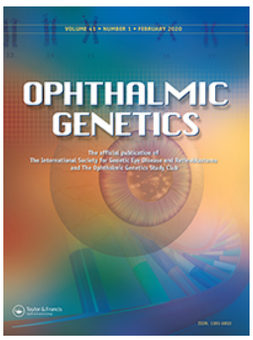

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CASE REPORT

Three cases of molecularly confirmed Knobloch syndrome

Irina Balikova[a,b], Nuri Serdal Sanak[c], Depasse Fanny[d], Guillaume Smits[e], Julie Soblet[e], Elfride de Baere[f], and Monique Cordonnier[c]

[a]Department of Ophthalmology, University Hospital Leuven, Leuven, Belgium; [b]Department of Ophthalmology, Children Hospital Queen Fabiola, Brussels, Belgium; [c]Department of Ophthalmology, University Hospital Erasme, Brussels, Belgium; [d]Ophthalmology Service, University Hospital Charleroi, Charleroi, Belgium; [e]Department of Genetics, University Hospital Erasme, Brussels, Belgium; [f]Center for Medical Genetics, University Hospital Ghent, Ghent, Belgium

ABSTRACT

Background: Knobloch syndrome (OMIM 267750) is a rare autosomal recessive disorder due to genetic defects in the *COL18A1* gene. The triad of high myopia, occipital defect, vitreoretinal degeneration has been described as pathognomonic for this condition. Patients with Knobloch syndrome have also extraocular problems as brain and kidney malformations. High genetic and phenotypic variation has been reported in the affected patients.

Materials and Methods: Here we provide detailed clinical description of 3 individuals with Knobloch syndrome. Ocular examination and fundus imaging have been performed. Detailed information about systemic conditions has been provided.

Results: Mutations in *COL18A1* were identified in all three patients. Patient 1 had congenital hip dislocation and patient 2 had renal atrophy, cardiac insufficiency and difficult skin healing.

Conclusions: With this report we add to the clinical and genetic knowledge of this rare condition.

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Knobloch syndrome; macular coloboma; COL18A1; encephalocele; myopia; skin healing; nephronophthisis; vitreoretinopathy; retinal detachment; lens subluxation

Introduction

Knobloch syndrome (OMIM 267750) is a rare autosomal recessive genetic disorder. It was initially described by Knobloch and Layer in 1971 in a big family with 5 affected family members. The patients were highly myopic, had vitreoretinal degeneration, retinal detachment and occipital encephalocele (1). Mutations in *COL18A1* cause Knobloch syndrome (2). The gene is located on the long arm of chromosome 21. In the eye, Col18a1 is shown to play a role in the anchoring of the vitreal fibrils to the inner limiting membrane providing an explanation for the myopia and the retinal detachment. Mice deficient in Col18a1 have also delayed the regression of the hyaloid vasculature during ocular development (3). The triad of high myopia, retinal detachment and occipital defect is pathognomonic for Knobloch syndrome. The symptoms can vary in severity and time of onset. Patients with Knobloch have also extraocular symptoms. Skull deformities range from meningoencephalocele to isolated scalp defect in the occipital region. Brain anomalies including migration anomalies, developmental delay and epilepsy have been described (4,5). Other organ anomalies such as unilateral duplex kidney with bifid ureter, congenital hydronephrosis and hypermobile joints have been shown in patients with this syndrome (6).

Here we describe three patients with Knobloch syndrome. The diagnosis was confirmed molecularly in all three individuals. These cases help to further understand the genotypic and phenotypic spectrum of this condition.

Material and methods

Three patients were seen in two University Hospitals in Belgium. The study is performed according to the tenets of the Declaration of Helsinki.

Each patient underwent full ophthalmic examination with age-appropriate methods.

Blood samples were taken from the patients after proper informed consent. DNA was extracted following standard procedures. Patient 1 and 2 – Sanger sequencing was performed in the *COL18A1* gene.

In Patient 3, clinical exome capture (3,638 genes) was achieved using the SeqCap EZ Choice XL (NimbleGen, Madison, WI). Samples were subsequently sequenced in a paired-end 125 bp run on a HiSeq 1500 instrument (Illumina, San Diego, CA, USA). Bioinformatics pipeline was launched by BRIGHTcore (BRIGHTcore, Brussels, Belgium) and filtering of the variants was accomplished using Highlander (http://sites.uclouvain.be/highlander). The results were further confirmed by Sanger sequencing.

Patient 1

The patient was a girl born from non-consanguineous parents. She was referred for ophthalmological examination at the age of 2 years because of reduced vision. She bumped into objects and had problems of seeing in the distance. Cycloplegic refraction revealed high myopia: −14.00/-3.50 at 140° and −17.00/-1.00 at 90° for the right and left eye, respectively.

