inherited disease with retinal vaso-occlusive findings. This conclusion was based on the lack of low birth weight and GA, the lack of a history of oxygen therapy, and the very early presentation for the development of ROP, as well as the presence of family history and cranial findings.

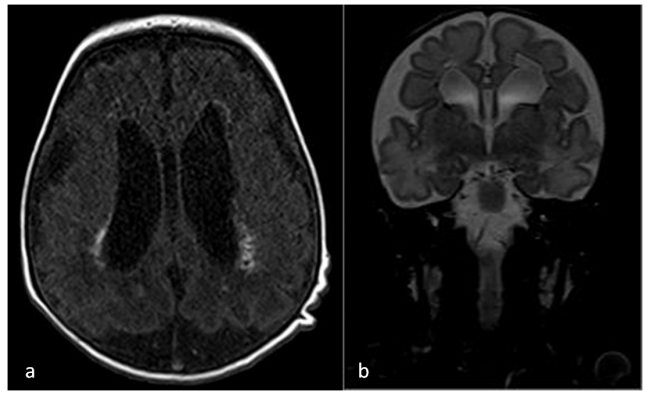

Figure 3. (a, b) Cranial MRI revealed diffuse calcification in the periventricular white matter, hydrocephalus, dilation of the ventricles, and cerebral atrophy
MRI: Magnetic resonance imaging

The Wnt signaling pathway is essential in ocular angiogenesis and the pathogenesis of inherited ocular vascular diseases such as Norrie disease, FEVR, and osteoporosis-pseudoglioma syndrome. *NDP, LRP5, FZD4,* and *TSPAN12* gene variants have been found to be related to the disruption of the Wnt signaling pathway.[2] Dysplastic retina with pseudoglioma appearance is the main characteristic ocular finding of Norrie disease.[3] The absence of a dysplastic retina in the present case may distinguish it from Norrie disease according to the ocular findings.

While subretinal exudation and radial retinal folds are remarkable findings of FEVR, the disease has a wide range of retinal and angiographic findings.[4,5] According to the clinical staging system, stage 1 can present with only avascular peripheral retina without extraretinal vascularization and exudation.[4] On the other hand, in later stages, patients can present with total retinal detachment. Although our case meets all three diagnostic criteria for FEVR that were previously defined by Kashani et al.[4] and Ranchod et al.,[5] we consider our case to have differential features from FEVR, such as the presence of intracranial pathologies and the lack of specific gene variants for FEVR, as well as the lack of remarkable findings such as retinal folds or subretinal exudation.

In addition to Wnt-related retinal vasculopathy, variants of the *IKBKG* gene (inhibitor of the kappa light polypeptide gene enhancer in B-cells, kinase gamma) play an essential role in the pathogenesis of IP and infantile retinopathy. Although IP is often considered a primarily dermatological disease, ophthalmic and intracranial pathologies may accompany skin lesions.[6] The vaso-occlusive nature of the disease may cause retinal avascularity, neovascularization, and exudative and tractional detachments.[6,7,8,9] Cerebral atrophy, dilated ventricles, hydrocephalus, and corpus callosum lesions have been reported in IP patients.[10] Therefore, the cranial imaging findings in the present case were comparable with previous reports of IP. Nevertheless, due to the lack of dermatological and dental lesions and *IKBKG* gene variant, the diagnosis of IP was ruled out.

In a recently published study conducted with an international collaborative network, bi-allelic variants in the *ESAM* gene were identified in these siblings as well as another 11 individuals with similar neurological findings.[11] However, severe extraretinal fibrovascular proliferation was noted during the neonatal period only in the present siblings. In the aforementioned study, retinal ischemia and retinal hemorrhage were reported in only two other individuals.[11] In one of them, vascular tortuosity, retinal ischemia, and new vessels were reported at the age of 10, although not as severe as the cases we presented, which seem to be in the same spectrum as our cases. This data suggest that *ESAM* gene variants may present different expressivity or other unidentified gene variants may contribute to these severe findings.

Laser photocoagulation of the ischemic avascular retina was the gold standard treatment for ROP and FEVR for the last three decades.[4,12] Nevertheless, combination therapy (laser and anti-vascular endothelial growth factor) for ROP and FEVR has been reported in the literature.[13,14,15] We preferred combination therapy because vitreous hemorrhage in the left eye prevented the completion of laser treatment and severe extraretinal fibrovascular proliferation was present in both eyes.

