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Familial atrial septal defect: a case report in Indonesia

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ABSTRACT

Familial atrial septal defect (ASD) is defined as the occurrence of ASD in the first-degree family of the ASD patient. Recently, familial ASD has been increasingly studied. Familial ASD could manifest as an isolated ASD or with other abnormalities. Furthermore, because ASD is usually asymptomatic, it is very difficult to recognize ASD in a first-degree family based only on symptoms. However, if the family was screened using electrocardiography or echocardiography, the occurrence of familial ASD could be found. Therefore, screening plays an important role in detecting familial ASD. We reported an ASD patient with several occurrences of familial ASD.

ABSTRAK

Atrial septal defect (ASD) familial didefinisikan sebagai terjadinya ASD di keluarga tingkat pertama pada pasien ASD. Studi mengenai ASD familial saat ini telah semakin banyak dilakukan. ASD familial dapat bermanifestasi sebagai ASD yang terisolasi ataupun ASD yang disertai dengan abnormalitas yang lain. Selain itu, karena ASD biasanya asimptomatik, sangat sulit mengenali ASD pada keluarga tingkat pertama hanya berdasarkan gejalanya. Meski demikian, jika keluarga tersebut diperiksa menggunakan elektrokardiografi atau ekokardiografi maka dapat ditemukan terjadinya ASD familial. Oleh karena itu, skrining memegang peranan penting dalam deteksi ASD familial. Kami melaporkan pasien ASD dengan beberapa kejadian ASD familial.

Keywords:
familial ASD;
screening;
first degree family;
electrocardiography;
echocardiography

INTRODUCTION

Congenital heart disease (CHD) is a problem with the structure and function of the heart due to abnormal heart development before birth. Congenital heart disease is the most common birth defect in newborns, with an estimated incidence ranging around 17.9 per 1,000 births worldwide.[1] Familial atrial septal defect (ASD), one of the CHDs, is defined as a condition of cardiac anomalies characterized by insufficient or absent tissue at the interatrial septum. It allows communication between atriums and blood shunting between systemic and pulmonary circulation.[2]

The incidence of ASD is 56 per 100,000 live births, and it is the most common CHD presenting in adulthood.[3] In Indonesia, ASD is also the most common finding in CHD screening from a 5-year single-center hospital registry.[4] Atrial septal defect is mostly sporadic with no secondary causes. However, the ASD were found in family clusters or familial ASD, suggesting an autosomal dominant pattern of hereditary modes of inheritance.[5]

Atrial septal defect can be classified as primum ASD, endocardial cushion defects, secundum ASD, sinus venosus ASD, and unroofed coronary sinus ASD.[6] Secundum ASD is the most common ASD

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that found in about 10% of all CHD and 8% of familial cases.[7] Atrial septal defect is linked to genetics abnormalities causing the disturbance of the development of the intraatrial septum, thus allowing a shunt between the left and right atrium, which persisted until birth. Currently, some genes such as T-BOX5, NKX2.5, EVC, and GATA4 may be involved in ASD both in isolated ASD or in ASD with syndromes.[8] Here we reported a family with several cases of ASD occurrences.

CASE 1

Subject C, a 50 y.o. male, the first of five siblings, has suffered from shortness of breath since he was 7 y.o. In 2017, he was admitted to the hospital because of a worsening symptom. On physical examination, cardiomegaly with an irregular heartbeat was found. Electrocardiography showed atrial flutter, right atrial and right ventricular hypertrophy.

Trans thoracal echocardiography (TTE) was conducted. An echo gap in interatrial septum with a diameter of 2.60 - 2.80 cm, left to right shunt, moderate tricuspid regurgitation, TR velocity of 3.64 m/s, dilatation of right heart chamber, normal TAPSE, left ventricular D-shape and high probability of pulmonary hypertension were observed. Furthermore, trans oesophageal echocardiography (TOE) was also conducted, showing superior sinus venosus ASD with a diameter of 1.8 cm. On laboratory examination, NT pro-BNP level was 789.3 pg/dL. Right heart catheterization was performed showing a mean pulmonary arterial pressure (mPAP) of 31 mmHg and pulmonary vascular resistance (PVR) was 1.18 woods units. He was diagnosed with sinus venosus superior ASD with high flow low resistance and mild pulmonary hypertension. Surgery was carried out in April 2018, followed by permanent pacemaker implantation in June 2018.

