Axenfeld-Rieger syndrome associated with truncus arteriosus: a case report

Özlem Gürbüz-Köz[1], Tuba Atalay[1], Cem Köz[2], Hatice Ilgın Ruhi[3]
Alper Yarangümeli[1], Gülcan Kural[1]

[1]*1st Eye Clinic, Ankara Numune Training and Research Hospital, [2]Department of Cardiology, Gülhane Military Academy of Medicine, and [3]Department of Medical Genetics, Ankara University Faculty of Medicine, Ankara, Turkey*

SUMMARY: Gürbüz-Köz Ö, Atalay T, Köz C, Ilgın-Ruhi H, Yarangümeli A, Kural G. Axenfeld-Rieger syndrome associated with truncus arteriosus: a case report. Turk J Pediatr 2007; 49: 444-447.

The aim of this presentation was to report a case with Axenfeld-Rieger syndrome (ARS) associated with truncus arteriosus (TA). We present a 14-year-old boy with ARS in whom the diagnosis was confirmed by ophthalmologic examination and developmental defects of the teeth and facial bones. Echocardiography revealed TA. With this case demonstrating the association between ARS and TA, the range of reported cardiac malformations is enlarged and the importance of cardiologic evaluation is emphasized in patients with ARS.

Key words: Axenfeld-Rieger syndrome, truncus arteriosus.

Axenfeld-Rieger syndrome (ARS) is a clinically and genetically heterogeneous disorder with an autosomal dominant mode of transmission and great intrafamilial variability, consisting of a family of developmental diseases including anterior segment abnormalities and a variety of systemic manifestations[1,2].

Axenfeld-Rieger syndrome can be classified as Axenfeld anomaly (limited to peripheral anterior segment defects), Rieger anomaly (peripheral abnormalities with additional changes in the iris), and Rieger syndrome (ocular anomalies and extraocular developmental defects especially of the teeth, facial bones, and periumbilical skin). Because of the marked genotypic and phenotypic overlap, it has been proposed that these diseases are best considered under the single ARS heading. These three variations are now recognized as a spectrum of the same syndrome[1-3]. In the literature, cases with ocular and extraocular manifestations are either defined as ARS or Rieger syndrome[4].

The most important ocular feature of the ARS is glaucoma, which develops in about 50% of affected individuals. The ocular anomalies are suggested to represent an arrest of tissues derived from neural crest cells in gestation[1].

In ARS, classical signs represented by dental hypoplasia, craniofacial anomalies, and involuted periumbilical skin can be associated with a wide diversity of other traits, such as limb anomalies, short stature, pituitary anomalies, empty sella syndrome, and a variety of neurological and dermatological disorders[1,3].

Among the associated extraocular features, cardiac malformations, including interatrial septal defects and semilunar valve stenosis or insufficiencies, have rarely been reported[5-9].

Here we present a case of ARS with truncus arteriosus (TA) type IV. This is the first case reported with TA accompanying ARS.

Case Report

The patient was a 14-year-old boy born from nonconsanguineous healthy parents. He was the 9th sibling of the family. The pregnancy was normal without any exposure to teratogenic agents. The delivery was also normal at term. The family history did not reveal any other similar cases in the family.

The patient had been referred to our clinic because of bilateral gradual visual impairment. Best corrected visual acuity was 0.3 in the right eye and 0.1 in the left eye. Slit lamp

examination displayed a prominent, anteriorly displaced Schwalbe's line in all quadrants of both eyes. The iris had stromal hypoplasia bilaterally. There were corectopia in the right and polycoria in the left eye (Figs. 1 and 2). Gonioscopy revealed iris strands attached to the Schwalbe line in both eyes. Cup/disc ratios were 0.3 in both eyes. Intraocular pressures were 13 mmHg in the right and 28 mmHg in the left eye. Results of visual field testing with automated perimetry were fairly reliable in both eyes. Nonspecific visual field defects were detected because of pupillary distortion in both eyes. There were no anomalies at the lens or fundus. The patient was given topical latanoprost 0.005% (Xalatan, Pharmacia & Upjohn, Uppsala, Sweden) once daily at 10:00 pm, and after one month of therapy, intraocular pressure was 18 mmHg in the left eye.

