Transplant Heart Murmur in the Late Neonatal Period: Its Origin and Relation to the Transition from Fetal to Neonatal Circulation

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Summary: To elucidate the origin of transient heart murmur during the late neonatal period, we examined 50 neonates with this type of heart murmur and compared them with 50 controls. We serially examined the morphology of and blood flow in the main pulmonary artery (MPA), the right pulmonary artery (RPA), and the left pulmonary arteries (LPA) using two-dimensional and Doppler echocardiography. The heart murmurs were first noticed at 6 to 60 days after birth (mean 33±14). At that time, the diameters of both the RPA and the LPA in the heart murmur group were significantly smaller than those in the control group, and the velocities of blood flow in the right and left pulmonary arteries in the heart murmur group were significantly greater than those in the control group. When the heart murmur disappeared, the diameters and the flow velocities of both the RPA and the LPA were not different compared with the control group. Two cases in the heart murmur group continued to have a heart murmur and were diagnosed as having intrinsic congenital peripheral pulmonary artery stenosis. In conclusion, our findings suggest that a transient heart murmur in the late neonatal period is caused by transient branch pulmonary arteries stenosis during the transitional circulation from fetus to neonates.

Key words transient heart murmur, neonate, peripheral pulmonary artery stenosis, perinatal circulation, Doppler echocardiography

INTRODUCTION

Several types of transient heart murmur are detected during the neonatal period [1]. In the early neonatal period, some of these may be caused by the functional shunting of the ductus arteriosus or atrial shunting at the foramen ovale. In 1971, Kato [2] reported “the transient heart murmur in late neonatal period,” which is detected from about 2 to 4 weeks after birth and subsequently disappears after a few months. This murmur is characterized as a moderately pitched early- to mid-systolic ejection murmur at the second intercostal space left sternal border, with the intensity of Levine 2-3/6. The second heart sound is sometimes fixed split. From the findings of cardiac catheterization and intracardiac phonocardiography in the infants with this murmur, Kato concluded that physiological peripheral pulmonary stenosis might contribute to this heart murmur. In order to elucidate the origin of this heart murmur, we serially examined the morphology of and blood flow in the main and peripheral pulmonary arteries using two-dimensional and Doppler echocardiography in 50 infants with this type of heart murmur, and compared them with those in 50 infants without a heart murmur.

METHODS

Studied groups

The heart murmur group consisted of 50 infants with the heart murmur characterized above. All of them were referred to our institution because of their heart murmur. The gestational ages at birth were 38±2.2 weeks, and their birth weights were an aver-
age of 2871±532 g. Their heart murmurs were first noticed at 6 to 60 days after birth (mean, 33±14).

The control group consisted of 50 infants without any heart murmurs who visited our institution for routine developmental evaluation. Their gestational ages at birth (38±1.5 weeks) and birth weights (3102±507 g) were not significantly different from those of the heart murmur group.

All infants in both groups were healthy and had normal clinical courses during the study period. Two pediatric cardiologists studied auscultation in all infants. Chest X-ray, electrocardiography, phonocardiography, and echocardiography were performed in order to exclude cases of cardiac anomaly.

Echocardiography

Two-dimensional and Doppler echocardiography were performed using Aloka SSD-730 or SSD-870 (Aloka, Tokyo) with a 5.0 MHz transducer. The diameter of the main pulmonary artery (MPA) was measured at the middle of the pulmonic valve and the bifurcation of the branch pulmonary arteries. The diameters of the right pulmonary artery (RPA) and the left pulmonary artery (LPA) were measured at the proximal end using the standard parasternal short-axis view. For measurement of the blood flow velocity at the MPA, a sample volume of the pulsed Doppler echocardiography was placed at the MPA where the maximal velocity was recorded. For measurement of the flow velocity at the RPA and LPA, a sample volume of the pulsed Doppler echocardiography was placed at the proximal right and left pulmonary arteries, respectively. The pressure gradients from MPA to RPA and LPA were calculated using a modified Bernoulli formula. The presence of shunts through the ductus arteriosus and the foramen ovale were evaluated by color Doppler mapping.