In conclusion, our case did not have gene variants that were previously described for the Wnt signaling pathway and *IKBKG* gene. Bi-allelic *ESAM* gene variants may cause extraretinal retinal vascularization during the neonatal period. Further investigations performed in collaboration with an international network may reveal more candidate gene variants that may be related to ROP-like ophthalmological findings such as extraretinal fibrovascular proliferation. While both eyes of the presented patient were treated successfully on postnatal day 3, her brother could not be treated for advanced disease. Therefore, newborn siblings of children with serious pathological retinal findings should undergo a detailed ophthalmic examination as soon as possible after birth to prevent total retinal detachment, even without a diagnosis of specific inherited retinal vascular diseases.

Ethics

Informed Consent: Obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E.B., N.S., M.E., S.D., A.G. M.Ç., Concept: S.E.B., A.G., Design: S.E.B., A.G., Data Collection or Processing: S.E.B., Analysis or Interpretation: S.E.B., N.S., M.E., S.D., A.G. M.Ç., Literature Search: S.E.B., Writing: S.E.B., A.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Higgins RD. Oxygen saturation and retinopathy of prematurity. Clin Perinatol. 2019;46:593-599.
2. Wang Z, Liu CH, Huang S, Chen J. Wnt Signaling in vascular eye diseases. Prog Retin Eye Res. 2019;70:110-133.
3. Walsh MK, Drenser KA, Capone A Jr, Trese MT. Early vitrectomy effective for Norrie disease. Arch Ophthalmol. 2010;128:456-460.
4. Kashani AH, Brown KT, Chang E, Drenser KA, Capone A, Trese MT. Diversity of retinal vascular anomalies in patients with familial exudative vitreoretinopathy. Ophthalmology. 2014;121:2220-2227.
5. Ranchod TM, Ho LY, Drenser KA, Capone A Jr, Trese MT. Clinical presentation of familial exudative vitreoretinopathy. Ophthalmology. 2011;118:2070-2075.
6. Swinney CC, Han DP, Karth PA. Incontinentia Pigmenti: A Comprehensive Review and Update. Ophthalmic Surg Lasers Imaging Retina. 2015;46:650-657.
7. Goldberg MF, Custis PH. Retinal and other manifestations of incontinentia pigmenti (Bloch-Sulzberger syndrome). Ophthalmology. 1993;100:1645-1654.
8. Holmström G, Thorén K. Ocular manifestations of incontinentia pigmenti. Acta Ophthalmol Scand. 2000;78:348-353.
9. Huang NT, Summers CG, McCafferty BK, Areaux RG, Koozekanani DD, Montezuma S. Management of retinopathy in incontinentia pigmenti: a systematic review and update. J Vitreoretin Dis. 2018;2:39-47.
10. Minić S, Trpinac D, Obradović M. Systematic review of central nervous system anomalies in incontinentia pigmenti. Orphanet J Rare Dis. 2013;8:25.

11. Lecca M, Pehlivan D, Suñer DH, Weiss K, Coste T, Zweier M, Oktay Y, Danial-Farran N, Rosti V, Bonasoni MP, Malara A, Contrò G, Zuntini R, Pollazzon M, Pascarella R, Neri A, Fusco C, Marafi D, Mitani T, Posey JE, Bayramoglu SE, Gezdirici A, Hernandez-Rodriguez J, Cladera EA, Miravet E, Roldan-Busto J, Ruiz MA, Bauzá CV, Ben-Sira L, Sigaudy S, Begemann A, Unger S, Güngör S, Hiz S, Sonmezler E, Zehavi Y, Jerdev M, Balduini A, Zuffardi O, Horvath R, Lochmüller H, Rauch A, Garavelli L, Tournier-Lasserve E, Spiegel R, Lupski JR, Errichiello E. Bi-allelic variants in the ESAM tight-junction gene cause a neurodevelopmental disorder associated with fetal intracranial hemorrhage. Am J Hum Genet. 2023;110:681-690.
12. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684-1695.
13. Ozdek S, Unlu M, Gurelik G, Hasanreisoglu B. Intravitreal anti-VEGF therapy as an adjunct to laser photocoagulation for severe aggressive posterior retinopathy of prematurity. J Optom. 2013;6:51-59.
14. Kim J, Kim SJ, Chang YS, Park WS. Combined intravitreal bevacizumab injection and zone I sparing laser photocoagulation in patients with zone I retinopathy of prematurity. Retina. 2014;34:77-82.
15. Lyu J, Zhang Q, Xu Y, Zhang X, Fei P, Zhao P. Intravitreal ranibizumab treatment for advanced familial exudative vitreoretinopathy with high vascular activity. Retina. 2021;41:1976-1985.