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Knobloch syndrome in a patient from Chile

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Abstract

Knobloch Syndrome (KS) is a rare autosomal recessive hereditary disease. Despite its clinical heterogeneity, it is characterized by vitreoretinal degeneration and high myopia, with or without occipital skull defects. It is caused by mutations in the *COL18A1* gene, which codifies for collagen XVIII, present in retina and vascular endothelium. Since the first description of the disease by doctors Knobloch and Layer in 1972, over 100 cases and 20 pathogenic or likely pathogenic mutations have been reported. We present the case of a child born from a consanguineous couple in Chile with congenital high myopia and dysmorphisms without an occipital skull defect. Whole exome sequencing analysis revealed an inherited homozygous variant in *COL18A1*, c.4224_4225delinsC, p.Pro1411Leufs*35.

KEYWORDS

COL18A1, high-grade myopia, Knobloch syndrome

1 | INTRODUCTION

Knobloch Syndrome (KS) is a rare autosomal recessive disorder (MIM #267750), characterized by congenital high-grade myopia and midline skull defects (mainly occipital skull defects). Clinical heterogeneity is described for both common clinical components (eye and skull defects). Typical eye manifestations are vitreoretinal degeneration (in the form of chorioretinal atrophy and white fibrillar vitrous condensation) and high myopia. Variable eye manifestations include anterior segment abnormalities (poor pupillary dilatation, smooth and atrophic iris, iris transillumination, shallow anterior chambers, pigment dispersion syndrome, early cataract, and ectopia lentis), macular lesions, persistent fetal vasculature, retinal detachment, and glaucoma.

The second component of KS is skull defects – occipital encephalocele, which may or may not be seen. Skull involvement might manifest as just focal scalp alopecia without underlying skull defect. There might be additional brain malformations (polymicrogiria, cerebral atrophy, pachygiria and heterotopia), intellectual disability (seen in approximately 20% of patients) and epilepsy (in 16.7% of patients) (Corbett et al., 2017; Hull et al., 2016). Involvement of other organs such as kidney and lungs has been inconsistently reported in some cases (Hull et al., 2016; Seaver, Joffe, Spark, Smith, & Hoyme, 1993).

KS is confirmed by the presence of biallelic mutations in the *COL18A1* gene and was first reported by Sertié et al., 2000.

COL18A1 encodes collagen type XVIII, widely expressed in basement membranes of practically all tissues (Suzuki et al., 2002). It is expressed into three different isoforms—alpha 1polypeptide chains differing in their N-terminal sequence and length (NC11–303, NC11–493, NC11–728) (Sertié et al., 2000; Suzuki et al., 2002). Short isoform collagen XVIII is thought to play an important role in maintaining eye structure, neuronal migration and closure of the neural tube during embryogenesis (Corbett et al., 2017; Passos-Bueno et al., 2006; Sertié et al., 2000; Suzuki et al., 2002). The long isoform is believed to play critical role in organization and maintenance of the human eyes.

Here, we report the first Chilean patient in the literature, an 8-year-old girl, with a homozygous pathogenic variant in *COL18A1*.

2 | CASE REPORT

The 8-year-old female patient is the second child born from healthy, consanguineous parents (first cousins). Her older sister is healthy and there is no other family history of note (Supplementary Figure 1). After an uneventful pregnancy, she was born at 38 weeks of gestation by cesarean section (due to a previous cesarean section) with normal Apgar score and anthropometry according to gestational age and sex.

Bilateral buphthalmos was detected by her pediatrician during her first month of life, which led to the diagnosis of congenital myopia by an ophthalmologist around that time. At 2 months age, facial dysmorphisms were documented (depressed nasal bridge, flat face profile, micrognathia) and echocardiogram showed a minimum permeable foramen ovale. Radiologic study of long bones, abdominal ultrasound and auditory screening (otoacoustic emissions) were normal. Karyotype in lymphocytes was normal (46,XX) and the patient was clinically diagnosed as Stickler Syndrome.

On follow up at 8 years 5 months, she was examined at our hospital by an Ophthalmologist. Her best corrected visual acuity was 20/800 in the right eye, and 20/400 in the left eye, both eyes (OU) with −22.00 spherical diopters, normal color vision and abnormal stereopsis. The right pupil showed miosis (1.2 mm) and the left was slightly larger (1.8 mm) suggestive of anisocoria. Slit-lamp examination showed clear cornea and normally located, clear lens with deep anterior chambers OU. No iris transilluminations were observed OU. In the left eye, inspection of the iris-pupil showed atrophy, and the right eye, iris was normal. Gonioscopy showed an open angle in both eyes. Intraocular pressure was 19 and 20 mmHg in the right and left eye, respectively. The cup-disc ratio was 0.4 in both eyes. The neuroretinal rim was lost slightly in the temporal optic disc sector in both eyes and retinas showed diffuse chorioretinal atrophy in both eyes. No lattice degeneration neither retinal tears was observed. The vitreous was clear in both eyes, with very small bundles of irregular thickened fibers in both eyes. She also had convergent strabismus of the right eye.

