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The prospective follow-up of the natural course of interatrial communications diagnosed in 847 newborns

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KEYWORDS
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Aims The aim of this study was to evaluate the prevalance of interatrial communications (IACs) and IAC types in a large series of newborns, to establish the incidence of spontaneous closure of IACs, to determine the relationship between spontaneous closure and the size and type of IACs, and to investigate the incidence of mitral valve prolapse (MVP) and atrial arrhythmia in newborn infants with atrial septal aneurysm (ASA).

Methods and results Between 2000 and 2001, a total of 1100 asymptomatic and term newborns were evaluated. Those who had congenital heart diseases and failed to attend the follow-up visits were excluded from the study. The remaining 847 newborns were followed until the closure time or in those where closure did not occur, for a maximum time of 45 months (mean 25 $\pm$ 3 months, range 1–45 months). The mean age at diagnosis was 1.7 $\pm$ 1.4 days (range 1–7 days). According to echocardiographic evaluation, cases were classified into four groups based on the initial size of IAC and into three groups based on the type of IAC. At the end of the 45th month IACs were closed spontaneously in 98.6% of the cases. There was significant relationship between the diameter of IAC and the timing of the closure ($P < 0.01$). The closure time in the cases with ASA was significantly longer than the cases with valve-like opening and multiple fenestration ($P < 0.01$). In female newborns, the defects remained open for a significantly longer period than male newborns ($P = 0.0397$). There was no significant relationship between ASA and atrial arrhythmias ($P = 0.294$). None of the newborns had MVP.

Conclusion The cases with IACs $<$3 mm do not need follow-up. However, the cases with IACs $>$3 mm do need to be followed until the defect closes completely. Those with ASA should be followed-up regularly, because these defects can remain open. Spontaneous closure occurs significantly earlier in cases with valve-like opening and multiple fenestration.

Introduction

The widespread recent use of Doppler echocardiography and colour flow mapping screening in healthy newborns referred for innocent heart murmurs has shown that the incidence of interatrial communications (IACs) and shunts in the newborn period may be fairly high.[1,2] Although previous studies have documented the natural course of IACs, most studies have not included large series of newborns.[1,3–7] Therefore, the aim of this study, including a large series of newborns and a long follow-up period (45 months), was to evaluate the prevalance of IACs and types of IACs, to establish the incidence of spontaneous closure of IACs, to determine the relationship between spontaneous closure and the size and type of IACs, and to investigate the incidence of mitral valve prolapse (MVP) and atrial arrhythmia in newborn infants with atrial septal aneurysms (ASAs).

Methods

Subjects

The study group consisted of 1100 consecutive asymptomatic and term newborns born in the department of obstetric and gynaecology of our institution between January 2000 and October 2001. Informed consent was obtained from the parents in each case. The pre-natal, natal, and post-natal data were obtained from each newborn's chart. Data regarding gestational age, birth weight, and Apgar scores were recorded. All cases had a complete physical examination, and electrocardiographic and echocardiographic evaluation. Ten newborns who had congenital heart disease (except for a patent ductus arteriosus, peripheral pulmonic stenosis, or tricuspid insufficiency), and 243 newborns who failed to attend the follow-up visits were excluded from the study.

Echocardiographic examination

Two-dimensional, M-mode, continuous Doppler, and colour Doppler echocardiography were performed on all cases using a 3–7 MHz ultraband transducer with Hewlett-Packard 5500. The echocardiographic examination comprised a complete sequential segmental analysis of each case. IAC diameters obtained by both two-dimensional and colour flow end-systolic mapping were measured

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in subcostal four-chamber and sagittal views. In some cases, the width of the colour jet obtained by colour Doppler mapping was considered to represent the size of the defect when the small defect could not be well visualized by two-dimensional echocardiography. Standard parasternal short axis and suprasternal views were used to confirm the patency of the ductus.

The newborns were classified into four groups based on the initial size of IACs.

