CLINICAL RESEARCH

Early neonatal death and congenital left coronary abnormalities: Ostial atresia, stenosis and anomalous aortic origin

Décès néonatal précoce par anomalies congénitales de la coronaire gauche : atrésie ostiale, sténose et naissance anormale de l’aorte ascendante

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KEYWORDS
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Summary
Background. — Congenital left coronary artery abnormalities such as ostial stenosis or atresia are extremely rare. Diagnosis in the neonate has not been reported.
Aims. — To describe five neonates with left coronary artery orifice abnormalities and discuss pathophysiology, diagnosis and treatment options, with a focus on the importance of autopsy in unexpected neonatal death.

Abbreviations: ALCAPA, anomalous left coronary artery from pulmonary artery; CABG, coronary artery bypass graft; CT, computed tomography; LCA, left coronary artery; RCA, right coronary artery.
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Neonatal coronary abnormality


Results. — Three neonates with anatomical (n = 2) and functional (n = 1) left coronary stenosis and two neonates with ostial atresia were identified. The three infants with coronary stenosis died within minutes to days after birth because of cardiac failure refractory to intensive care treatment; at autopsy, left coronary ostial stenosis (n = 2) and high take-off with acute angle origin and tangential vertical course (n = 1) were diagnosed. The fourth neonate was in cardiac failure due to critical aortic stenosis; left coronary ostial atresia was diagnosed during an emergency catheterization procedure and the infant died after aortic valve dilatation. The fifth infant had a cardiac arrest on the third day of life; she was diagnosed with left coronary ostial atresia by coronary angiography and died during attempted revascularization surgery at 2 weeks of life.

Conclusion. — Congenital coronary ostial abnormalities can lead to severe heart failure and unexpected neonatal death. Systematic examination of the coronary arteries should be part of any neonatal autopsy. Coronary angiography remains the diagnostic method of choice despite advances in non-invasive imaging. Revascularization surgery seems indicated in symptomatic children based on small patient series.

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Background

Congenital abnormalities of the left coronary orifice such as ostial stenosis or atresia are rare cardiac defects, with the exception of those seen in common arterial trunk [1]. Only a few autopsy or case reports and small surgical series of adult and paediatric cases have been reported in the literature [2—5]. The clinical picture is heterogeneous and depends on age at onset of clinical symptoms. In the infant or small child, cardiac failure due to severe biventricular dysfunction can be the clinical presentation in case of left coronary artery (LCA) atresia or severe ostial stenosis, the latter being extremely rare. Coronary ostial atresia can thus mimic the clinical picture usually seen in case of anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA), which is far more frequent in this age group [2]. In the older child, adolescent or adult, clinical symptoms are those of chest pain during exercise or at rest, suggestive of coronary abnormality.

Proximal tangential coronary course is recognized as a rather rare congenital coronary abnormality but there are few reports on functional impact, even though secondary myocardial ischaemia as a consequence seems possible. Acute coronary angle take-off has been associated with sudden death in adults [6].

To our knowledge, neonatal diagnosis of LCA ostial stenosis or atresia has not been previously reported. Here, we describe five neonates with anomalies of the LCA orifice (atresia/stenosis/acute angle take-off with tangential proximal course) whose common particularities are the early
onset of symptoms and fatal outcome. This report underlines the importance of a well-conducted neonatal autopsy to elucidate unexpected neonatal death.

Methods

We searched our institutional database for neonates with the diagnosis of congenital LCA abnormalities (ostial atresia/stenosis, abnormal course, ectopic ostium) seen at our centre from January 2000 to October 2012. All medical files, including autopsy protocols and available pictures, were reviewed.

Results

Five neonatal cases of congenital abnormalities of the LCA orifice were finally identified in our institutional database. Two patients had isolated severe LCA ostial stenosis and one patient had a high take-off with acute angle of origin and proximal tangential LCA course. All three anomalies were diagnosed at autopsy. The other two neonates had atresia of the LCA orifice, both diagnosed by coronary angiography; in one case it was an isolated abnormality and in the other it was associated with severe neonatal aortic stenosis.

