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Ocular ultrasonography and cross-sectional imaging in the diagnosis of Knobloch syndrome: a rare case report

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ABSTRACT

Knobloch syndrome is a rare, autosomal recessive disorder that is characterized by ocular abnormalities causing progressive vitreoretinal degeneration leading to severe visual impairment with or without occipital skull bone defect/encephalocele. Mutations in the *COL18A1* gene are implicated in the molecular pathogenesis of this condition. Collagen XVIII performs various functions in ocular and neurological development, including basement membrane maintenance and angiogenesis. Recently, Knobloch syndrome has been associated with variable phenotypes apart from the classical syndrome described in early literature. Cases with multisystemic involvement in the form of renal, pulmonary, and haematological abnormalities have also been reported. Radiological investigations such as ocular ultrasonography using B scan ultrasound are valuable tools to study the various ocular manifestations of the syndrome, whereas cross-sectional imaging techniques, namely Computed tomography as well as Magnetic resonance imaging, play an important role in the assessment of neurological abnormalities. Genetic analysis revealing mutations in the *COL18A1* gene is required for confirmation of diagnosis. This syndrome may go undiagnosed without proper evaluation of ocular abnormalities and neurological manifestations. Thus, a multimodality radiological imaging approach involving a combination of ocular ultrasonography with cross-sectional imaging techniques is advocated for the diagnosis of Knobloch syndrome in suspected cases.

KEY WORDS: Knobloch syndrome; ocular ultrasonography; cross-sectional imaging; vitreoretinal degeneration; encephalocele

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INTRODUCTION

Knobloch syndrome was first described by William Knobloch in 1971 [1]. It is a rare disorder that shows an autosomal recessive inheritance pattern [2]. It is characterized by ocular abnormalities in the form of progressive vitreoretinal degeneration with or without occipital skull bone defects. Classical ocular manifestations of the disease include high myopia and proliferative vitreoretinopathy followed by retinal detachment leading to complete blindness bilaterally. Recent studies have identified several phenotypic variants that show distinct ocular and neurological manifestations apart from the classical features syndrome described in the original syndrome [3]. Few studies have also highlighted the rare occurrence of systemic involvement in the form of renal anomalies and pulmonary system and haematological involvement [4].

The causative gene implicated in the molecular pathogenesis of this condition is *COL18A1*, located

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on the long arm of chromosome 21 [5]. Collagen XVIII is distributed in various tissues throughout the human body and plays a significant role in ocular and neurodevelopment, including basement membrane stability and angiogenesis. Radiological investigations play a crucial role in the diagnosis of this condition. Ocular B scan ultrasonography is used to assess vitreoretinal degeneration, lens dislocation as well as retinal detachment. Cross-sectional imaging, such as computed tomography (CT) scan and magnetic resonance imaging (MRI), provides insight into the neurological manifestations of the disease.

CASE REPORT

An 18-year-old female patient presented to the ophthalmology outpatient department with complaints of gradual onset loss of vision in both eyes. The patient had a history of extreme nearsightedness since early childhood. The patient had no history of ocular infections or trauma. The patient also complained of intermittent headaches localized to the occipital region. However, it was not associated with any focal neurological deficits.

Ophthalmological examination revealed loss of light perception in both eyes. Fundoscopy examination of the left eye showed vitreoretinal degeneration with retinal detachment (Fig. 1). Due to technical limitations, a fundoscopy examination of the right eye was not possible.

The patient was referred to the Radiology department for further evaluation. Ocular B Scan Ultrasonography was performed using a high-frequency linear transducer. The ultrasound revealed the following findings: Changes of proliferative vitreoretinopathy were noted in both eyes (left > right) with the presence of a V-shaped flap of retina converging at the optic disc suggestive of retinal detachment bilaterally (Fig. 2). Additionally, the dislocation of an intraocular lens into a dependent portion of the posterior (vitreous) segment of the eyeball was noted in the right eye (Fig. 3).

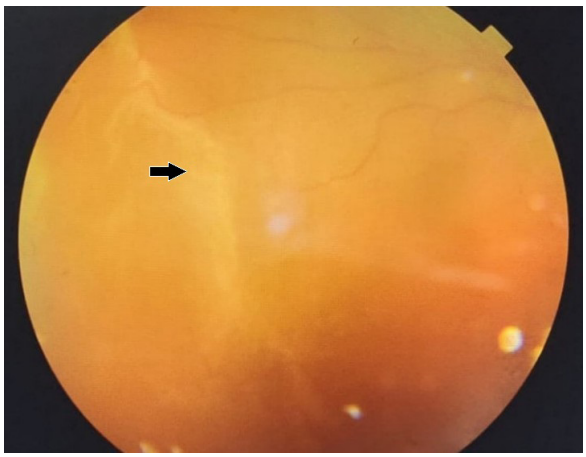

FIGURE 1. Fundoscopy image of left eye reveals extensive area of retinal detachment (black arrow)