Group 1: <3 mm; Group 2: 3–4 mm; Group 3: 5–7 mm; Group 4: ≥ 8 mm.

In addition, the cases were also divided into three groups according to the type of IAC. These were valve-like opening, multiple fenestrations, and ASA.

Criteria of Gallet *et al*.[8] were used for the diagnosis of ASA:

(1) protrusion of the interatrial septum, or part of it, into either of the atrias >6 mm beyond the plane of the septum; or
(2) phasic excursion of the protrusion ≥ 6 mm during the cardiac cycle; and
(3) base of the protruding portion of the septum measuring at least 6 mm.

In multiple fenestration type of IACs, the sum of the measured opening sizes was considered as the size of the defect.

In the newborns with ASA and the control group, including the other newborns without ASA, criteria of Nascimento *et al*.[9] were used for the diagnosis of MVP. Mitral valve morphology was evaluated from parasternal long-axis, apical 5–4, and 2-chamber views by two-dimensional and parasternal long-axis by M-mode. Two-dimensional diagnostic criteria for prolapse were posterosuperior motion of one or both mitral leaflets beyond the annular plane in the parasternal long-axis view or of the posterior leaflet in any view. M-mode recordings were obtained at the tips of mitral leaflets under direct two-dimensional echocardiographic control. Diagnostic criteria for prolapse included ≥ 3 mm abrupt late systolic posterior motion of the mitral valve.

All examinations were done by the same paediatric cardiologist and all studies were recorded on videotape for later analysis.

Follow-up

The 847 newborns were prospectively followed. The control visits were performed at the first month, third month, and every 3 months for a maximum time of 45 months. At each visit, all cases had a physical examination and echocardiographic evaluation. Electrocardiographic evaluation was only performed in the cases of arrhythmia. Each case was followed until the closure time and resolution of the arrhythmia or, in those where closure did not occur, for a maximum time of 45 months.

Statistical analysis

The results were expressed as mean $\pm$ standard deviation. χ^2 and Fisher's exact tests were used for comparisons. A Kaplan–Meier survival function was used to produce a graphic representation of the closure of IACs as a function of time. A log-rank test was used for comparison of the curves. *P*-values of <0.05 were considered statistically significant.

Results

The mean age at diagnosis was 1.7 ± 1.4 days (range 1–7 days). The mean gestational age was 39 ± 0.9 weeks (range 38–42). The mean birth weight was 3.3 ± 0.47 kg (range 2.5–5). The mean follow-up duration was 25 ± 3 months (range 1–45 months). Of the cases, 419 (49.4%) were male and 428 (50.6%) female. The mean echocardiographic examination was 4 ± 2 echocardiograms (range 2–15) per case.

All newborns had normal Apgar scores and normal findings on physical examination. IAC was found in all cases. On echocardiographic examination, valve-like opening was determined in 745 newborns (88%), multiple fenestrations in 59 newborns (7%), and ASA in 43 newborns (5%). At the end of the 45th month, IACs were closed spontaneously in 98.6% of the cases (*Figure 1*). In the IACs which were smaller than 3 mm, the incidence of spontaneous closure was 100%. The incidence of spontaneous closure was 99% in Group 2 (3–4 mm), 71% in Group 3 (5–7 mm), and none in Group 4 (≥ 8 mm) (*Figure 2*). There was a significant relationship between the diameter of the IACs and the timing of closure ($P < 0.01$) (*Figure 3*). The mean follow-up duration was similar for Group 1 (<3 mm) and Group 2 (3–4 mm), but was significantly longer for Group 3 (5–7 mm) and Group 4 (≥ 8 mm) ($P = 0.0356$). The incidence of spontaneous closure was 100% in multiple fenestrations type of

