Multifactorial pulmonary hypertension in infantile scimitar syndrome

Hypertension pulmonaire d’origine multifactorielle dans la forme infantile du syndrome du cimetiére

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KEYWORDS
Scimitar syndrome; Pulmonary hypertension; Congenital heart disease; Multifactorial; Pulmonary vascular disease

Summary
Background. — Pulmonary hypertension in infantile scimitar syndrome is highly prevalent at diagnosis, and has a multifactorial origin.
Aims. — To analyse the constellation of anatomical anomalies and initial physiology, and their contribution to pulmonary hypertension and outcome in infantile scimitar syndrome.
Methods. — Pulmonary hypertension causes were classified into five categories: associated with systemic supply to the right lung; associated with left-to-right shunt; postcapillary; related to respiratory or developmental lung disease; and “idiopathic-like” pulmonary arterial hypertension. Co-morbidities contributing to pulmonary hypertension were also classified according to the World Symposium on Pulmonary Hypertension (WSPH) and Panama classifications.

Abbreviations: CHD, Congenital Heart Defect/Disease; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; WSPH, World Symposium on Pulmonary Hypertension.
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**Results.**— Of 111 patients, 64 had pulmonary hypertension; 24 patients had one cause of pulmonary hypertension, 23 had two potential causes and 17 had at least three potential causes. Co-morbidities contributing to pulmonary hypertension described the multifactorial origin in > 80% of patients, with associated congenital heart disease being the main contributor. Mortality was 41% in patients with and 7% in patients without pulmonary hypertension. The proportions of deaths among patients with one, two or more than two causes of pulmonary hypertension were similar. Eight of 38 survivors had persisting pulmonary hypertension at last follow-up. The risk of death was associated pulmonary hypertension at diagnosis ($P = 0.002$) and the presence of an associated congenital heart disease requiring surgical repair ($P = 0.039$).

**Conclusions.**— Scimitar syndrome is an archetypal example of multifactorial causes of pulmonary hypertension, with associated congenital heart disease and pulmonary vascular anomalies being the main contributors. Infants with scimitar syndrome require accurate phenotyping to guide management and predict outcome.

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**Résumé** L’hypertension pulmonaire est très fréquente au diagnostic dans la forme infantile du syndrome du ciméterre et d’origine multifactorielle.

**Objectif.**— Analyser les diverses anomalies anatomiques et la physiologie cardiopulmonaire initiale des nourrissons ayant un syndrome du ciméterre afin de déterminer leurs rôles dans l’hypertension pulmonaire initiale et son évolution.

**Méthodes.**— Cinq causes d’hypertension pulmonaire ont été définies : associées à une perfusion systémique du poumon droit, associée à un shunt gauche-droite cardiaque, d’origine post-capillaire, associée à un pathologie respiratoire ou du développement du poumon, et « pseudo-idioptathique ». Les comorbidités contribuant au développement d’une hypertension pulmonaire ont été classées selon les classifications internationales, WSPH et Panama.

**Résultats.**— 64/111 patients avaient de l’hypertension pulmonaire. Une seule cause d’hypertension pulmonaire était retrouvée chez 24 patients, deux causes chez 23 patients, et au moins 3 causes chez 17 patients. La présence de co-morbidités contribuant au développement d’une hypertension pulmonaire d’origine multifactorielle étaient notées chez plus de 80 % des patients, la plus fréquente étant la présence d’une cardiopathie congénitale associée. La mortalité a été de 41 % chez les patients ayant une hypertension pulmonaire comparée à 7 % chez les patients sans hypertension pulmonaire. La présence d’une ou plusieurs causes conjointes d’hypertension pulmonaire n’avait pas de rôle sur la mortalité. 8/38 survivants conservaient une hypertension pulmonaire au dernier suivi. Les facteurs de risque de mortalité étaient le jeune âge au diagnostic ($p < 0,0001$), la présence d’une hypertension pulmonaire au diagnostic ($p < 0,0001$), et celle d’une malformation cardiaque requérant une intervention chirurgicale ($p = 0,003$). 

**Conclusion.**— Le syndrome du ciméterre est l’archétype de l’hypertension pulmonaire d’origine multifactorielle; les malformations cardiaques congénitales et les anomalies vasculaires pulmonaires congénitales associées étant les principaux contributeurs à cette hypertension pulmonaire. Une analyse anatomique et physiologique individualisée et précise est indispensable pour guider le traitement et établir un pronostic.