Based on the patient's genealogy data, he is the first child with two brothers and two sisters. His father passed away at 42 y.o.

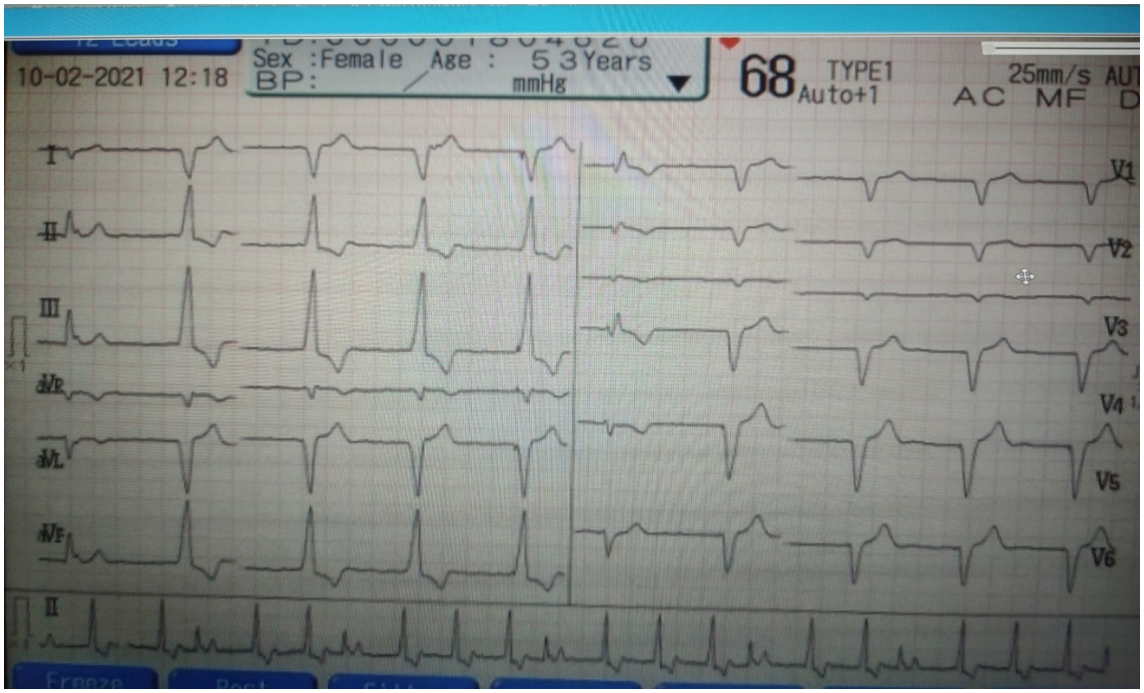

FIGURE 1. Electrocardiography of subject C

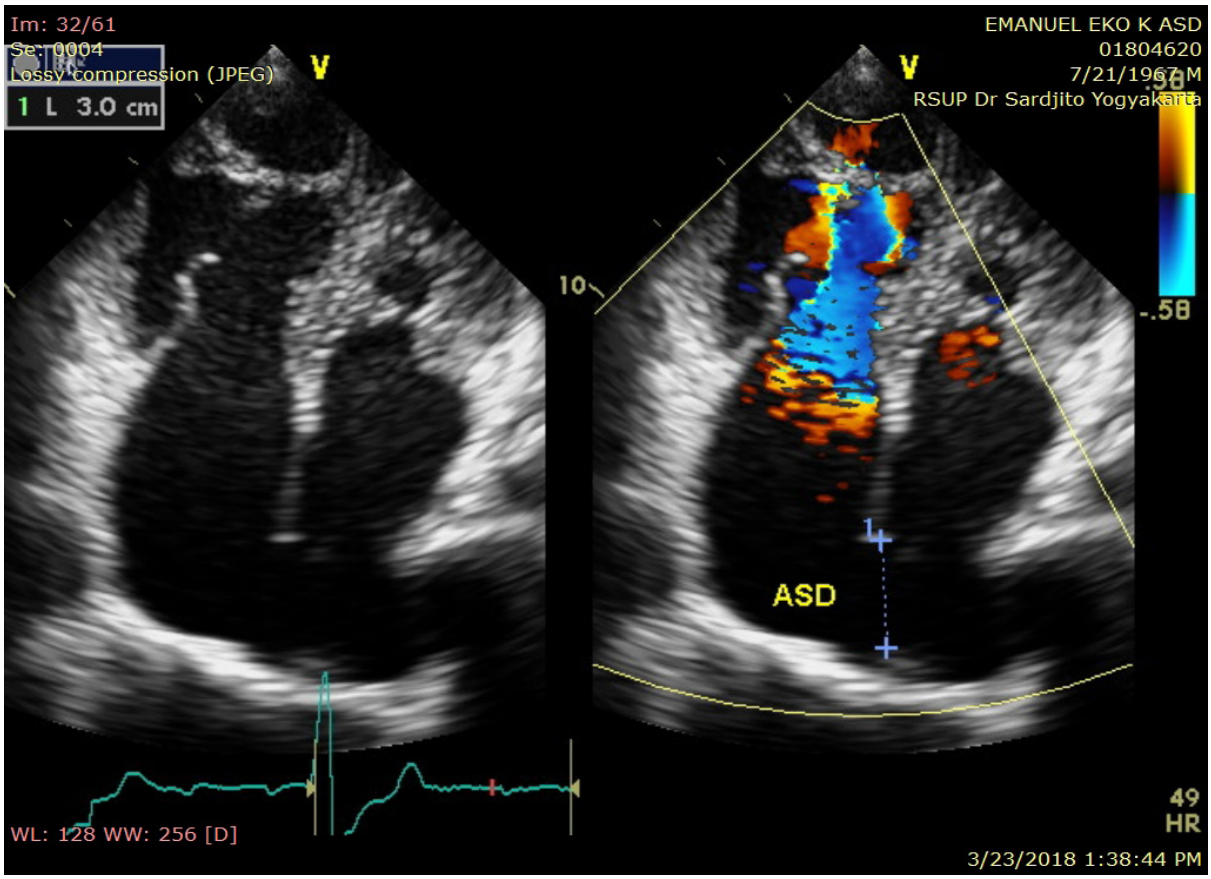

