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Familial partial atrioventricular septal defect in four related kindreds: case series and review of the literature

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Abstract

Background: Atrioventricular septal defects are common congenital heart defects and comprise a spectrum of anomalies, these defects were described in few pedigrees suggesting a familial pattern of inheritance, and they are more common in patients with chromosomal abnormalities. The familial occurrence of this particular type of congenital heart disease is uncommon and few cases have been identified as partial atrioventricular septal defect in adults apart from other chromosomal abnormalities.

Case presentation: We report four cases of adult females who were diagnosed with partial atrioventricular septal defect in four related families, our patients do not have the morphology of Down syndrome.

Conclusions: Further researches on genotyping such patients might contribute to our knowledge regarding this particular cardiac malformation.

Keywords: Congenital heart defects, Atrial septal defect ostium primum, Partial atrioventricular septal defect

Background

Atrioventricular septal defects (AVSD) account for about 7–17% of all cardiac malformations [1], they can be categorized as complete, partial, intermediate, and transitional types. The complete form has atrial and ventricular septal defects as well as a common atrioventricular valve that connects both sides of the heart. Whereas the partial form of AVSD consists of ostium primum atrial septal defect (ASD) with separate atrioventricular (AV) valves and a common annulus as well as a cleft in the anterior leaflet of the left AV valves [2] and generally associated with atrioventricular cushion defect in patients with major chromosomal anomalies predominantly Down syndrome [3], the intermediate and transitional forms of AVSD have a restrictive ventricular septal defect consistent with anatomical and physiological features of partial and complete AVSD respectively [2, 4].

While the majority of ASDs are sporadic, isolated defects and unrelated to chromosomal abnormalities or malformation syndromes [5], few families have the defect as a part of genetic abnormality [6] and various patterns of inheritance, especially in cases of secundum defects, have been identified, most notably autosomal dominant [5, 7]. AVSD has also been described in few pedigrees indicating a familiar pattern of recurrence and several mutated genes involved in cardiac development have been identified in those patients [8].

Most non-chromosomal congenital heart defects (CHD) are believed to be a result of a combination of genetic and environmental factors [5] which include exogenous drugs, toxic agents such as alcohol, and congenital infections such as Rubella [5, 9]; moreover, consanguineous marriage has been reported in several studies as a risk factor for many CHDs including AVSD [10, 11].

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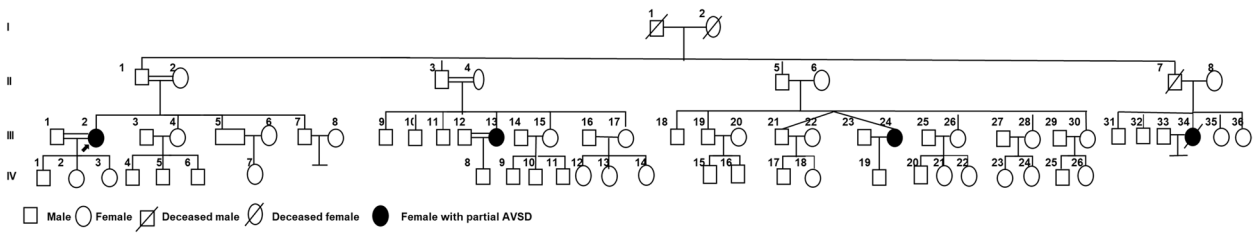

Fig. 1 Pedigree of the kindreds indicating the confirmed cases of partial AVSD or primum type ASD

İn this report, we present four patients in four relative families who were diagnosed with partial AVSD, all of them except one were operated on and followed up by the same surgeon. None of these patients had features suggestive of Down syndrome. There was no history of either Down syndrome or any CHD in any of the members of the extended family, although they were not examined for it, no environmental or pharmacological etiology was involved. Few cases regarding familial recurrence of partial AVSD were reported decades before, all reported cases were diagnosed in one sibship at earlier ages [7, 12]. To the best of our knowledge, familial aggregation of this particular form of CHD is a rare finding and few cases have been reported as partial AVSD in adults apart from Down syndrome, the pedigree of the investigated family is shown in Fig. 1.

Case presentation

Case 1

A 36-year-old young woman (III-2, Fig. 1) was admitted to our department with a history of shortness of breath on exertion, physical examination revealed a regular rhythm and rate with 2/6 holosystolic murmur during auscultation. The parents (II-1, 2, Fig. 1) had a consanguineous marriage and are healthy, the patient also had a consanguineous marriage, she is a mother of three children who were born by vaginal delivery uneventfully, she has got 3 siblings and all are doing well, echocardiography with color flow showed presence of left to right shunt, further examination with transesophageal echocardiogram revealed a primum type ASD of 12 mm size and the pulmonary artery pressure was 40 mmHg, no left AV valve cleft was present, the patient underwent surgical closure with autologous pericardium patch via limited right anterolateral thoracotomy and the postoperative course was uneventful.

Case 2

A 27-year-old young woman (III-13, Fig. 1) was referred to our department in 2005 due to palpitation during delivery, the parents (II-3,4, Fig. 1) and the patient herself had a consanguineous marriage, cardiac examination revealed a regular rhythm and rate with 2–3/6 holosystolic murmur in all areas, transthoracic echocardiography with color–doppler evaluation revealed a partial AVSD with primum type ASD with left to right shunt, also there was a cleft in the left AV valve, so the patient was diagnosed as having a partial AVSD, surgical repair with pericardial patch for ASD and direct suture repair with ring annuloplasty for left AV cleft was performed via median sternotomy, in 2009; 4 years after the operation, the patient was admitted to the emergency department of the same center with severe shortness of breath, and she was diagnosed with pulmonary edema; transthoracic echocardiography revealed acute mitral insufficiency due to ring dehiscence, and the patient was admitted to the intensive care unit and intraaortic baloon pumb was placed, nitroprussid infusion was initiated, however , the patient's condition dramatically deteriorated and the patient was taken up to the surgery emergently, during the operation suture and ring dehiscence was found on the side of the anterior annulus, mitral valve replacement was performed and the patient was discharged on the 7th postoperative day uneventfully.