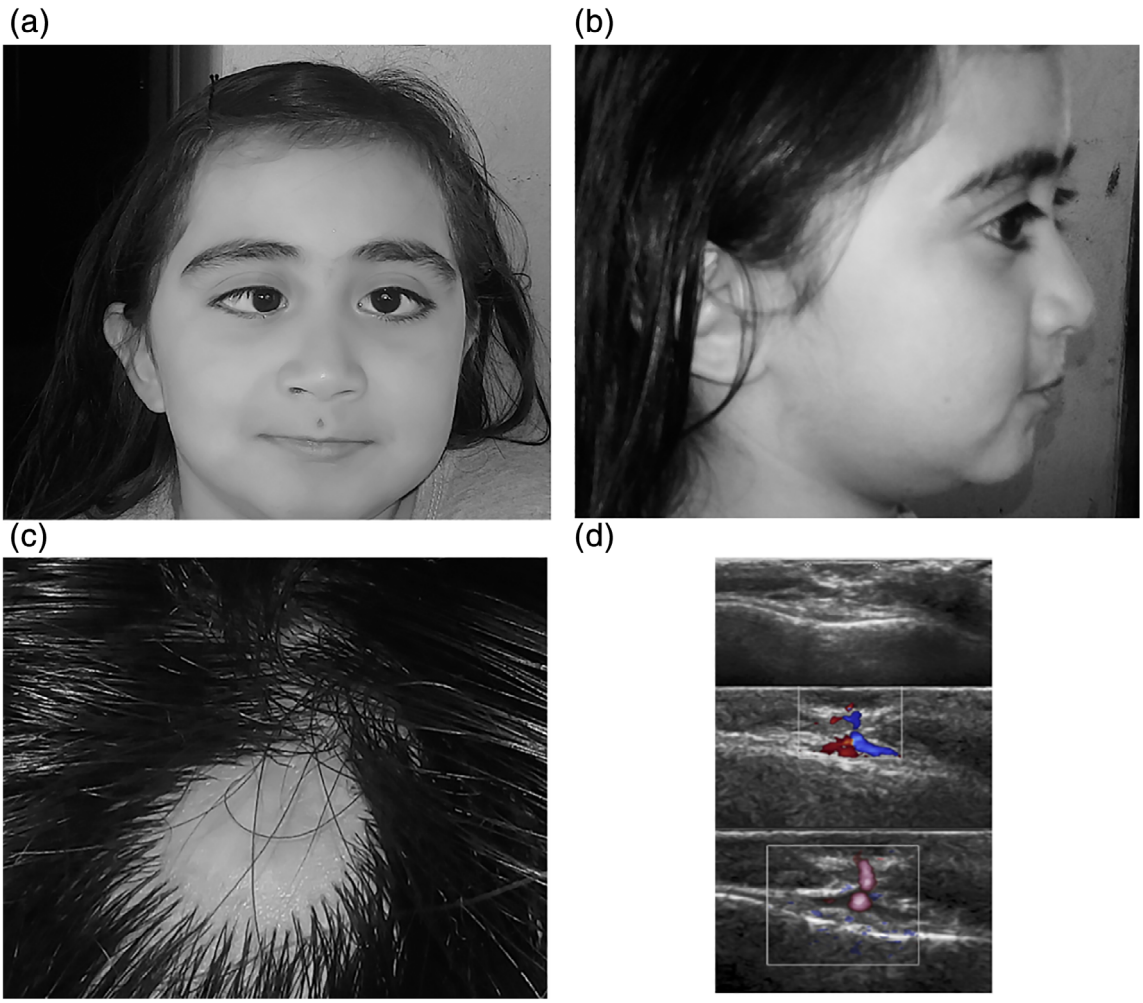

FIGURE 1 (a, b) Facial features. Flat face profile with apparently enlarged eyeballs, a depressed nasal bridge, mild anteverted nares, smooth philtrum, thin vermilion of the upper lip, micrognathia, low set ears and a short neck. (c) Flat, focal occipital alopecic lesion, with well-defined borders and measuring 1 cm in diameter. (d) Ultrasound examination of occipital lesion: an occipital scalp mass is seen at the region of the palpable lesion, with color Doppler flow. There appears to be a communication between superficial veins and dural venous sinuses, suggestive of *sinus pericranii* [Color figure can be viewed at wileyonlinelibrary.com]

Despite her vision impairment, the patient performed adequately at school and everyday activities with the help of glasses. Her cognitive functions were appropriate for her age and there was no history of seizures.

