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Unusual Association of Aniridia with Aicardi-Goutières Syndrome-Related Congenital Glaucoma in a Tertiary Care Center

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Male, 4
Final Diagnosis: Aicardi-Goutières syndrome
Symptoms: Congenital glaucoma
Medication: —
Clinical Procedure: Trabeculectomy procedure with mitomycin C
Specialty: Ophthalmology

Objective: Rare disease

Background: Aicardi-Goutières syndrome (AGS) is a rare autosomal recessive encephalopathy of early onset. AGS visual dysfunction range from nystagmus and optic atrophy to cortical blindness in affected individuals; however, congenital glaucoma has been recently noticed among AGS pediatric patients. According to the literature, aniridia has never been recognized among AGS patients.

Case Report: We report the case of a 4-year-old boy with AGS who had multiple congenital anomalies in the eyes. He was found to have congenital glaucoma, nystagmus, spherophakia with shallow chambers, and aniridia in both eyes. Family history was positive for glaucoma, with consanguineously married parents. According to the genetics report, both parents are carriers of congenital glaucoma genes. A whole-exome sequencing identified IFIH1 heterozygous missense mutation of the patient, which is associated with AGS Type 7. Also, he was diagnosed as having congenital glaucoma with CYP1B1 mutation, homozygous recessive. This case demonstrates the unusual coexistence of bilateral aniridia, a feature not previously reported in ocular findings of AGS.

Conclusions: In summary, this is the first reported case of aniridia with AGS-related congenital glaucoma in the literature. This paper summarizes the usual ocular manifestation of AGS, also it highlights atypical ocular features in both; AGS as well as congenital glaucoma. The aim of this paper is to lay the foundation for a national database on AGS in Saudi Arabia, which will help create a bridge between genetic data and clinical findings of AGS patients.

MeSH Keywords: Aicardi Syndrome • Aniridia • Saudi Arabia • Tertiary Care Centers

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Background

Aicardi-Goutières syndrome (AGS) is a rare autosomal recessive encephalopathy of early onset, most prominent in consanguineous parents, affecting both males and females [1]. It is characterized by microcephaly, calcification of the basal ganglia, a chronic cerebrospinal fluid (CSF) lymphocytosis, a leukodystrophy, negative serology for prenatal infections, and significantly elevated levels of interferon alpha (IFN-α) in the cerebrospinal fluid (CSF) and serum [1]. AGS was first described in 1984 by Jean Aicardi and Françoise e Goutières [2].

The International Aicardi-Goutières Syndrome Association (IAGSA) was founded in 2000 to collect and analyze all available information to increase knowledge of the pathology and the number of reported cases [3].

AGS is divided into 7 subtypes (AGS1-AGS7). Multiple genes are found to be associated with AGS leading to the emergence of diverse heterogeneity. The mutations are TREX1, RNASEH2B, RNASEH2C, RNASEH2A, SAMHD1, ADAR, and IFIH1 [4].

The early signs of AGS are extreme irritability, disturbed sleep-wake patterns, and feeding difficulties. Eventually, the neurological manifestations start to appear – tetraplegia, poor head control, and pyramidal and extrapyramidal signs – commonly appearing in the course of the first year of life [5]. Ocular symptoms of AGS include nystagmus, cortical blindness, and optic atrophy in affected individuals [1]. Glaucoma is reported in multiple publications to be present at birth or to develop later [1].

Here, we present a case of AGS with congenital glaucoma. Additionally, this case demonstrated significant aniridia bilaterally, a feature that is not previously reported in ocular findings of AGS. The paucity of the literature regarding ocular manifestation in AGS was an essential motivation to report this case. The purpose of this case report is to encourage establishing clear guidelines and diagnostic criteria for AGS in order to enrich the treatment capacity.

Case Report

We report the case of a 4-year-old boy with a diagnosis of AGS, global developmental delay, glucose-6-phosphate dehydrogenase (G6PD) deficiency, patent ductus arteriosus (PDA), congenital glaucoma, and aniridia. This patient was referred to the Ophthalmology Department at King Faisal Specialist Hospital and Research Center (KFSH&RC) in Saudi Arabia, as a case of congenital glaucoma in both eyes since birth.