Case 3

A 27-year-old young woman (III-24, Fig. 1) was admitted to the department of cardiac surgery in 2011 with shortness of breath, fatigue, palpitations, which had been increasing for months, there was no consanguineous marriage history in that family, she has one son and a twin brother (III-21) who are completely normal, two-dimensional transthoracic echocardiography was performed, a large primum ASD was found, also there was a cleft in the left AV valve, she had a pericardial patch closure of primum ASD and direct suture repair of the cleft via median sternotomy, the patient had no complaints and was discharged on the 5th day after the operation.

Case 4

This patient (III-34, Fig. 1) underwent surgical intervention of primum type ASD closure and mitral valve

replacement at the age of 16 years, the patient passed away 3 years ago at the age of 40 years and the cause of death is unknown, so we could not get further information on the inquiry regarding the perioperative course.

Discussion

AVSD has been reported in various pedigrees indicating a pattern of familiar recurrence. Multiple genes involved in cardiogenesis and cardiac septation have been defined as mutated in AVSD patients [8], including mutations in the cardiac transcription factor gene NKX2-5 [13], GATA4, TBX5 [14], MYH6 [15], and some other mutations [16].

AVSD has also been reported with extracardiac disorders in about 75 % of cases, genetically, such defects have a strong association with Down syndrome or other chromosomal abnormalities including Deletion 8p23 syndrome and Deletion 3p25 syndrome [17]; however, partial forms of AVSD were reported to be more frequent when the chromosomes are normal [18].

In the kindred reported here, chromosome analysis has not been conducted, yet no findings, typically associated with chromosomal abnormalities, such as the existence of other congenital malformations, uncommon dermatoglyphic configurations, or mental retardation, have been found in the affected members.

Several studies have shown that genetic factors are involved in the etiology of ASD. Autosomal dominant and autosomal recessive traits have been proposed to clarify family aggregations [12, 19]; nevertheless, the incidence of ASDs in these families appears to be lower than that expected for a single gene defect and multifactorial type of inheritance [5, 20], or incomplete penetrance and variable expressivity [9] has been suggested.

Most cases of AVSD including those not associated with Down syndrome are non-familial [5]; however, there seems no doubt that the cause is genetic in the cases described here. The clinical phenotype combined with generational skips is consistent with the autosomal recessive type of inheritance, in contrast, since the pedigree is small, the assumption that the etiology of this particular type of CHD is multifactorial and attributable to the interaction of polygenic traits can not be ruled out [20]; furthermore, prenatal environmental agents can probably be excluded, particularly since one of the affected members was a dizygotic twin (III-24,21, Fig. 1).

Segregation studies in AVSD families revealed an autosomal dominant inheritance pattern associated with a major gene [5, 21]. İn his analysis of patient series, Digilio et al. stated that AVSD followed a monogenic or polygenic type of inheritance which is consistent with the clinical findings that CHDs in offspring were concordant with the cardiac defects in parents [21]. However, previous researches on larger pedigrees demonstrated lower family concordance rates and emphasized the importance of gender and ethnic differences as a risk factor for familial recurrence [22], these observations support the polygenic origin of familial AVSD, which may exhibit complex patterns of inheritance with incomplete penetrance [22].

Although analysis of the pedigree has led us to the hypothesis that an autosomal recessive trait might be segregated in each family, the four cases and the pedigree presented here illustrate the challenges of determining the heritable nature of this cardiac defect. It is noteworthy that two of the patients reported here (III-2,13 in Fig. 1) were products of first-cousin marriages, and it is well known that consanguinity concentrates autosomal recessive genes in the offspring [23]; yet, this does not explain the pattern of inheritance in the other two cases; assuming that the other members of the extended family have normal cardiac phenotype despite they were not examined for it, thus, it can be suggested that this model requires incomplete penetrance to elucidate the cardiac phenotype of the affected members and clinical status of the other members of the reported families.

Limitations

All the reported cases except for the first one were operated on many years ago in different centers so we were unable to obtain accurate data records, besides genotyping and linkage analyses were not able to be performed due to long-distance issues which limits our evaluation.

Conclusions

The hereditary cause of AVSD tends to be heterogenous and those cases not associated with Down syndrome or other chromosomal abnormalities are often polygenic, although a limited number of cases indicate a single gene mutation. healthy parents of affected individuals may indicate a variable or incomplete gene penetration. While there is still no routine genetic investigation available, the genotyping of these families might be the next step in the investigation and we believe that this will be achievable in the immediate future.

Abbreviations

AVSD: Atrioenticular septal defect.; ASD: Atrial septal defect.; CHD: Congenital heart defect.; AV: Atrioventricular valve..

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Not applicable.

Authors' contributions

All authors contributed equally in the case report as follows: FÇ operated on the patient as the first surgeon and wrote the draft copy of the case report. SA

wrote and revised the manuscript and the discussion. ZE drew the pedigree. VB searched the literature and collected the data to write the case report. All authors have read and approved the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current case report are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This is a case report and not a study. However, the ethical committee in our trust is approving the publication of this case report. There were no animals/plants involved in this case.

Consent for publication
We declare that this case report is sent for publication after having the patients' verbal consent by phone calls due to long distances. İnformation regarding patients' identities were anonymized.

Competing interests
All authors declare that they have no competing interests.

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