Examination at 8 years, 9 months revealed a head circumference 54 cms (25th percentile), height 140 cms (90th percentile) and weight 44 kgs (98th percentile). Facial features included a flat face profile with apparent proptosis, depressed nasal bridge, anteverted nares, smooth philtrum, thin vermilion of the upper lip, micrognathia, low set ears and a short neck. Additionally there was a round, flat and focal alopecic lesion in the occipital region, measuring 1 cm in diameter, with well-defined borders, depressible and nonfluctuating. There was palpable underlying bone with a depression not central to the injury (Figure 1). Ultrasound imaging suggested a possible *sinus pericranii* (Figure 1), but a posterior cranial contrast-enhanced CT scan showed no apparent communication between the intracranial dural sinuses and extracranial venous structures. The same CT scan showed axial globe lengths of 26,8 mm and 27,1 mm in the left and right eye, respectively (Supplementary Figure 2).

Whole exome sequencing was performed to confirm the clinical diagnosis using a HiSeq 4,000 Illumina platform. A homozygous small indel was detected in exon 34 of the *COL18A* gene (ENST00000359759.8: c.4224_4225delinsC, p.Pro1411Leufs*35), generating a frameshift in aminoacid 1,411 and generating a premature stop codon 35 positions down the new aminoacid chain.

Carrier status of the parents and homozygous status in the proband were confirmed by Sanger sequencing (Supplementary Figure 1). There is no allele frequency reported for this mutation in gnomAD, 1000Genome project or Exome Sequencing Project databases.

We believe the premature termination would result in nonsense-mediated-decay of the mRNA of the three isoforms of type XVIII collagen (Suzuki et al., 2002). This mutation is reported in ClinVar as pathogenic -although there is no available phenotypic description of the patient carrying the mutation- and is "likely pathogenic" according to ACMG guidelines.

3 | DISCUSSION AND CONCLUSION

Our patient presents with early onset high myopia and other characteristic eye findings of KS, along with a focal occipital alopecic lesion (OAL). Diffuse chorioretinal atrophy and abnormal vitreous condensations like hers have been described as key features of vitreoretinal degeneration (Hull et al., 2016). Variable presentations include abnormalities of the anterior segment and an asymmetric involvement of eye globes (Corbett et al., 2017; Hull et al., 2016), both of which are also observed in our patient. High myopia usually presents in infancy as nystagmus and/or strabismus and can eventually lead to a collapsed abnormal vitreous, glaucoma, ectopia and retinal detachment during childhood. Pigmentary changes such as retinal epithelium and cone-rod dysfunction have also been reported (Hull et al., 2016). Usually all eye abnormalities progress to bilateral blindness (Suzuki et al., 2002), and our patient is considered "legally disabled" in Chile due to her progressive myopia, with no history of retinal detachment. Close ophthalmologic follow-up is necessary to identify and address these complications in KS.

Simple OALs have been described in KS (Hull et al., 2016) and are considered part of a spectrum of manifestations of skull defects in this syndrome. OAL association with underlying bone and vascular defects has been observed histologically, but without involvement of dural venous sinuses and other intracranial contents (Seaver et al., 1993) as suggested by CT brain, although Doppler US examination of our patient showed *sinus pericranii*. Contrast enhanced cranial CT did not show possible pinhole defect in the skull at *sinus pericranii* position or other findings, maybe due to its insufficient resolution or the small size of the defect. However, it allowed for estimations of bilaterally increased globe axial length while not being as accurate as an orbit CT or US (Song, Kim, Lee, & Moon, 2007).

Some of our patient's facial features are consistently reported in KS (flattened face profile, flattened nasal bridge, anteverted nares), while others are not usually associated with the syndrome (smooth philtrum, thin vermilion of the upper lip, micrognathia, low set ears and a short neck). She does not show other frequent facial traits (telecanthus, hypertelorism, epicanthic folds) (Seaver et al., 1993; Sertié et al., 2000), further demonstrating the clinical variability between patients.