CONTACT Irina Balikova Irina.Balikova@uzleuven.be Department of Ophthalmology, University Hospital Leuven, Leuven, Belgium

Visual acuity using Key Picture Test was 0.9logmar and less than 1.3logmar at the right and left eye with the optical correction. She had horizontal nystagmus. Her eye examination showed normal anterior segments – no cataract or lens subluxation was present. The eye fundus showed thin retina with visible choroidal vessels. A retinal defect was present in the right macular region (Figure 1a). On the left side, a less well-demarcated atrophic region was present. The ERG showed the presence of scotopic and photopic responses, but severely reduced amplitudes and delayed latencies.

The patient had a congenital occipital mass of 4 cm with serosanguineous secretion. Transfontanel echography diagnosed occipital meningoencephalocele (Figure 2a). Surgical correction was performed at the first day of life. The patient had a normal postnatal neuromotor development.

The genetic analysis identified two mutations within the *COL18A1*. The patient is a compound heterozygote for c.2960_2969dup (p.Gly991Argfs*96) and c.3514_3515del (p.Leu1172Valfs*72).

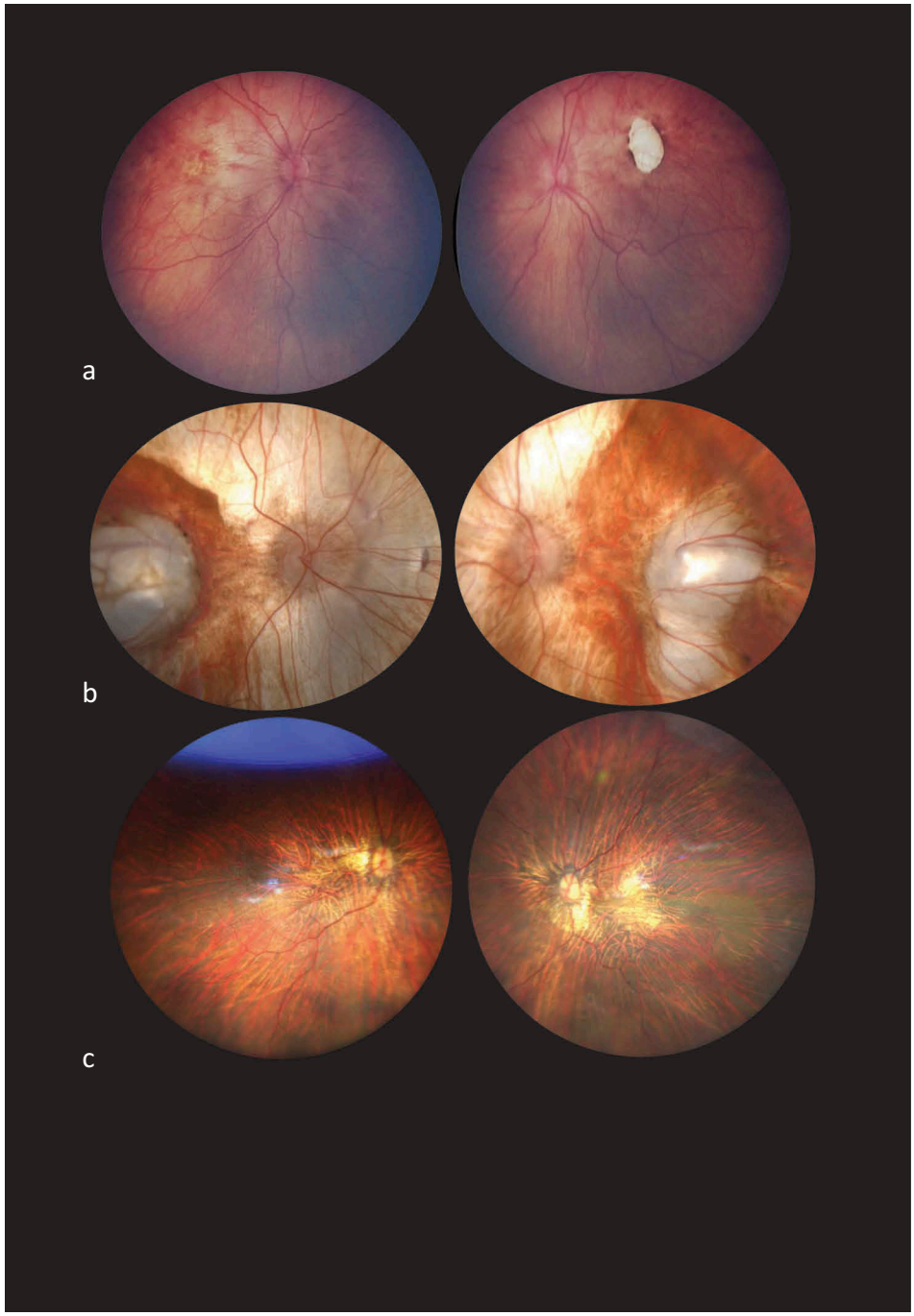

Figure 1. Macular defects. Ocular fundus showing different degrees of macular defect: (a) Irregular macular region in the right fundus and atrophic lesion in the left fundus in Patient 1 (b) Punched out pseudocoloboma in Patient 2 (c) Pigment epithelium alterations on the right side and macular atrophy on the left side in Patient 3.

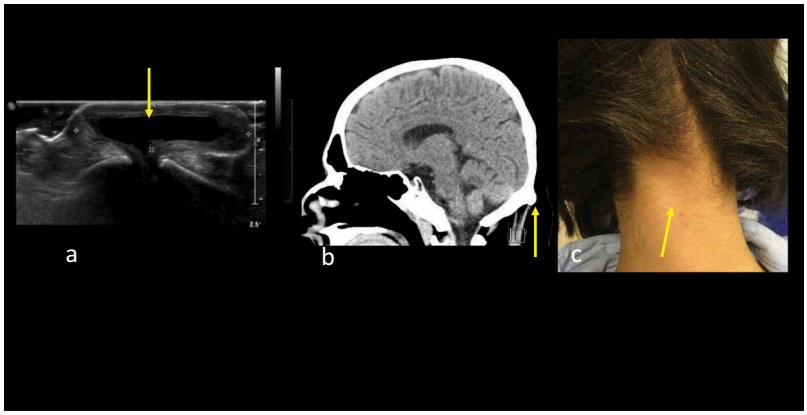

Figure 2. Occipital defects. (a) Ultrasound image, an arrow indicating the communication between the occipital defect and the meningocele cavity in Patient 1 (b) Cerebral CT showing the occipital bone defect in Patient 2 (c) Pigmented lesion in the occipital area in Patient 3.

Patient 2

The second patient was a 46y old man born from a consanguineous marriage. He complained from a loss of vision and photophobia. He had low vision since childhood. At examination – the visual acuities were 1,3 logmar on the right side and Counting Fingers on the left side. Automatic refraction showed +2.75/+1.25 at 147 and +2/+1.5 at 74 and the axial length was 29.17 mm and 28.81 mm for the right and left eye, respectively. The