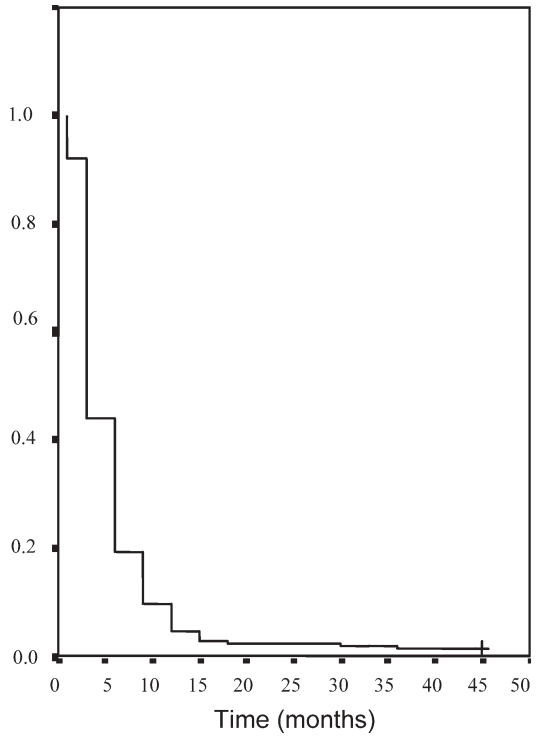

Figure 1 Proportion of interatrial communications remaining open as a function of time for total group of 847 newborns.

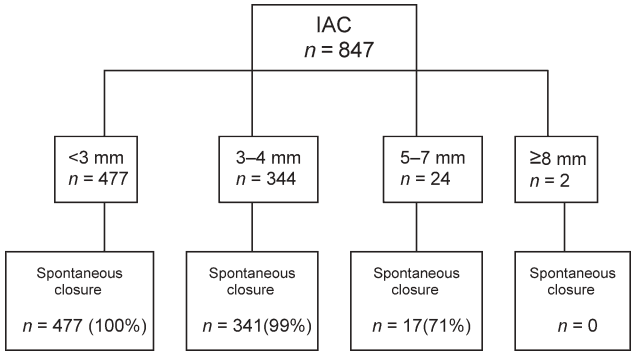

Figure 2 The percent of spontaneous closure of interatrial communications according to initial diameters at the end of 45 months.