The severity of phenotypic traits in KS has been associated with the deficiency of specific collagen XVIII isoforms. Although few, reports of pathogenic variants affecting the first two exons of *COL18A1* produce an exclusive deficiency of collagen XVIII short isoform, and a phenotype consisting of high myopia and occipital encephalocele with relative less severe ocular phenotype and absence of seizures. Pathogenic variants occurring downstream exon 3 in *COL18A1* (mainly located between exons 30–42) cause deficiency of its three isoforms along with low endostatin levels resulting in relatively more severe ocular manifestations and often associated with abnormal neuronal cell migration and recurrent epilepsy (Passos-Bueno et al., 2006; Suzuki et al., 2002). Our patient's pathogenic variants belong to the latter category (exon 34), which may account for her rapidly progressing myopia. However she has no history of seizures so far.

Since ocular features are seen in all patients with KS, it is important to consider different diagnosis. Differential diagnoses in patients with early onset high myopia with other eye findings mentioned earlier in patients with KS (although pathognomonic), include Stickler syndrome, Marfan syndrome & related disorders, Marshall syndrome, Wagner syndrome and autosomal dominant high myopias. However, some peculiar ocular findings, craniofacial anomalies, skeletal manifestations and other system involvements help in differentiating KS from other overlapping syndromes. Further molecular diagnosis using next generation sequencing helps in confirming the diagnosis.

In conclusion, we report a Chilean case of Knobloch syndrome with high myopia, apparently mild occipital skull defect and characteristic facial dysmorphism, caused by pathogenic homozygous *COL18A1* mutation. We documented *sinus pericranii* at OAL, probably a manifestation of subtle occipital skull defect in patients with KS.

CONFLICT OF INTEREST

None of the authors have any conflicts to declare.

AUTHOR CONTRIBUTION STATEMENT

Nicole Nakousi-Capurro and Jonathan Huserman contributed to the literature review, conception and writing of the manuscript. Pablo Romero, Felipe Pizarro, and Luisa Herrera contributed to data acquisition, data interpretation, and also clinical writing. Silvia Castillo, Cristian Quezada, and Francisco Cea revised and approved the final version of this manuscript.

ETHICS STATEMENT

Both parents agreed to the use of clinical information and photographs for purposes of this publication.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Corbett, M., Turner, S., Gardner, A., Silver, J., Stankovich, J., Leventer, R., … Gecz, J. (2017). Familial epilepsy with anterior polymicrogyria as a presentation of *COL18A1* mutations. *European Journal of Medical Genetics*, *60*(8), 437–443. https://doi.org/10.1016/j.ejmg.2017.06.002

Hull, S., Arno, G., Ku, C., Ge, Z., Waseem, N., Chandra, A., … Moore, M. (2016). Molecular and clinical findings in patients with Knobloch syndrome. *JAMA Ophthalmology*, *134*(7), 753–762. https://doi.org/10.1001/jamaophthalmol.2016.1073

Passos-Bueno, M., Suzuki, O., Armelin-Correa, L., Sertié, A., Errera, F., Bagatini, K., … Leite, K. (2006). Mutations in collagen 18A1 (*COL18A1*) and their relevance to the human phenotype. *Anais da Academia Brasileira de Ciências*, *78*(1), 123–131. https://doi.org/10.1590/s0001-37652006000100012

Seaver, L., Joffe, L., Spark, R., Smith, B., & Hoyme, H. (1993). Congenital scalp defects and vitreoretinal degeneration: Redefining the Knobloch syndrome. *American Journal of Medical Genetics*, *46*(2), 203–208. https://doi.org/10.1002/ajmg.1320460221

Song, H., Kim, Y., Lee, S., & Moon, Y. (2007). Relations between age, weight, refractive error and eye shape by computerized tomography in children. *Korean Journal of Ophthalmology*, *21*(3), 163–168. https://doi.org/10.3341/kjo.2007.21.3.163

Sertié, A. L., Sossi, V., Camargo, A., Zatz, M., Brabe, C., & Passos-Bueno, M. R. (2000). Collagen XVIII, containing an endogenous inhibitor of angiogenesis and tumor growth, plays a critical role in the maintenance of retinal structure and in neural tube closure (Knobloch syndrome). *Human Molecular Genetics*, *9*(13), 2051–2058. https://doi.org/10.1093/hmg/9.13.2051

Suzuki, O., Sertié, A., Der Kaloustian, V., Kok, F., Carpenter, M., Murray, J., … Passos-Bueno, M. (2002). Molecular analysis of collagen XVIII reveals novel mutations, presence of a third isoform, and possible genetic heterogeneity in Knobloch syndrome. *The American Journal of Human Genetics*, *71*(6), 1320–1329. https://doi.org/10.1086/344695

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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