Follow-up examinations

The infants in the heart murmur group were examined every 2 to 3 months at the cardiac clinic until their heart murmurs disappeared. The presence of a heart murmur was evaluated by means of auscultation and phonocardiogram. The same measurements were obtained by means of echocardiography at each follow-up visit.

Statistics

The differences between the heart murmur group and the control group in terms of each measurement were evaluated by an unpaired t test. For the follow-up study in the heart murmur group, the differences between both periods were evaluated by a paired t test. P values less than 0.05 indicated statistically significant differences between the groups.

RESULTS

Characteristics of the heart murmur and its outcome

All infants in the heart murmur group had the characteristic heart murmur, which was an early- to

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<tr>
<th>TABLE 1. Comparison of heart murmur (group A) and control (group B) with peripheral pulmonary artery</th>
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<tr>
<td>Heart murmur (group A)</td>
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<tr>
<td>n=50</td>
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<tr>
<td>at the time when heart murmur appeared</td>
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<tr>
<td>age (days)</td>
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<tr>
<td>MPA diameter (mm)</td>
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<td>RPA diameter (mm)</td>
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<td>RPA/MPA</td>
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<td>Vmax (m/sec)</td>
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mid-systolic ejection murmur at the second intercostal left sternal border with an intensity of Levine of 2-3/6. This murmur radiated widely over either side or both sides of the chest. The quality of the murmur was moderately pitched in most cases but soft and high-pitched in about 20% of the cases. The second heart sound was fixed split with a slightly increased pulmonary component in 32 cases (64%). Phonocardiograms revealed a crescendo-decrescendo (diamond-shaped) early- to mid-systolic murmur (Fig. 1).

It was observed at the follow-ups that the heart murmur disappeared at 33 to 190 days (mean, 118 days) after birth for 48 of 50 cases in the heart murmur group. The second heart sound had become a normal respiratory split in all cases. However, the heart murmur continued to be heard in the remaining two cases (4%). The intensity of the pulmonic component of the second heart sound increased in both cases. These cases were diagnosed as intrinsic congenital peripheral pulmonary artery stenosis (Fig. 2).

Echocardiographic findings

The echocardiographic measurements are shown in Table 1. In all studies, there was no shunt flow at the ductus arteriosus. Some of the cases had shunt flow through the interatrial septum. All of them were diagnosed as patent foramen ovale, since the width of the shunt flow was less than 3 mm.

At the time the heart murmur was heard, the diameters of both the RPA and the LPA in the heart murmur group were significantly smaller than those in the control group. In the meantime, the flow velocities in both the RPA and the LPA in the heart

Fig. 1. Serial evaluation of the phonocardiograms and pulse Doppler echocardiograms in a case of the transient heart murmur. A: Heart murmur was detected at 14 days after birth. Diameters of both branch pulmonary arteries were relatively small compared with that of the main pulmonary artery. The flow velocity at the right pulmonary artery was 2.45 m/sec. Phonocardiogram revealed a moderate- to high-pitched ejection systolic murmur at the second intercostal left sternal border. B: The heart murmur disappeared at 5 months of age. The diameters of both branch pulmonary arteries grew large, and the flow velocity at the right pulmonary artery decreased to 1.43 m/sec.

Fig. 2. Two of the 50 cases in the heart murmur group continued to have the heart murmur and were diagnosed as having intrinsic peripheral pulmonary artery stenosis. The flow velocity (Vmax) at the bifurcation of the pulmonary artery gradually increased during follow-up.
Fig. 3. Serial measurement of the ratio of the flow velocity (Vmax) at the right pulmonary artery to the main pulmonary artery (RPA/MPA) [left panel], and the left pulmonary artery to the main pulmonary artery (LPA/MPA) [right panel]. At the time when the heart murmur was detected, both the RPA/MPA Vmax ratio and LPA/MPA Vmax ratio in the transient murmur group were significantly greater than those in the control group (p=.0001). When the heart murmur disappeared, both the RPA/MPA Vmax ratio and LPA/MPA Vmax ratio in the transient murmur group decreased and were not significantly different from those in the control group.