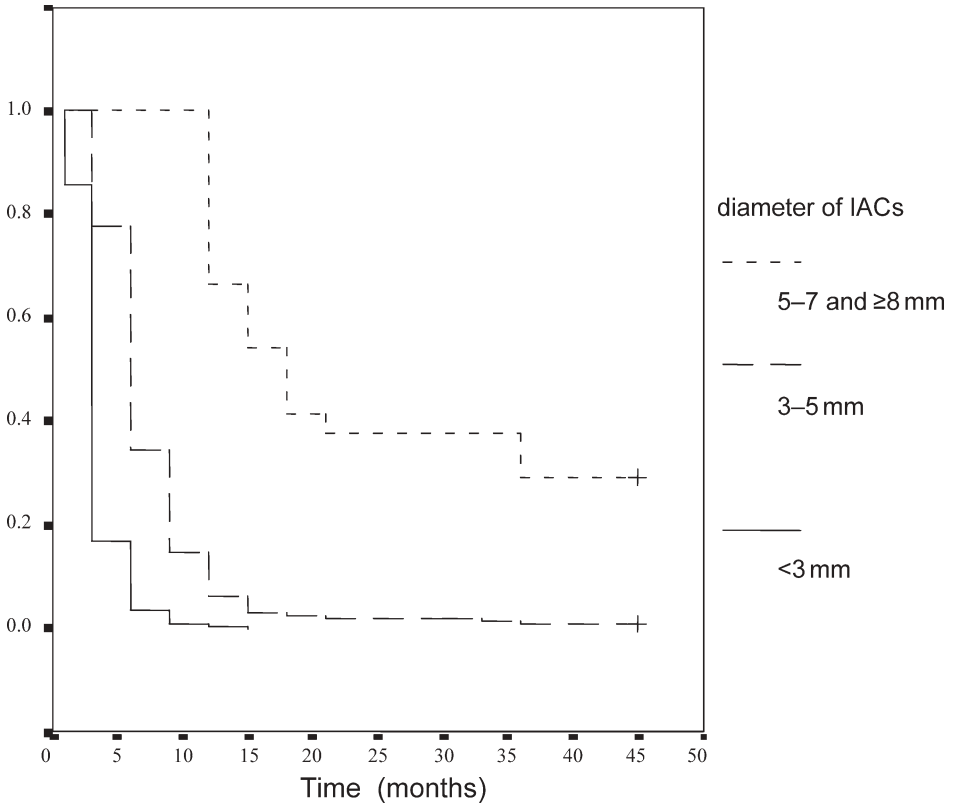

Figure 3 Proportion of interatrial communications remaining open as a function of time for the total group of 847 newborns according to the initial diameter.

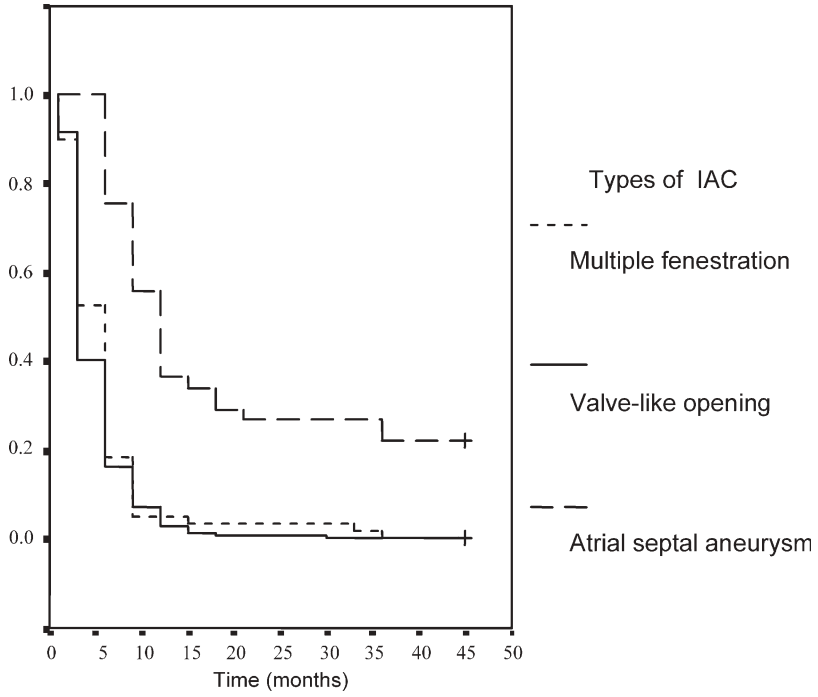

Figure 4 Proportion of interatrial communications remaining open as a function of time for the total group of 847 newborns according to the type of IAC.

IAC, 99.6% in valve-like opening type, and 79% in ASA. The closure time in the cases with ASA was significantly longer than the cases with valve-like opening and multiple fenestrations ($P < 0.01$) (*Figure 4*). The IACs remained open for a significantly longer period in girls compared with boys ($P = 0.0397$). Patent ductus arteriosus was determined in 343 newborns (40.5%). During follow-up, ductus arteriosus did not close in only one case. There was no significant relationship between spontaneous closure of IAC and ductus arteriosus ($P = 0.347$).

In this study, atrial arrhythmia was determined in seven cases. Only one of whom had ASA. There was no significant

relationship between ASA and atrial arrhythmia ($P = 0.294$). None of the newborns had MVP.