Case 1

The first neonate was born at 35 weeks’ gestation with a birth weight of 2230 g and an Apgar score of 10-8-5; he became quickly hypoxic with respiratory distress requiring mechanical ventilation and transfer to a neonatal intensive care unit. Emergency echocardiography showed signs of persistent pulmonary hypertension with normal cardiac anatomy (including normal pulmonary veins) but with associated severe biventricular dysfunction. The neonate died after a few hours in refractory hypoxia with multiorgan failure, despite all the intensive care treatment strategies that were undertaken. Autopsy showed an anatomically normal heart except for a pinpoint LCA orifice (Fig. 1A and B). The right coronary artery (RCA) was completely normal. No other congenital extracardiac malformations were visible. There was no macroscopic congestion of liver, kidney or bowels. Ischaemic alterations of the grey matter were seen in both hemispheres. Histological analysis of samples from different sites in the left ventricle did not reveal any myocardial necrosis or ischaemia. The pulmonary parenchyma showed moderate quantities of hyaline membranes in the alveoli without significant obstruction of the airways.

Case 2

This neonate was prematurely born at 33 weeks’ gestation with a birth weight of 1700 g after an uneventful pregnancy without obstetrical complications. Neonatal adaptation was characterized by immediate bradycardia. Usual neonatal resuscitation manoeuvres were unsuccessful and the baby died 30 min after delivery. Autopsy was performed and the heart was anatomically normal except for a slit-like LCA orifice (Fig. 2). The right coronary artery (RCA) was normal in origin and branching pattern. Histopathological analysis of samples systematically taken from different sites in both ventricles did not reveal signs of myocardial necrosis or ischaemia. There were no associated extracardiac congenital malformations.

Case 3

This neonate (twin pregnancy) was delivered by Caesarean section due to maternal metrorrhagia at 31 weeks’ gestation with a birth weight of 1500 g; on the third day of life she brutally deteriorated with a clinical low cardiac output syndrome. Emergency echocardiography showed two

Figure 1. Case 1: macroscopic view of the opened aortic root. Aortic root opened from the left ventricle and exposure of the sinuses with their respective cusps. The black arrow in (A) and the blue probe in (B) indicate the localization of the pinpoint orifice and thus ostial stenosis of the left coronary artery situated in the middle of the left coronary sinus. The normally sized right coronary artery ostium can be seen in normal position in the right coronary sinus.
Case 2

This neonate was born at full term with a birth weight of 3370 g and a normal neonatal adaption; she was referred to our department after a cardiac arrest at the third day of life because of persistent biventricular dysfunction and dilated cardiomyopathy. Echocardiographic assessment showed a retrograde flow in the LCA. A computed tomography (CT) scan revealed suspected LCA ostial atresia (Fig. 4A and B), which was confirmed by coronary angiography. The infant was referred for surgical revascularization. During surgery, the angiographical diagnosis was confirmed by the surgeon. At the end of coronary artery bypass graft (CABG) surgery with an internal mammary arterial graft the infant became haemodynamically unstable, was started on circulatory support and eventually died on the operating table.

Case 4

This neonate was born at full term with a birth weight of 3310 g and a good neonatal adaptation. Some days later she presented with acute cardiac failure and was diagnosed with critical aortic stenosis with consequent biventricular dysfunction and systemic patent arterial duct. An emergency catheter procedure was performed to dilate the stenosis. Coronarography during the procedure demonstrated unexpected LCA orifice atresia (Fig. 5A and B). Despite the successful aortic valve dilatation and intensive medical treatment, the infant died a few hours after the catheter procedure in refractory cardiac failure.

Discussion

LCA ostial atresia or stenosis are rare congenital coronary artery abnormalities included in the subgroup ‘coronary
Figure 4. Case 4: computed tomography images of a neonate with left coronary artery (LCA) atresia. The right coronary artery (RCA) can clearly be seen connecting to the aortic root (Ao) without any stenosis. The proximal part of the LCA is visible but does not connect to the aortic root (white arrow), suggesting severe ostial stenosis or atresia. PA: pulmonary artery; LV: left ventricle; RV: right ventricle.