FIGURE 2. Trans thoracal echocardiography of subject C showing ASD

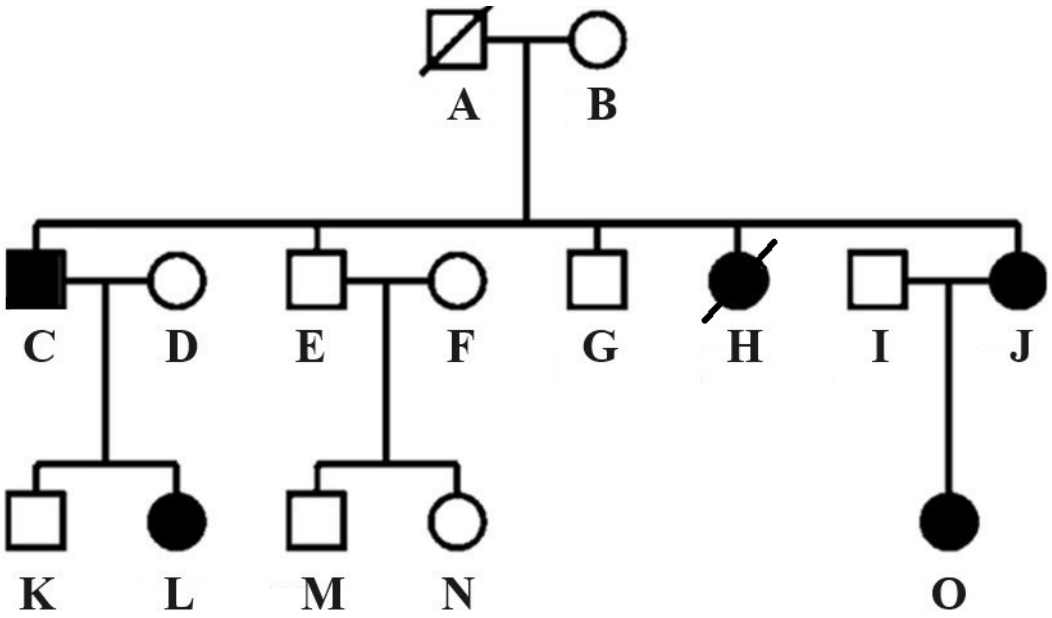

FIGURE 3. Family pedigrees of ASD patients. Squares represent male subjects, and circles represent female subjects. Black-shaded shapes represent ASD. Crossed symbols represent deceased individuals.