Non-ocular abnormalities consisted of facial configuration with flattening of the mid-face, a thin upper lip, and protruding lower lip (Fig. 3). Hypodontia and microdontia were also present (Fig. 4). Physical examination revealed the absence of redundant skin around the umbilicus. We considered this patient's ocular and non-ocular abnormalities to be typical of ARS. After informed consent was obtained, peripheral blood sample was obtained. Chromosome analysis revealed a 46-XY normal male karyotype.
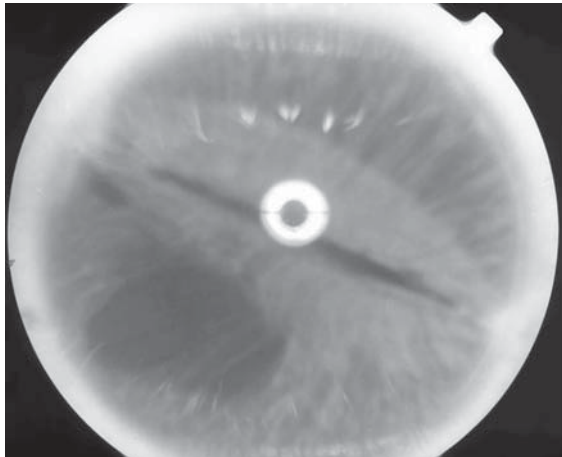

Fig. 1. Biomicroscopic appearance of the right eye showing distortion and displacement of pupil with thinning of iridic stroma, peripheric anterior synechiae at 4 and 10 o'clock positions.
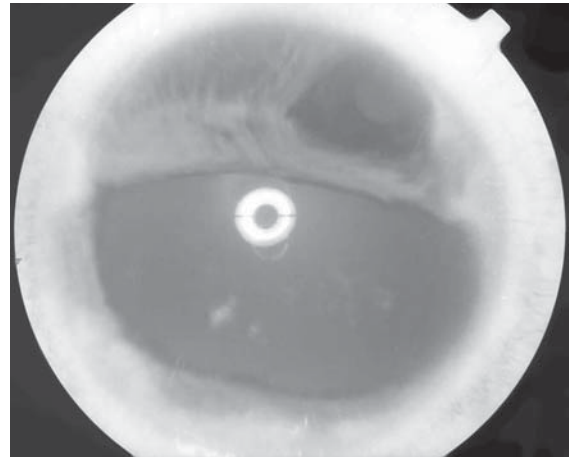
Fig. 2. Biomicroscopic appearance of the left eye showing distortion and displacement of pupil with full-thickness hole formation and thinning of iridic stroma.

Fig. 3. The patient's facial configuration with flattening of the mid-face, thin upper lip, protruding lower lip and maxillary hypoplasia.
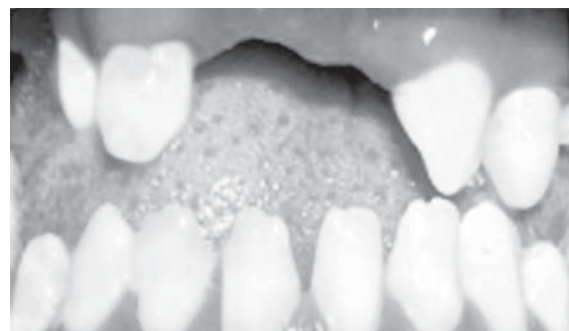
Fig. 4. Photograph illustrating dental anomalies such as hypodontia and microdontia.

Owing to clubbing and history of shortness of breath, the patient was referred to a cardiologist, who found a soft systolic thrill along the left sternal border and loud apical pansystolic murmur at the left lower sternal border, radiating to the whole precordial area and especially to the right side. A two-dimensional echocardiographic examination revealed TA (Figs. 5 and 6). The patient was admitted to another hospital for cardiac surgical treatment.
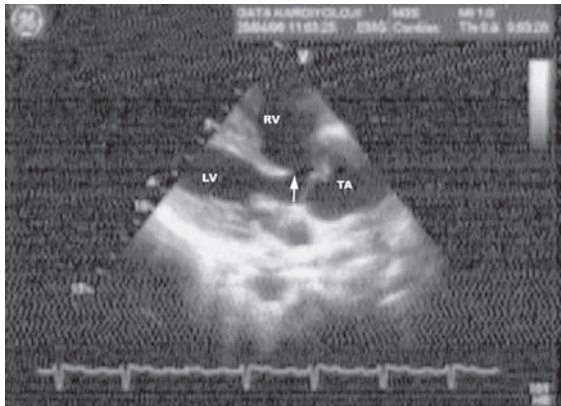