Figure 5. Case 5: left coronary artery (LCA) atresia demonstrated by coronarography in an infant with aortic stenosis. A. During the aortic dilatation procedure, non-selective injection of contrast agent in the aortic root is performed and shows the right coronary artery (RCA) without stenosis, while the LCA cannot be visualized. Aortic valve appears to be bicuspid (profile image). B. Selective injection of the RCA shows anterograde flow in this coronary artery while the LCA is only palely visible, being perfused in a retrograde fashion via collaterals (profile image). The white arrow indicates the void space in which the proximal segment of the LCA should normally be visualized by angiography.

artery anomaly, other’ according to the Diagnostic Short List of the International Paediatric and Congenital Cardiac Code [7]. High take-off and tangential course of the LCA is in the subgroup ‘coronary artery anomaly, anomalous aortic origin’ [7].

Concerning LCA ostial atresia, approximately 50 cases have been described in the medical literature so far, 50% of which were paediatric cases. LCA ostial atresia can be associated with other cardiac defects, such as supravalvular aortic stenosis, bicuspid aortic valve, pulmonary stenosis, tetralogy of Fallot, mitral prolapse and ventricular septal defect [4,8], as in the last patient of our series who had critical valvular aortic stenosis.

Coronary ostial stenosis such as that encountered in the first two patients of this series has been described in transposition of the great arteries but mainly in common arterial trunk, especially concerning the LCA orifice with slit-like or pinpoint variants [1,9]. In the latter, these abnormalities can be responsible for biventricular dysfunction [9] and even cardiac death before initial repair. Isolated variants of ostial abnormalities without associated congenital heart disease exist and have been reported occasionally in autopsy series [3]. Congenital bilateral ostial stenosis has also been described [10].

Ectopic ostial origin with high take-off and tangential proximal coronary course as described here in the third neonate has been reported in adults and is associated with possible myocardial ischaemia and increased risk of fixed coronary atherosclerotic disease [11]. One case has been reported in a 15-month-old boy with severe biventricular dysfunction and sudden death [12].

ALCAPA, LCA atresia/stenosis and other abnormal connections of the main right and left coronary arteries to the aorta potentially share the same embryological mechanism. Indeed, it can be hypothesized from the findings of Theveniau-Ruissy et al. in mouse embryos [13] that the
position of the coronary orifices is determined by the spatial position of a 'subpulmonary coronary-refractory myocardial domain'. This domain would be repulsive for the developing epicardial coronary arteries, which would have to circle around this repulsive domain to reach their respective aortic sinus, if they ever do so. Abnormal position or size of this subpulmonary coronary-refractory domain (and its mirror domain 'subaortic coronary-permissive domain') could explain these different anomalies. The molecular and cellular bases of coronary artery connection to the appropriate aortic sinus, one of the later cardiac developmental events, are scarcely known.

Atresia and stenosis of the LCA orifice both cause ischaemic heart disease in small infants. Their diagnosis is challenging as the first cardiac defect suspected in this setting will usually be the more frequently encountered ALCAPA, which is responsible for the same clinical picture and severe myocardial dysfunction [14]. Both LCA ostial atresia/stenosis and ALCAPA may present at different ages. The youngest reported patient with LCA atresia in the literature became symptomatic at 12 days of life but was diagnosed by coronary angiogram only 2 months later [15].

The presence of important collateral flow from RCA to LCA explains why clinical presentations are known into adulthood, with the oldest recently reported patient being an 85-year-old woman with angina pectoris [16]. Variation in age at presentation is also common in ALCAPA [14]. The usual age for ALCAPA diagnosis is infancy, probably because the coronary steel phenomenon is temporally related to the evolution of pulmonary vascular resistances. In our series, the early and dramatic onset of symptoms is probably due to a frail and insufficiently developed network of coronary collaterals. Why these collaterals do not develop in this defect is unknown. The distal coronary bed might also be hypoplastic due to low anterograde flow, depending on when in development the coronary ostium becomes stenotic or atretic. In both neonatal cases of LCA ostial stenosis, the abnormality identified at autopsy represents an anatomical substrate for critical reduction in coronary flow when loading conditions and oxygen demand on the left ventricle change drastically after birth. In the third case the ectopic ostium and the tangential vertical course with an acute angle might represent the causal anatomical substrate for a functional coronary stenosis. Acute angle take-off has been associated with sudden death in adults in autopsy series [2] and in a young child [12].