At the age of 10 months, he was referred to Pediatric Ophthalmology for evaluation and was found to have congenital glaucoma, nystagmus, nonreactive pupils, and wondering eye movements, and was not able to fixate or follow with either eye. He was vitally stable; heart rate: 103 beats per minute, respiratory rate: 23 breaths per minute, blood pressure: 87/62 mmHg, temperature: 36.9°C. He was anemic with hemoglobin 9 g/dl, a metabolic panel showed high indirect bilirubin of 2.1 mg/dL, G6PD was 3.1 units/gram of hemoglobin, and the rest of his lab results were within normal range. The patient underwent trabeculectomy procedure with mitomycin C in both eyes in another hospital; unfortunately, the intraocular pressure before the procedure was not documented. A few months later, his intraocular pressure had increased to 30 millimeters of mercury (mmHg) in the right eye (OD) and 10 mmHg in the left eye (OS). The patient had spherophakia with shallow chambers and aniridia in both eyes. On follow-up, he was found to have light perception in both eyes, wandering eye movements, and pupils sluggishly reacting, with cloudy cornea. An examination under general anesthesia showed conjunctival injection hazy cornea with the absence of Haab's stria more in the right eye than the left eye, corneal diameter measures 14×14 mm, shallow anterior chamber (AC), and spherophakia with no lens-corneal touch (Figure 1).

The corneal diameter measured (15 mm H×14 mm) OD and (14×13 mm) OS, and there was aniridia in both eyes (OU), and more prominent OD. Using both Perkins and Tono-Pen tonometers, the intraocular pressure was 40 mmHg OD and 10 mmHg OS. Corneal pachymetry measured a thick cornea of 635 OD and 595 OS. The axial length was 24 mm OD, 21 mm OS, using B-Scan Ocular Ultrasound.

Family history was positive for glaucoma, with consanguineously married parents. According to the genetics report, both parents were carriers of congenital glaucoma genes. His father had an angle-closure glaucoma in his late 40s. His paternal uncle was a carrier for both AGS and congenital glaucoma mutations, but he did not manifest any ocular symptoms; however, his son (the cousin of our case) has the same presentation as in our case. Multiple congenital anomalies can occur in consanguinity, but to the best of our knowledge congenital glaucoma has not been reported to be associated with the syndrome.

Brain magnetic resonance imaging (MRI) showed no punctate calcifications of the putamen and the subcortical white matter with progressive ventricular atrophy. Frank leukoencephalopathy was not seen. Brain atrophy was noticed. The optic nerve of the right eye was slightly stretched, along with increased corneal thickness of the same eye (Figure 2).

Discussion

Aniridia is a rare congenital disorder in which there is a variable degree of hypoplasia or absence of iris tissue. It is often

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Figure 1. Extraocular pictures; (**A, B**) Right eye showing aniridia with complete absence of the iris with positive signs of congenital glaucoma show corneal clouding, increased corneal diameter, and congested conjunctiva. (**C, D**) Left eye showing partial absence of iris (irregular iris), a sign of aniridia, with increased corneal diameter, a sign of congenital glaucoma.

associated with multiple ocular features that can present at birth or develop progressively over time. Most cases are associated with dominantly inherited mutations or deletions of the PAX6 gene [6]. Aniridia can also lead to the development of other developmental abnormalities such congenital glaucoma. Congenital glaucoma in aniridia usually develops during childhood, due to either open- or closed-angle mechanisms. In a study done by Aniridia Foundation International (AFI) members, it was noticed that approximately half of the subjects who developed glaucoma in the presence of aniridia also had increased central corneal thickness [7].

In our case, the patient was diagnosed by the Ophthalmology Department at KFSH&RC as a case of aniridia with AGS-related congenital glaucoma, which are 2 ocular conditions that rarely present simultaneously. Based on the patient's family history, the father manifested glaucoma symptoms at a late age. Based on clinical examination, the patient had congenital glaucoma, aniridia, nystagmus, nonreactive pupils, and wandering eye movements, and was not able to fixate or follow with either eye. In addition, to prevent misdiagnosing AGS as a congenital infection or as leukoencephalopathy of unknown origin [8], a whole-exome sequencing was performed and the genetics report noted that after the removal of the common

