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A Case of Dandy-Walker Malformation Complicated by Axenfeld-Rieger Syndrome

Case Report

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Abstract

Purpose: To report a case of Dandy-Walker malformation complicated by Axenfeld-Rieger syndrome.
Case: A 20-day-old female infant underwent ventriculo-peritoneal shunt for hydrocephalus associated with Dandy-Walker malformation when she was 2 days old. She was referred to us because she had corneal opacity and ocular hypertension in both eyes. At the initial examination, her intraocular pressure (IOP) was 35 mmHg in the right eye and 28 mmHg in the left eye, and corneal opacity and extended corneal diameter was present in both eyes. Trabeculotomy was performed twice in both eyes. Her father had also undergone trabeculotomy on both his eyes when he was 3 months old.
Results: Her IOP stabilized to within the normal limit, but iris atrophy later developed in her left eye. After confirming a mutation in *FOXC1*, we diagnosed her with Axenfeld-Rieger syndrome. Genetic tests revealed the same mutation in her father.
Conclusion: Since *FOXC1* mutations are associated with Axenfeld-Rieger anomaly as well as Dandy-Walker malformation, these diseases can coexist. Genetic tests may be useful for the diagnosis, treatment, and prognosis determination of patients with congenital glaucoma.

Keywords: Axenfeld-Rieger Syndrome; Dandy-Walker Malformation; *FOXC1*.

Introduction

One of the developmental anomalies associated with congenital glaucoma is Axenfeld-Rieger Syndrome (ARS). ARS consists of a spectrum of developmental defects of the anterior chamber of the eye, with wide variability of expression. The Axenfeld anomaly is a white line in the posterior aspect of the cornea, near the limbs, and tissue strands extend from the periphery of the iris to this prominent line. The Rieger anomaly involves mesodermal digenesis of the cornea and iris. When these defects are associated with extra ocular findings of maxillary hypoplasia, hypodontia, microdontia, and umbilical abnormalities, the disorder is defined as ARS. This disorder is seen in approximately 1 per 200,000 live births. Its penetrance is complete, although expressivity is variable, and it is associated with a 50% risk of glaucoma. ARS is a genetically heterogeneous group of abnormalities, caused by mutations in at least four different gene loci. Mutations in *PITX2* on ch 4q25, *FOXC1* on 6p25, *PAX6* on 11p13, and *FOXO1A* on 13q14 have been associated with the development of ARS [1-5].

On the other hand, Dandy-Walker malformation (DWM) is a congenital condition that occurs during embryonic development of the cerebellum and the fourth ventricle [6]. DWM has a frequency of approximately 1 per 25,000-35,000 live births and affects more females than males. Although there are some reports that DWM is caused by heterozygous loss of zinc finger genes

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(*ZIC1* and *ZIC4*) or mutations affecting *FOXC1* and *FGF17* [6-11], the etiology is still unclear.

Previously, there have been a few reports regarding patients with a combination of DWM and Axenfeld-Rieger anomaly or glaucoma (but not ARS) [11, 12]. In this report, we present a rare case of a patient with ARS complicated with DWM, whose father was also diagnosed with ARS.

Case Report

A 20-day-old female infant was diagnosed with DWM with enlargement of the fourth ventricle, severe cerebella atrophy, and posterior fossa cyst. When she was delivered by caesarean section at 35 weeks of gestation, corneal opacity was found in both her eyes (Figure 1). She underwent an ophthalmic examination on Day 6 after birth. Both her corneas were cloudy and intraocular pressure (IOP) was 32mmHg in her right eye (OD) and 25mmHg in the left eye (OS) by icare® (ICARE FINLAND OY, Vantaa, Finland). Since she had been diagnosed with congenital glaucoma, treatment with anti-glaucoma eye drops was initiated. However, treatment with dorzolamide (Trusopt®) and latanoprost (Xalatan®) for about 2 weeks were not sufficiently effective. Therefore, she was referred to us for glaucoma surgery.

At her first visit to our clinic, a slit-lamp examination revealed hazy corneas, round pupils, but not iris atrophy. Her corneal diameter was 11mm (horizontal)×10mm (vertical) OD and 11.5 mm (horizontal)×10mm (vertical) OS. Gonioscopic findings show ednumerous of adherent iris strands on Schwalbe's line. IOP was 35 mmHg OD and 28 mmHg OS by Tono-Pen AVIA® (Depew, NY), a handheld tonometer, under sedation. Both eyeballs had an axial length of 17 mm. Fundus examination revealed no apparent enlargement of optic disc cupping in either of her eyes.

She underwent trabeculotomy in the temporal inferior area of both eyes under general anaesthesia on Day 22 after birth. In the pre-surgical examination, IOPs were 39 mmHg OD and 37mmHg OS (Tono-pen AVIA®). Because the first surgery for glaucoma had not been effective (IOP levels remained unchanged in both her eyes), she underwent trabeculotomy for the second time in the nasal inferior area of both eyes on Day 36 after birth. After the second surgery, her IOPs stabilized at 11-12 mmHg OD and at 12-14 mmHg OS (Tono-Pen AVIA®) under sedation.

She had a saddle nose and isolation of both eyes. Her father had undergone glaucoma surgery once in both his eyes at the age of 3 months. He had post-operative ventricular septal defect and impaired hearing. Both the patient and her father underwent genetic tests for a definitive diagnosis of DWM, which revealed that both of them carried a mutation of *FOXC1*.