patient had horizontal nystagmus. The anterior segment showed hypoplastic iris crypts, iris transillumination, correctopia on the left side and bilateral lens dislocation. The left lens became luxated at age of 13y and the right at 43y. The ocular fundus revealed bilateral large macular pseudocolobomas. The retina was extremely thin with retinal pigment epithelium and choroidal atrophy (Figure 1b). The sclera was visible through the thinned atrophic retina giving a white appearance of the fundus.

In the occipital region, the patient had a small oval area of alopecia. Computed tomography scanning revealed an occipital bone abnormality, without the involvement of the meninges (Figure 2b).

The patient had normal mental development. He had terminal kidney insufficiency with bilateral renal atrophy for which dialysis was started. He had chronic cardiac hypertension, dyslipidemia and sleep apnoea. He had accessory spleen. The patient had venous insufficiency of the lower limbs. He had multiple atrophic skin lacerations on the lower limbs caused by mild trauma and reported slow healing of wounds.

The genetic analysis revealed homozygous frameshift mutation *COL18A1* c.1610del (Pro537Glnfs*16).

Patient 3

The third patient is a 15y old girl of consanguineous parents. She was followed in the ophthalmology clinic because of high myopia diagnosed since the age of 9 months. At the age of 15 years, her refraction was: −19D (−4 at 3) and – 20D (−5.75 at 173). Despite the correction, she had reduced vision. Her best-corrected visual acuities were 0,9 logmar on the right and left side. Her anterior segment examination showed bilaterally flat iris with atrophic crypts and normal lenses. The vitreous was fibrillary. The retina had pigment epithelium alterations in both macular regions with generalised thinning and visible choroidal vessels (Figure 1c). She developed retinal detachment macula off at age of 6y in the left eye.

In the occipital region, the patient had an area of a darker coloured skin as an only anomaly (Figure 2c). Mild dysmorphic features were present with bilateral epicanthus and upslanting palpebral fissures. She had congenital hip subluxation. The patient had delayed language development and had learning difficulties. The motor development was normal.