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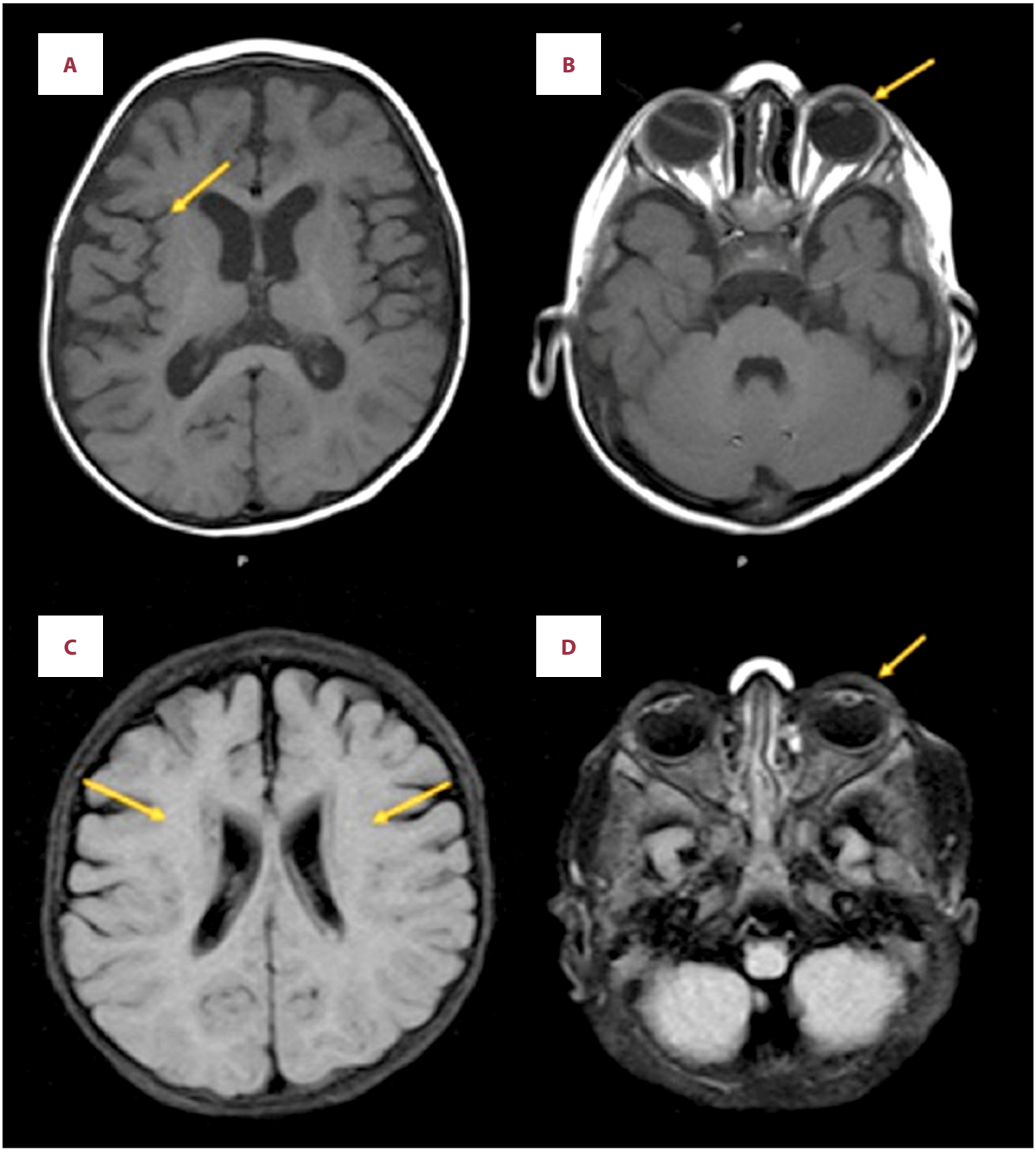

Figure 2. MRI brain; (**A**) Reveals moderate cerebral atrophy, the ventricular dilatation is proportionate to the amount of cortical atrophy. (**B**) Prominent optic nerve on the right side as a sign of starching, most likely due to the severe congenital glaucoma of the same side. (**C**) There is no basal ganglia calcification on MRI, which is unusual in AGS. (**D**) Increased corneal thickness is appreciated more on the right side.

polymorphisms found in the database of Single Nucleotide Polymorphisms (dbSNP), an IFIH1 heterozygous missense mutation was identified, which is associated with AGS type [7]. Despite the absence of Haab's stria of the Descemet membrane, the increased intraocular pressure, increased corneal diameter, and the cloudy corneal were all suggestive of congenital glaucoma. In addition, the patient was confirmed to be a case of congenital glaucoma with CYP1B1 mutation, homozygous recessive. Finally, an MRI scan was performed, showing brain atrophy, stretched optic nerve of the right eye, and

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increased corneal thickness of the same eye due to the severe form of congenital glaucoma on the same side. No signs of basal ganglia calcifications were appreciated on MRI, which is unusual for AGS. Considering the clinical findings of this case, the patient was diagnosed as having a triad of aniridia with AGS-related glaucoma. Therefore, this report can lay the foundation for a national database of AGS in Saudi Arabia, which will help to create a bridge between genetic data and clinical findings of AGS patients.

It is worth mentioning that AGS is completely distinct from the similarly named aicardi syndrome (AS), which is a rare X-linked disorder. AS is classically characterized by a triad of agenesis of the corpus callosum, chorioretinal lacunae, and seizures, predominantly infantile spasms [9]. The hallmark ocular defining feature of AS is the cluster of distinctive chorioretinal lacunae surrounding the optic nerve(s) [10].

Conclusions

This is the first reported case of aniridia with AGS-related congenital glaucoma in literature. There is no report of a similar case in Saudi Arabia or the region. This paper summarizes the usual ocular manifestation of AGS, and also highlights atypical ocular features in AGS as well as congenital glaucoma. This tool will enhance the understanding of the Saudi patient population and thus help provide better medical care to these patients.

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Conflict of interest

None.

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