Discussion

In this study, IAC was found in all cases and 98.6% of those closed spontaneously in a period of 45 months. The incidence of spontaneous closure of IAC was found highest during the first 3 months of life (*Figure 1*). In previous studies, the incidence of spontaneous closure of IACs was reported to range from 14 to 98.7%.[1–3,5,6] The studies done in the newborn period reported a higher incidence of spontaneous closure.[1,5,6] Some of these studies which reported the lower incidence of spontaneous closure had focused on cases aged above 1 year at the time of diagnosis, whereas the highest incidence of spontaneous closure probably occurred earlier.[10,11]

The size of IAC at initial examination was the most important predictive factor. The smaller the diameter, the more likely and the earlier was defect closure. In our study, IACs closed spontaneously in all cases of Group 1 (<3 mm). The previous echocardiographic studies also supported the earlier outcomes.[1,5,6] We considered that most cases of Group 1 probably had foramen ovale, and spontaneous closure of the defect in all cases in this group favours this opinion. However, Ghisla *et al.*[3] reported that spontaneous closure may be observed in larger defect. We observed a 65% rate of spontaneous closure in cases with IAC larger than 5 mm at the end of 45 months follow-up.

In this study, the type of IAC was also found to be an important predictive factor. The incidence of spontaneous closure of valve-like openings was established as 99.6%. Şenocak *et al.*[6] also reported that spontaneous closure incidence in valve-like opening was higher. Probably, these openings were also a patent foramen ovale, because there was an atrial septal tissue flap originating from anatomical septum primum. Multiple fenestrations were determined in 7% of the cases. There was no information about multiple fenestrations in previous studies. However, the presence of these openings was reported in the literature.[12,13] This type of openings probably occur as a result of programmed cell death in particular areas of the septum primum during embryogenesis.[14] The spontaneous closure rate of these openings was 100%.

ASA is an uncommon congenital malformation of the interatrial septum. Several studies reported that an aneurysm formation was observed at the localization of fossa ovalis in spontaneous closure cases.[1,3,6] In our study, ASA was established in 43 newborn infants (5%) and interatrial shunt was shown in all cases with ASA. Unlike previous studies, the closure time in cases with ASA was significantly longer than the other types, and at the end of 45 months the defect remained open in 21%. The aneurysm disappeared in cases with ASA who had spontaneous closure of the opening but persisted in all cases whose opening did not close. The investigations performed in adults demonstrated that ASA was associated with mitral valve prolapse.[15,16] Moreover, several recent publications have noted an increased incidence of atrial arrhythmia in cases with ASA.[17] Rice *et al.*[18] who evaluated 105 consecutive foetuses with foetal echocardiograpy found that the association of ASA with atrial arrhythmia was highly significant. Casta *et al.*[19] also reported ASA in four foetuses with supraventricular tachycardia. In the intrauterine period, the frequent occurrence of ASA can be considered as a stage of the normal embryogenic development. Brand *et al.*[20] prospectively evaluated the incidence of ASA in 3500 children, aged 1 day to 15 years, and found in 35 children (1%). In these cases with ASA, MVP was not observed, and atrial arrhythmia was found in only three newborns. In our study, atrial arrhythmia was established in one of the cases with ASA, but no MVP was observed. There was no significant relationship between ASA and arrhythmia. Considering all these studies, this relationship between ASA and arrhythmia can require echocardiographic evaluation of the newborn with arrhythmia with respect to ASA.

In this study, patent ductus arteriosus was observed in 40.5% of the cases. During follow-up, ductus arteriosus did not close in only one case. There was no significant relationship between spontaneous closure of IAC and ductus arteriosus ($P = 0.347$). Rigss *et al.*[21] reported that ductus arteriosus did not have any significant effect on spontaneous closure of IAC in the studies comparing term and preterm newborns. However, in preterm infants it was observed that ductus arteriosus delayed the spontaneous closure.

In our study, it was found that spontaneous closure of IACs between 5–8 mm in female newborns was lower than that in male newborns ($P = 0.0342$). In other studies, there was no significant difference in spontaneous closure of IACs between female and male newborns.[1,5,6] Şenocak *et al.*[6] reported that defects more than 5 mm were present more in female newborns. However, in their study there was no significant difference between female and male newborns.