The axial length of the right eye was 26.89 mm. The measurements of the left eye failed due to bad fixation.

Genetic analysis identified a homozygous mutation in *COL18A1* c.4492 del G (p. Glu1498Lys*fs). Parental testing showed that both parents are heterozygous carriers.

Discussion

We present the clinical details of three molecularly proven patients with Knobloch syndrome. In all three patients, biallelic mutations have been identified within the *COL18A1* gene. All mutations are novel and lead to frameshift.

All patients had severe myopia with the low vision below 0.9 logmar despite the optical correction. The ocular fundus showed abnormalities within the macular region ranging from pigment epithelial alterations to a macular pseudocoloboma. Two of the patients developed complications – patient 2 had lens luxation in both eyes and patient 3 had a retinal detachment in the left eye. These complications lead to further deterioration of the vision.

In all patients, occipital changes have been noticed. Only one had encephalocele. The occipital defects ranged from alopecic area with bone abnormality (patient 2) to a pigmented skin spot on the back of the head (patient 3). Although the occipital skull defect was described in the classical triad, reports have shown that it is not obligatory for the diagnosis of the syndrome (7). We further show that these defects can be very mild.

Patient 2 had important extraocular anomalies – kidney atrophy, accessory spleen and showed delayed skin cicatrisation. The end-stage renal disease in a relatively young age

could be related to the mutation in *COL18A1*, since at least in the col18a1 knockout mice there are ultrastructural changes in the kidney (8) which might lead to altered renal function and stress tolerance predisposing to renal insufficiency. In addition, *Col18a1* knockout mice have elevated creatinine levels (9) which also indicates that Col18a1 affects renal filtration and function. However, terminal end-stage renal disease and renal atrophy related to renal insufficiency can be secondary to the elevated blood pressure, vascular defects or diabetes. Another observation is the difficult skin healing which can be related to the *COL18A1* insufficiency. The *COL18A1* gene is expressed in the skin (10) and takes part in the basal membrane. The role of COL18A1 in modulating the wound healing has been shown by Seppinen et al. (11). The authors conclude that the lack of *Col18a1* accelerates wound healing while the overexpression of the endostatin domain leads to delayed healing in mice. However, in oral mucosa, the lack of *Col18a1* leads to a dramatic decrease in the markers of keratinisation (12). In addition, Maeba et al. recently showed that COL18A1 has a role in the dermal-epidermal junction during wound healing (13). The genetic defect in patient 2 leads to loss of function of *COL18A1* including the endostatin isoform. Possibly this causes delayed epithelialisation. Again, this has to be further investigated since systemic (hypertension, dyslipidemia, kidney insufficiency) and local (venous insufficiency in lower limbs) factors affect wound healing as well. Accessory spleen is present in 11% in the normal population and its link with the syndrome is not certain (14). The mental development of the patients ranged from normal to learning difficulties. None of the patients had epilepsy or severe mental problems.

Knobloch syndrome has clinical overlap with other connective tissue disorders as Stickler (OMIM 609508), Weill – Marchesani (OMIM 608328) and Marfan (OMIM 154700) syndromes. Patients with these syndromes also have high myopia, risk for retinal detachment and lens subluxation (15,16,17). In comparison with patients affected with Knobloch syndrome who typically have macular defects and early onset macular dystrophy, the patients with Stickler and Marfan often have better vision in childhood unless complications occur since there is no macular dystrophy. However, chorioretinal atrophy mainly around the vasculature can develop also in individuals with Stickler syndrome (16). Goldmann–Favre (OMIM 268100) and Wagner (OMIM 143200) syndromes similarly to Knobloch are vitreoretinopathies characterized by abnormal vitreous and retinal dystrophy. Goldmann–Favre is caused by mutations in *NR2E3* encoding a nuclear receptor. While the vitreous in these patients is abnormal, their refraction most often shows mild hyperopia in contrast to the Knobloch patients. The retina shows characteristic heavy pigment clumps outside the arcades. The ERG is abnormal and pathognomonic with maximal scotopic ERG resembling the photopic response (18). Wagner syndrome is caused by mutations in the *VCAN* gene (19). Affected individuals present with optically empty vitreous with typical vitreal veils. In addition, these patients have cataracts and often develop a retinal detachment. The electroretinogram is abnormal with reduced responses confirming the retinal dystrophy (20).

With this report, we add to the clinical knowledge of patients with Knobloch syndrome. Systemic evaluation is important in the follow-up. Further investigations and case reports of the systemic conditions in these patients will help to better understand the spectrum of associated anomalies. Finally, this syndrome should be considered in the diagnostic workup of patients with pathological myopia.

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Declaration of interest

The authors have no conflict of interest to declare.

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