It has also been hypothesized that some coronary anomalies only manifest under extreme conditions, such as important exertion, eventually causing autocrine and endothelial dysfunction and possibly a coronary spasm [11,17]. Why this coronary anomaly was apparently fatal in this premature neonate remains unclear, even if immaturity of the child (gestational age 31 weeks) might play a crucial role. In all three neonates, histopathological signs of chronic ischaemic damage could not be identified, supporting the concept of an acute event related to perinatal dramatic changes in haemodynamics.

It is of note that only LCA atresia was diagnosed in living neonates, while the diagnosis was established at autopsy in the other three cases. This underlines, in our opinion, the extreme importance of a thoroughly conducted neonatal autopsy in case of neonatal or perinatal death. This implies a good knowledge of neonatal and perinatal disorders, including congenital cardiac disease, and a systematic inspection of the whole heart, including the coronary orifices, after opening the aortic root. The identification of the coronary abnormality allowed post-mortem parental counselling, helping to relieve parental tension and anxiousness due to the perinatal child loss.

For the two cases of LCA orifice atresia, the diagnosis was established by coronary angiography and subsequently confirmed during surgery in one case. Cardiac CT imaging to identify coronary artery disease and malformation has been extensively used in adults and in children [18,19]. It still has limitations in neonates even if the electrocardiogram gating technique considerably improves reliability of detection of neonatal coronary abnormalities [20]. Coronary angiography remains the first-choice diagnostic method, even if LCA atresia was suspected with CT in one of our patients.

The outcome was fatal in all reported cases in this small series. Successful revascularization surgery has been reported in paediatric and adult patients with congenital coronary ostial atresia and stenosis. Systematic surgical revascularization is usually proposed, as late cardiac deaths have been reported years after the diagnosis [21]. Internal mammary arterial or saphenous venous grafts for CABG as well as surgical angioplasty by pericardial or polytetrafluoroethylene patch are different surgical approaches that have been reported [4,5,22]. Very recently, Kaczkowski et al. described successful homograft patch ostioplasty in three patients with LCA atresia [23]. In our series, the CABG attempt in the fourth neonate was unsuccessful. Technically, both patch ostioplasty and CABG appear extremely difficult, as the typical form of LCA orifice atresia is characterized by a hypoplastic left main coronary artery. In cases of isolated LCA atresia or stenosis with a normal-sized main stem, ostial angioplasty is probably the most interesting surgical option. Long-term follow-up is lacking in both techniques as no larger series are available, especially in the paediatric subgroup. However, some studies have shown encouraging midterm results for revascularization in children with different coronary pathologies, including LCA ostial atresia [23,24]. As a last resort, prolonged circulatory support and eventually neonatal heart transplantation could be considered as treatment options in critically ill infants after unsuccessful revascularization or in cases of dramatic clinical course. Because donors are extremely scarce in this very young age group, this remains more of a hypothetical approach than a realistic treatment option for this rare disease.

**Conclusion**

Congenital abnormalities of the LCA orifice, such as atresia/stenosis and acute angle take-off with tangential course, are rare congenital heart diseases. Neonatal diagnosis has not been reported, probably because immediate neonatal distress with severe biventricular dysfunction is commonly due to perinatal asphyxia and post-mortem examination is not systematically performed. Autopsy should be considered as a major diagnostic tool in case of unexpected neonatal death. Careful examination of the heart and particularly of the coronary orifices and course should be performed. Neonatal biventricular dysfunction of unknown origin should
also lead to a thorough examination of the coronary arteries by echocardiography and, in case of doubt regarding their origin, coronary angiography should be proposed. Techniques for surgical revascularization still carry a high risk but should systematically be proposed in case of heart failure. Neonatal heart transplantation is technically possible but donors are rarely available in this very young population.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