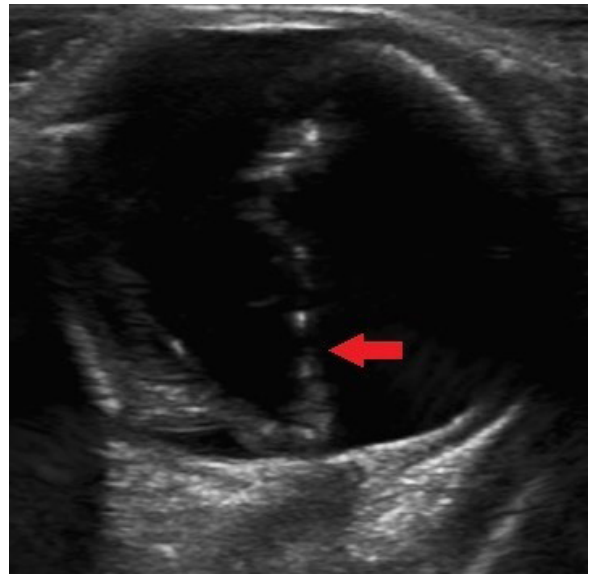

FIGURE 2. B scan ultrasonography of left eye reveals proliferative vitreoretinopathy with V-shaped retinal flap having apex at optic disc consistent with retinal detachment (red arrow)

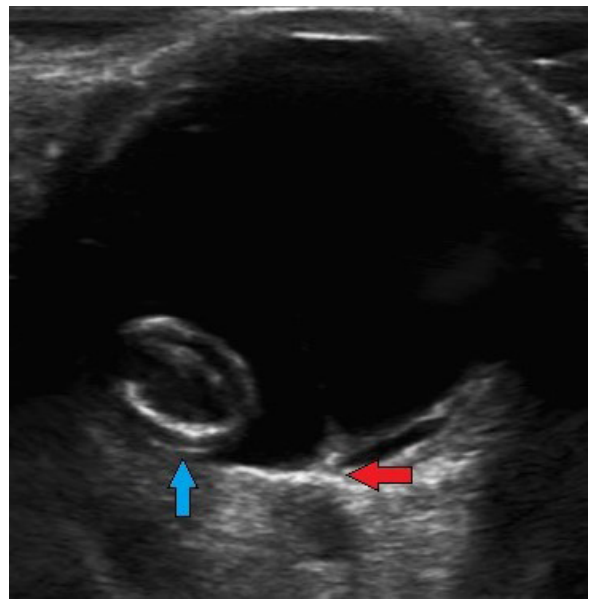

FIGURE 3. B scan ultrasonography of right eye reveals retinal detachment (red arrow). Also note the presence of dislocated intraocular lens noted in dependent part of posterior segment (blue arrow)

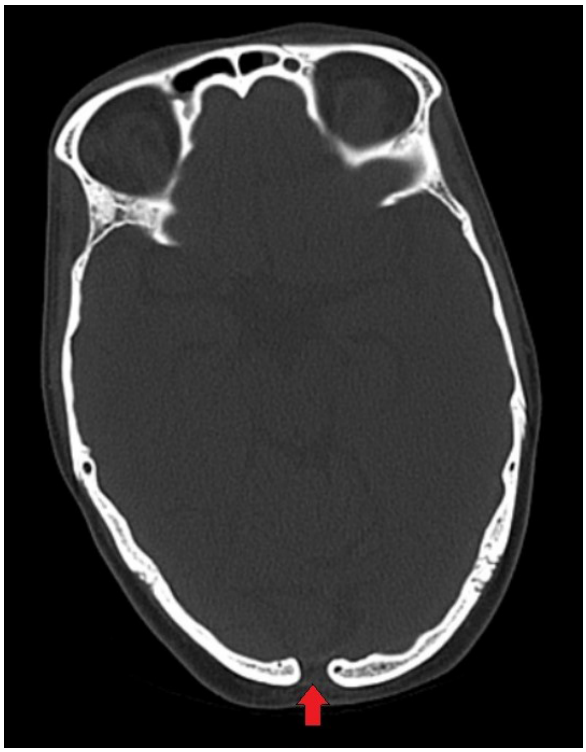

FIGURE 4. Axial image of computed tomography brain (bone window) showing occipital bone defect (red arrow)