Fig. 5. Echocardiographic characterization of truncus arteriosus is ventricular septal defect (arrow) with truncus arteriosus. LV: Left ventricle. RV: Right ventricle. TA: Truncus arteriosus.
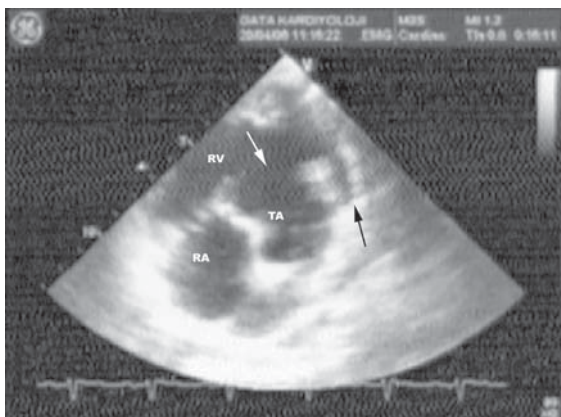

Fig. 6. Truncus arteriosus type IV, ventricular septal defect (white arrow) with pulmonary arterial agenesis (black arrow). LV: Left ventricle. RV: Right ventricle. TA: Truncus arteriosus.

Discussion

The rare association of ARS and cardiac malformations has been described, but TA has not been reported before[5-9]. With this case demonstrating the association between ARS and TA, the range of reported cardiac malformations is enlarged and the importance of cardiologic evaluation is emphasized in patients with ARS.

Very few cases of cardiac malformations accompanying ARS have been described. In 1994, Tsai et al.[5] described a patient with aortic stenosis associated with ARS. Cunningham et al.[6] then described ARS coexisting with atrial septal defects and sensorineural hearing loss, affecting multiple members of a single family. In 2000 Bekir et al.[7] reported a 20-year-old girl with ARS associated with an atrial septal defect and interatrial aneurysm. Recently, Baruch and Erickson[8] described two siblings presenting with ARS, hypertelorism, clinodactyly, and cardiac anomalies such as patent ductus arteriosus and atrial septal defect. Most recently, Grosso et al.[9] reported a family with a clinical picture overlapping that described by Cunningham et al.[6] and characterized by ARS in association with cardiac malformations and sensorineural deafness, without facial dysmorphisms, dental hypoplasia, or involuted periumbilical skin. However, in their patients, cardiac malformations were represented by mitral and tricuspid valve defects instead of the atrial septal defects observed in the patients of Cunningham et al.[6].

Many hypotheses have been proposed for the pathogenesis of ARS on the assumption that the lesions have a common developmental origin during embryonic life. Because subsequent research has shown that the involved ocular tissues originate from the neural crest, ARS is now theorized as developing from the abnormal migration of neural crest cells[10,11], despite this disease having first been described as mesodermal dysgenesis. Shields[11] has proposed that there is a developmental arrest of certain anterior segment structures derived from neural crest cells that leave primordial endothelial layer on portions of the iris and anterior chamber angle, appearing to account for the iridocorneal strands and the changes in the central iris.

A developmental arrest of neural crest tissue is believed to account for the ocular and most of the systemic abnormalities in ARS[1-3]. Embryological studies demonstrated that neural crest cells play a key role in the development of cardiac structures such as the outflow tract and the aortic arch system. Takamura

and associates[12] have also shown that neural crest cells are intimately associated with the formation of both the aortic and pulmonic semilunar valves.

Genetic heterogeneity of ARS has been documented with association to chromosome 4[13] chromosome 6[14], and chromosome 13[15]. Congenital heart defects were reported with association to these chromosomes[16-18]. Conventional cytogenetic analysis in our case revealed a normal male karyotype 46-XY, but further evaluation is crucial to determine the genetic role in ARS and TA association.

In the families described by Grosso et al.[9] and Cunningham et al.[6], ARS, cardiac malformations and sensorineural hearing loss were present. The difference between these families in terms of cardiac anomalies was interpreted as the variable expression of the same genetic defect. Grosso et al.[9] indicated that the inherited traits in members of the presented families were connected and were not coincidental and proposed that patients were affected by a provisionally unique genetic syndrome as hypothesized by Cunningham et al.[6]. Genetic studies will clarify whether they manifest a unique phenotypic expression of ARS or validate the hypothesis of Cunningham et al.[6] in terms of a possibly new genetic syndrome.

To the best of our knowledge, this is the first case in the literature of ARS with coexisting TA. In light of this association, we suggest that the diagnosis of ARS should be followed by systemic evaluation for congenital heart diseases. In patients with anterior segment dysgenesis and TA, analysis of the genes that cause anterior segment dysgenesis or other related genes should be pursued to determine their possible role in the pathogenesis of this syndrome.

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