In conclusion, some features of IACs diagnosed in the newborn period gave us some ideas about its natural course. These results suggest that the cases with IAC <3 mm do not need follow-up. However, the cases with IACs of more than 3 mm do need to be followed until complete closure. The type of IACs was also found as an important predictive factor. Those with ASA should be followed-up regularly because these defects can remain open. Spontaneous closure occurs significantly earlier in cases with valve-like opening and multiple fenestration. We think that these results are important to determine the natural course of IAC and to inform the parents about the prognosis of the defect.

Conflict of interest: none declared.

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Clinical vignette

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Steroid responsive aortitis

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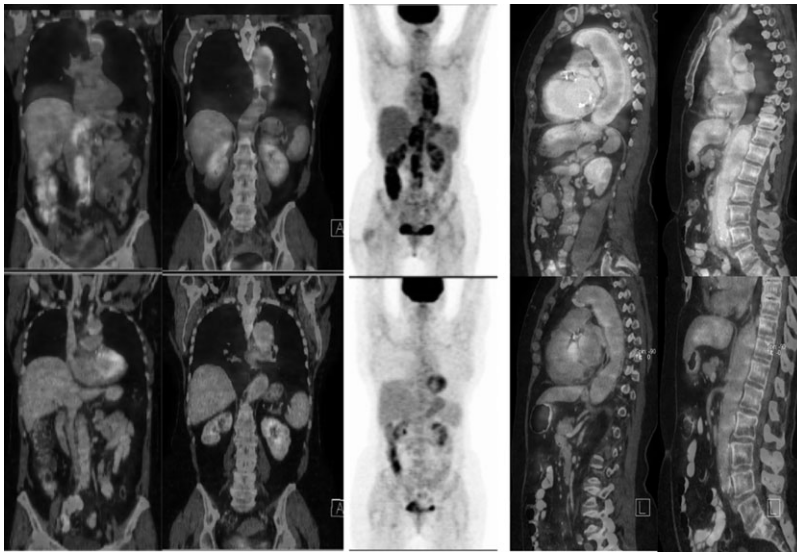

A 57-year-old woman with a history of nephrolithiasis, hypertension, and hypercholesterolaemia presented with a 4-day history of episodic back pain localized between the scapulae. Blood pressure was 155/60 mmHg on both arms and temperature was 36.2°C. Cardiopulmonary, arterial pulsation, and abdominal examinations were unremarkable without inducible back pain. C-reactive protein (C-reactive protein: 40 mg/dL) and erythrocyte sedimentation rate (ESR: 70 mm/h) were elevated. Chest CT scan with contrast demonstrated ascending aorta dilatation (40 mm diameter), aortic arch calcification, and wall thickening of the entire aorta. Assuming a mural thrombus or intramural haematoma, patient was treated with analgetics, anti-hypertensive drugs, and immobilization. Her condition worsened with persistent back pain, low-grade fever (<38.5°C), and ongoing C-reactive protein and ESR elevation (maximum 180 mg/dL and 110 mm/h); blood cultures were negative. After an overnight fast, a fused CT and ^{18}F-labelled deoxyglucose (FDG) positron emission tomography (PET) scan showed pathological FDG uptake in the entire aorta, suggestive of aortitis (upper panels). Autoantibodies against antinuclear antigens and antineutrophil cytoplasmatic antibodies were negative, and lues was excluded. Patient was treated with prednisone 60 mg/day for 2 months. A follow-up PET–CT scan demonstrated resolution of the increased aortic FDG uptake (lower panels), in addition to a reduced C-reactive protein (5 mg/dL) and ESR (36 mm/h), and relieve of her symptoms, suggestive of an inflammatory origin of the aortitis. Our patient did not meet the criteria for giant cell- and Takayasu arteritis. The diagnose was set for a steroid responsive idiopathic aortitis with aorta dilatation. Dose reduction of prednisone will be attempted, her prognosis is unknown.