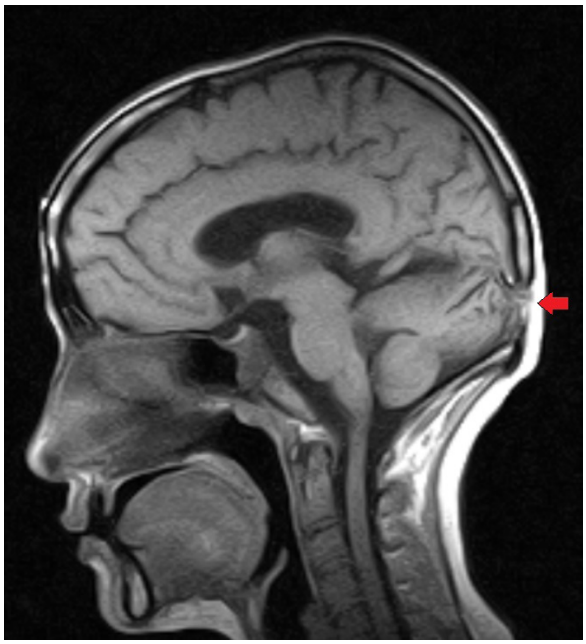

FIGURE 5. T1 weighted sagittal image of magnetic resonance imaging of brain showing atretic meningocele in occipital region (red arrow)

The patient was then advised to have a brain CT (plain) scan to evaluate the cause of the headache. The scan revealed the presence of a bony defect in the occipital region of the skull (Fig. 4). The patient was then subjected to a brain MRI (plain) scan. The MRI revealed a soft tissue band extending from the posterior cranial fossa up to the occipital bone defect. This soft tissue band followed cerebrospinal fluid (CSF) signal intensity on all sequences. However, no evidence of herniation of neuroparenchyma was seen through the skull defect. The above findings were consistent with occipital skull bone defect with atretic meningocele (Fig. 5).

Based on the combined findings of ocular sonography and cross-sectional imaging, a radiological diagnosis of Knobloch syndrome was proposed. The patient was referred for genetic testing to confirm the diagnosis molecularly.

DISCUSSION

Knobloch syndrome is a rare disorder that follows an autosomal recessive pattern of inheritance. The classical manifestations of the syndrome include high myopia, vitreoretinal degeneration progressing to retinal detachment, and occipital encephalocele [6]. However, a number of phenotypic variants have been described in recent literature involving ocular and neurological manifestations apart from the classical syndrome.

The Knobloch locus was mapped to 21q22.3, which led to the *COL18A1* gene being implicated in the pathogenesis of this condition. This gene encodes for collagen alpha-1(XVIII) chain, which is universally expressed in vascular and epithelial basement membranes.[7] Collagen XVIII has an important role in ocular and neurodevelopment, including stability of basement membranes, neo-angiogenesis, and the Wnt/beta-catenin signaling pathway maintenance [8]. Three distinct isoforms of the *COL18A1* gene have been identified with around 22 possible pathogenic mutations. This explains the phenotypic variability associated with Knobloch syndrome.

COL18A1 encodes the collagen alpha-1(XVIII) chain, which is widely expressed throughout the ocular tissues, including the iris, ciliary body, trabecular meshwork, Schlemm canal, inner limiting membrane, retinal vessels, retinal pigment epithelium basement membrane, and the Bruch's membrane. The additional ocular manifestations that have been identified include early onset cataracts, smooth irides, lens subluxation, and persistent fetal vasculature [9,

10]. Features of pigment dispersion syndrome with pigmentary glaucoma have also been described [11]. Ocular B scan ultrasonography can help in the assessment of the ocular abnormalities associated with the syndrome, especially in cases of opaque media or cataracts, where clinical examination and fundoscopy have limited value.

The classical neurological feature associated with Knobloch syndrome was the presence of occipital skull defect with encephalocele/meningocele [12]. Skull bone defect is best identified on CT scan examination in bone window setting. MRI of affected patients revealed various additional neuroparenchymal abnormalities such as polymicrogyria, subependymal nodules, and cerebellar vermian atrophy [13, 14]. Scalp abnormalities such as cutis aplasia have been identified in the absence of any neuroradiological anomalies. This underlines the importance of clinical scalp examination in a suspected patient of Knobloch syndrome [15]. Other less documented neurological disorders include epilepsy, neurocognitive impairment, and developmental delay [16, 17].

Systemic involvement has been reported in some cases involving the renal, pulmonary, and haematological systems. Renal anomalies include the presence of a congenital unilateral duplex kidney with a bifid ureter and congenital hydronephrosis [18]. Pulmonary system involvement was noted in the form of abnormal pulmonary lymphatic dilatation. Haematological disorders such as acute lymphoblastic leukaemia have also been documented [19].

CONCLUSION

Knobloch syndrome is a rare disorder causing severe visual impairment with or without neurological involvement. This syndrome may go undiagnosed without proper evaluation of ocular abnormalities and adequate neuroimaging to look for neurological manifestations. Imaging modalities have an important role to play in the diagnosis of Knobloch syndrome. This case report emphasizes the need for a multimodality approach combining ocular ultrasonography with cross-sectional imaging techniques like CT scans and MRI to evaluate suspected cases.

Ethics statement

Written and informed consent has been obtained from the patient to publish this case report.

Author contributions

Z.I.: writing manuscript, collection of data, final acceptation of manuscript; M.K.: critical review of manuscript, final acceptance of manuscript; M.A.: critical review of manuscript; A.R.: collection of data.

Conflict of interests

Authors declare no conflict of interests.

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