Ophthalmic examination on her father's eyes revealed clear corneas and iris atrophy (Figure. 2). His IOP was 15mmHg, the cup-to-disc ratio was 0.3, and the visual field test was within normal limits, in both his eyes. His congenital glaucoma was thought to be caused by ARS. The patient was diagnosed with ARS, complicated with DWM based on the result of genetic tests, although her iris was not atrophic at that time. These individuals are therefore suspected of being familial cases of ARS carrying a *FOXC1* mutation.

The patient is currently three and half years old; her IOP levels are around the low teens, and both eyes have clear corneas, although mild iris atrophy has been detected in her left eye (Figure. 3). This iris atrophy appeared approximately at the age of 1 year. Fundus examination revealed that the cup-to-disc ratio is 0.5 OD and < 0.4 OS. She has a mild developmental delay.

Discussion

This is a report of a rare case of a patient with DWM complicated by ARS. Both the patient and her father had a mutation of *FOXC1*, although her father had ARS without DWM. *FOXC1*

Figure 1. Photographs of the Anterior Segment of Eyes before Surgery (A: Right Eye, B: Left Eye). Corneal Opacity and Extended Corneal Diameters are Present.

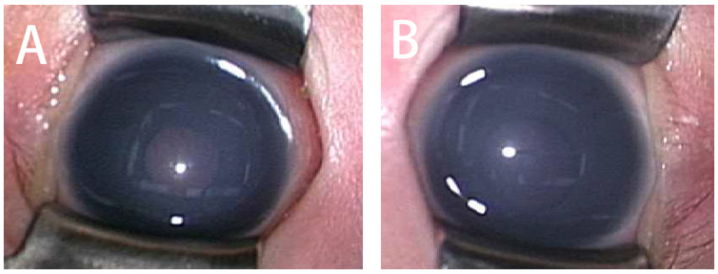


Figure 2. Photographs of the Anterior Segment of Eyes 10 Months after the Second Surgery (A: Right Eye, B: Left Eye). Both Corneas are Clear and Mild Iris Atrophy is seen in her Left Eye (Arrow).

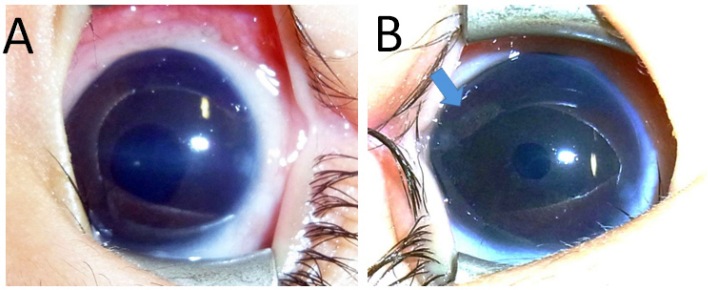
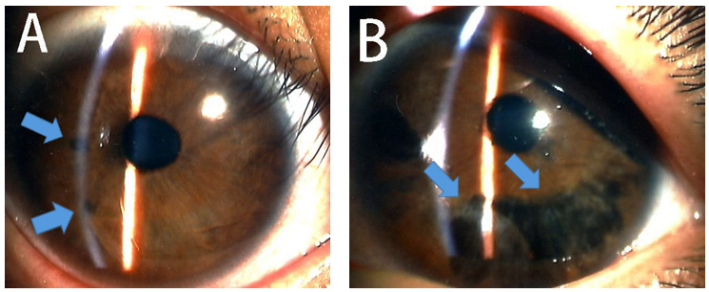


Figure 3. Photographs of the Anterior Segment of the Father's Eyes (A: Right eye, B: Left eye). Iris Atrophy is Apparent in both his Eyes (Arrows).



deletion, duplication, and mutations are reportedly associated with Axenfeld-Rieger anomaly and with DWM [8, 11]. Various combinations of ocular and cerebellar malformations have been found in three fetuses with 6p25 deletions encompassing *FOXC1* [11]. Considering these facts, our patient shows that DWM and ARS can coexist.

This patient required trabeculotomy twice to control IOP. On the contrary, her father's first surgery (trabeculotomy) was sufficiently effective. These different clinical courses might suggest that the disease is more severe in the patient than in her father. Kawase et al. reported 6 Japanese ARS cases in 4 families with *FOXC1* mutations [13]. In 3 of the 4 families, a *FOXC1* mutation was present in the mothers of the index cases, who had corectopia and iris hypoplasia, but without glaucoma. This report indicated that younger generations may have more severe symptoms than their parents' generation [13]. This feature is similar to our case.

At her first examination, our patient did not have typical ophthalmological changes of ARS, such as iris atrophy and pupil deformation. Therefore, we did not diagnose her with glaucoma caused by ARS. During follow-up, she underwent genetic tests for definitive diagnosis of DWM, which revealed a mutation in *FOXC1* genes. In addition, iris atrophy and pupil deformation appeared in her left eye thereafter. We have therefore changed her diagnosis to that of ARS complicated with DWM. Our case indicates that genetic tests are useful for diagnosing patients with ARS as well as for predicting their prognosis.

Conclusion

Because some ARS cases may not show typical findings, a detailed family history, repeated ophthalmic examinations, and genetic tests are useful for making a definitive diagnosis and predicting prognosis.

Acknowledgement & Declarations

We would like to thank Edit age for editing this manuscript. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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