The pressure gradient was 15.4 to 30.2 mmHg between the MPA and the RPA, and 15.8 to 36.2 mmHg between the MPA and the LPA (Fig. 3). The diameter and flow velocity at the MPA were not significantly different between the heart murmur and control groups.

According to the follow-up echocardiography at the time the heart murmur disappeared, the diameters of both the RPA and the LPA had significantly increased, and the flow velocities in both the RPA and the LPA had significantly decreased. Although the diameter of the MPA had significantly increased during the same period, the RPA/MPA and LPA/MPA diameter ratio had significantly increased, which represented the fact that the growth of the diameters of the RPA and LPA were greater than those of the MPA.

DISCUSSION

Transient heart murmur in the late neonatal period was first described by Kato in 1971 [2]. This murmur is noted during the late neonatal period and subsequently disappears after a few months. Kato had examined 3 infants with this murmur by means of intracardiac phonocardiography and cardiac catheterization. He found that this murmur originated at the bifurcation of the RPA and LPA and that there was a mild pressure gradient at these sites. Soon after, Dunkle and Rowe reported the same transient murmur described as “simulating pulmonary artery stenosis” in premature infants [3].

The serial echocardiographic evaluation in the present study clearly demonstrated the relation between this transient heart murmur and transient branch pulmonary arteries stenosis. Infants with this transient heart murmur had branch pulmonary arteries with significantly smaller diameters and with faster flow velocities than those without heart murmurs. Furthermore, after a few months, these smaller diameters and faster flow velocities of the branch pulmonary arteries came within a normal range when the heart murmur disappeared. These longitudinal morphological and physiological changes proved that this type of transient heart murmur is caused by transient branch pulmonary arteries stenosis.

The cause of this transient stenosis of the branch
pulmonary arteries can be explained by changes from the fetal to neonatal circulation. During the fetal period, most of the blood flow from the right ventricle passes through the ductus arteriosus [4]. Only about 20\% of the total cardiac output enters the lungs via the branch pulmonary arteries, and hence, the diameters of the branch pulmonary arteries are relatively small compared with that of the MPA. After birth, the ductus arteriosus closes within a few days. Then, all of the blood from the right ventricle suddenly starts to pass through these relatively narrow branch pulmonary arteries [5]. After a few weeks, the resistance of the pulmonary artery declines, and the pressure gradients from MPA to RPA or to LPA occur [6]. Danilowicz et al. [7] reported these physiologic pressure differences between the MPA and branch pulmonary arteries in infants. After that, diameters of the branch pulmonary arteries grow as we showed in the present study, and the pressure gradients may disappear in about a few months. These perinatal hemodynamical changes may cause transient stenosis of the branch pulmonary arteries [8,9].

Other hemodynamical changes in the neonatal period are thought to cause heart murmurs. In particular, the shunt flows through the ductus arteriosus and the foramen ovale dramatically change during the neonatal period. The closing of the ductus arteriosus is one of the causes of heart murmurs in the early neonatal period [1]. However, this ductal flow may not contribute to transient heart murmurs in the late neonatal period because we did not find the ductal shunt in any infants in the heart murmur group when the murmur appeared. Although a left-to-right shunt through the foramen ovale was detected in some cases, it is unlikely that this shunt contributes to the transient heart murmur. The amount of blood flow must be trivial since the width is less than 3 mm and may not increase the flow at the pulmonary artery.

In a clinical setting, diagnosis of a transient heart murmur needs particular attention in order to make a differential diagnosis from congenital heart disease, such as mild pulmonary stenosis, atrial septal defect, or organic pulmonary artery stenosis. In particular, the findings of this heart murmur are quite similar to those of intrinsic peripheral pulmonary arteries stenosis. In fact, 2 of our 50 cases with this type of heart murmur actually had an intrinsic abnormality. Hence, it is very important to follow the neonate with this heart murmur until the heart murmur disappears in order to exclude the possibility of an intrinsic abnormality.

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REFERENCES