CASE 2

Subject H, a 30 y.o. female, was another family member with ASD. She is the younger sister of subject C. She was diagnosed three years earlier than his brother. She was admitted to the hospital with a complaint of shortness of breath. On physical examination, cardiomegaly and wide-fixed split S2 were found. Electrocardiography shows sinus rhythm with right atrial and right ventricular hypertrophy.

On TTE, we found significant dilatation of the right heart chamber and an echo gap in the interatrial septum with a diameter of 1.1 cm and 1.5 cm, left to right shunt, moderate tricuspid regurgitation, TR velocity of 5.87 m/s, normal TAPSE, left ventricular D-shape, and high probability of pulmonary hypertension. Meanwhile, results from TOE were multiple ASDs with diameters of 1.1 cm and 1.5 cm. On laboratory examination, NT-pro BNP was 2,383 pg/dL. Right heart catheterization was also performed. The hemodynamic data showed that mPAP was 59 mmHg. This patient then diagnosed with secundum ASD high flow high resistance and severe pulmonary arterial hypertension (PAH). She was treated conservatively with sildenafil (20 mg tid) and beraprost (20 mg tid).

CASE 3

In 2005, subject J, a 39 y.o. female, was admitted due to dengue hemmoragic fever. She never experienced any cardiac complaints such as shortness of breath or palpitations. However, during the examination, irregular heart rhythms and ASD were found. She was then referred to the hospital and underwent surgical ASD closure and permanent pacemaker implantation. Unfortunately, she never went to follow-up in years.

CASE 4

Subject L, an 11 y.o. female, the daughter of subject C, was diagnosed with secundum ASD and arrhytmia when she was 4 y.o. Radiofrequency ablation was performed a year later, followed by ASD closure afterwards.

After ablation electrocardiography showed sinus rhythm, right bundle brach block, right atrial and right ventricular hypertrophy.

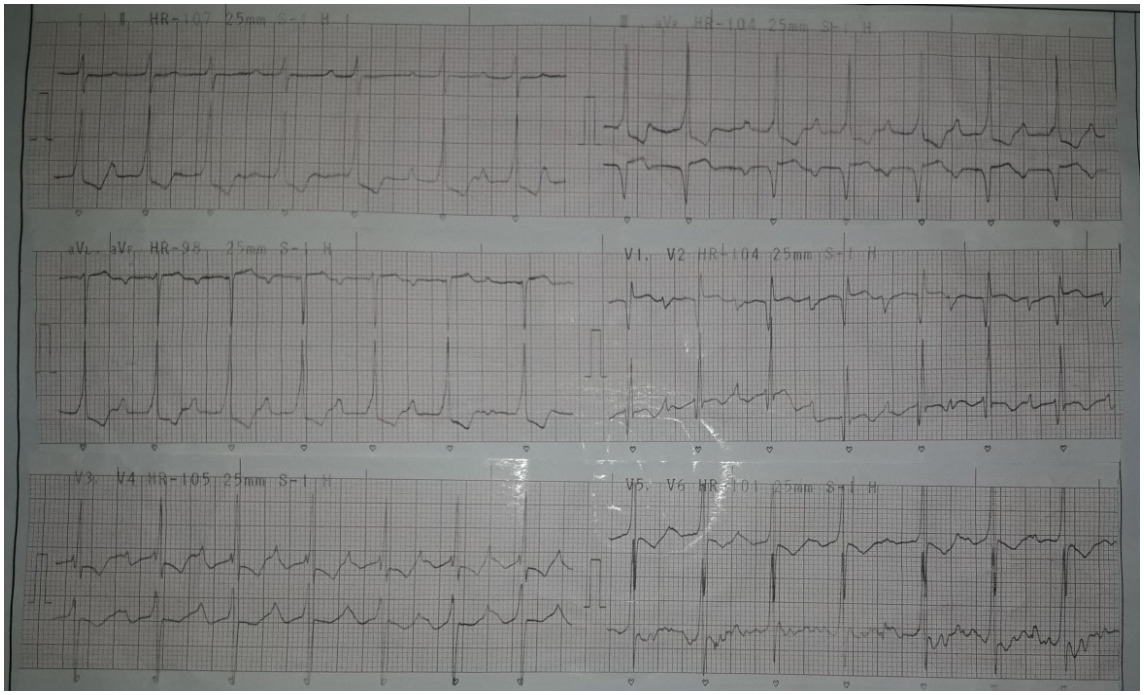

FIGURE 4. Electrocardiography of subject H

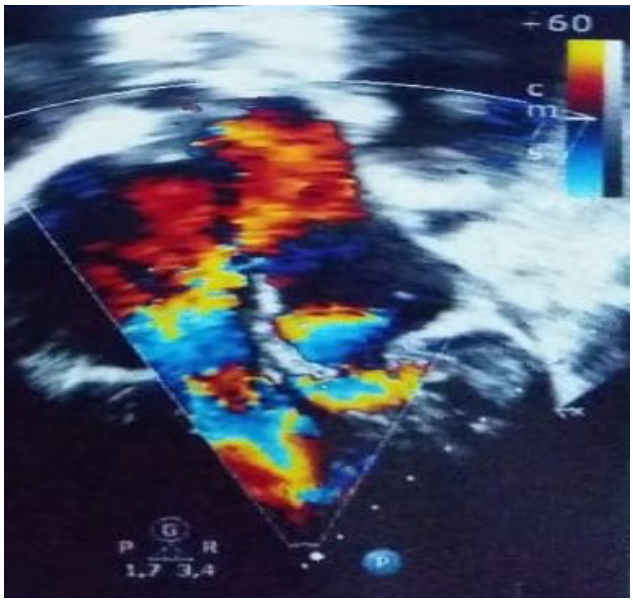

FIGURE 5. Trans thoracal echocardiography of subject L showing ASD

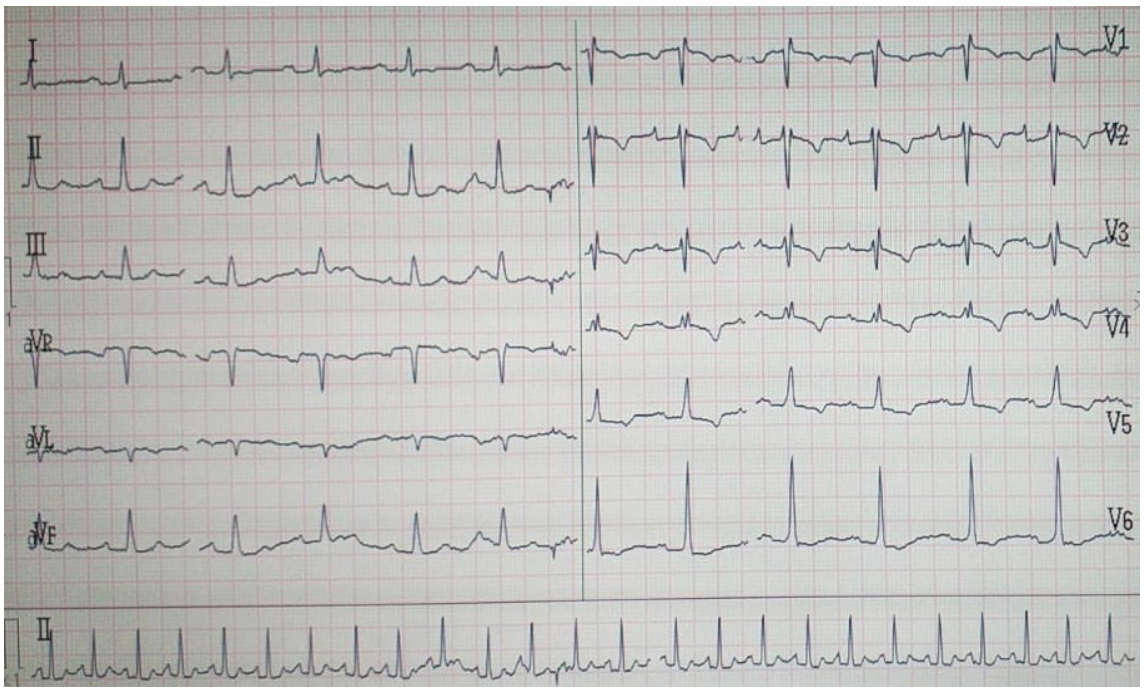

FIGURE 6. Electrocardiography of subject L

CASE 5

Subject O, a 10 y.o. female daughter of subject J, was diagnosed with ASD in 2014. She was asymptomatic and never complained of shortness of breath or palpitations. Echocardiography revealed a defect in the interatrial septum with a diameter of 1.8–2.0 cm, left to right shunt and mild tricuspid regurgitation. The patient underwent surgical ASD closure in 2018.

DISCUSSION

Atrial septal defect is an anomaly condition which is marked by a defect interatrial septum of the heart.[2] The diagnosis of ASD is shown in echocardiography images showing a shunt at the interatrial as a communication that results from a deficiency of the partition between the left and right atrium. Despite its high incidence rate, ASD patients are usually asymptomatic until adulthood.[9] This phenomenon increases the number of adults with ASD, which has more fatal complication.[10] Several studies showed that ASD is inherited; therefore ASD patients' families should be screened to achieve early diagnosis and treatment.[11] These cases show the benefit of screening through examination and verbal interview.

Women with CHD are three times more likely to have children with CHD than women with healthy hearts, with the recurrence rate of ASD alone being 1.5%.[12] The largest study on recurrent familial ASD was conducted by Caputo *et al.*[13] The study found an insignificantly higher risk of isolated secundum ASD subjects who were born from isolated secundum ASD patients as compared to non-isolated secundum ASD patients. Meanwhile, the recurrence risk of secundum ASD between siblings is 10.8% in siblings of isolated secundum ASD patients.[13]

In these cases, ASD is diagnosed in 4 of 5 first-degree family members. The types of ASD are different from each other. We found one sinus venosus ASD and three secundum ASDs. All family members with secundum ASD are women. One of the children with sinus venosus ASD also has secundum ASD and arrythmia. And the other secundum ASD patient has a daughter with secundum ASD.

Genetically, many regulatory genes play important roles during heart development. The morphogenesis of the heart involves many processes that require tight regulation; otherwise, a CHD could occur. The key player in this regulation is transcription factors, which titrate the expression of tissue-specific genes and mediate molecular responses to environmental stimuli.[14] Mutations in these gene regulators could result in anomalies of the heart, with ASD being one of the most common phenotypes. Several genes mutations have already been identified to cause ASD.[15] These genes are inherited between generations and shared between siblings, even though they are not always expressed.

Arrythmia observed in these patients resulted from anatomical complications of ASD. Volume overload in the right atrial chamber could change its shape and also alter the conduction system in the heart. The prevalence of atrial arrythmia is higher in older patient, larger shunts and patients who have developed comorbidities such as pulmonary hypertension. Mutations in the NKX2.5 and GATA4 genes, which are found in familial ASD patients, could change the atrio-ventricular conduction system and result in arrythmia.[16] Genetics could cause isolated ASD without arrhythmia, ASD with arrhythmia, and ASD in syndromes.[8] Furthermore, there is still interaction between genetics and environmental causes. For example, alcohol consumption and smoking habits during pregnancy can cause ASD of the newborns.[17,18] On the other hand,

pesticides still do not have a strong connection with the occurrence of ASD.[19]

CONCLUSION

This case report showed a familial occurrence of ASD. Therefore, screening the first-degree family of an ASD patient became an important step to detect ASD and confirm the diagnosis of familial ASD. Physical examination, electrocardiography, and echocardiography would become important tools to detect those with familial ASD. Our cases emphasize the important role of screening in familial ASD in order to diagnose and treat patients with ASD before the complications of ASD occur. However, because this study has not completed deep and thorough genetic testing, we cannot draw on the strength of genetics to predict the occurrence of ASD in this study.

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