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**Background**

Scimitar syndrome is a rare association of congenital cardiopulmonary anomalies with anomalous drainage of one or more of the right pulmonary veins into the inferior caval vein. The constellation of anomalies that are commonly observed in scimitar syndrome are: hypoplastic right lung, frequently with a small right pulmonary artery; rightward position of the heart secondary to the small right lung; anomalous drainage of the right pulmonary veins into the inferior caval vein; and an anomalous systemic artery supplying a portion of the right lung [1–3]. The different forms of the syndrome have been recorded extensively, as has its place in the spectrum of bronchopulmonary foregut malformations [4].

The syndrome can present immediately after birth, with heart failure and severe pulmonary hypertension (PH) of various causes, or later in life, with a wide clinical spectrum.
[5]; it can also be fully asymptomatic, and can be diagnosed from the peculiar curvilinear image of the anomalous draining right pulmonary veins on the frontal chest radiograph [6]. Dupuis et al. also described a form associated with congenital heart defects (CHDs), which are indeed present in a fifth to a third of patients [7].

Recently, the European Congenital Heart Surgeons Association (ECHSA) reviewed a series of patients with scimitar syndrome who underwent surgery [8, 9], and observed that the overall mortality in this surgical series was relatively low, and that late morbidity was limited to residual scimitar drainage stenosis. As with others, they confirmed that the infantile form of scimitar syndrome confers a higher risk of mortality, related to associated PH and CHD. Dusenbery et al. showed that PH and left pulmonary vein stenosis are risk factors for death, whereas patients without significant PH or associated congenital heart disease (CHD) did well without scimitar vein surgery [10]. Critically ill infants with scimitar syndrome continue to be a therapeutic challenge, because there are potentially numerous issues contributing to the congestive heart failure and PH in this group. Conversely, there remains considerable discussion about the benefits, if any, of intervening in the minimally symptomatic or asymptomatic patient with normal pulmonary arterial pressures and a pulmonary-to-systemic blood flow ratio of less than 2:1.

PH is a major risk factor in scimitar syndrome. Here, we analysed the outcome predictors in children aged < 2 years with scimitar syndrome, and we also sought to identify the weight of the different contributors to PH in this condition.

Methods

A review of medical records and computerized hospital data was approved by our local Clinical Investigation Committee, and the procedures followed were in accordance with the institutional guidelines for retrospective record review and protection of patient confidentiality.

We reviewed the hospital charts of all patients aged < 2 years identified in our database as having scimitar syndrome between 1985 and 2017.

Variables analysed included prenatal history, demographic and clinical data, a detailed description of associated vascular and cardiac anomalies (from echocardiography, computed tomography scan, magnetic resonance imaging, angiographies or autopsies), right heart catheterization data (pulmonary-to-systemic blood flow ratio, pulmonary artery pressures, wedge pressure) and surgical and percutaneous procedures.

Right heart catheterization data were obtained at time of diagnosis for this study. In patients who had embolization of systemic arterial supply to the right lung, right heart catheterization could have been performed simultaneously or during a repeated procedure. Finally, patients could have undergone repeated right heart catheterization during follow-up, but only the first set of haemodynamic data was used in this study. The presence of PH was defined as a mean pulmonary pressure > 25 mmHg at right heart catheterization. Pulmonary wedge pressure was considered elevated when > 15 mmHg in either pulmonary vein. Pulmonary-to-systemic blood flow ratio was calculated with the Fick principle, with assumed oxygen consumption. As PH in this condition can have various origins, the haemodynamic data were reviewed by two investigators (D.B. and M.L.), and PH types were classified in the following categories: PH associated with systemic supply to the right lung; PH associated with left-to-right shunt; postcapillary PH; PH related to respiratory or developmental lung disease; and, finally, “idiopathic-like” pulmonary arterial hypertension, when none of the previously listed causes could be found. A given patient could be described as having different causes of PH at the time of diagnosis. To identify the co-morbidities that could contribute to PH, the potential causes of PH were also classified according to the World Symposium on Pulmonary Hypertension (WSPH) and Panama classifications [11, 12].

Outcomes included mortality, cardiac status and PH status at last follow-up.

Statistical analysis

Continuous variables are presented as means ± standard deviations if normally distributed, and as medians with 95% confidence intervals if not. Categorical variables are presented as percentages. Comparisons of categorical variables were made using the χ² test or Fisher’s exact test, as appropriate. Times to death are shown in Kaplan-Meier curves. For all analyses, a two-tailed P-value < 0.05 was used as the criterion for statistical significance.

Results

Population

One hundred and eleven patients (68 female, 43 male) were diagnosed with scimitar syndrome. Fifteen patients had a prenatal diagnosis of a CHD, including left-right asymmetry (n = 7), anomalous drainage of pulmonary vein (n = 4), tetralogy of Fallot (n = 1), hypoplastic left heart (n = 1), hypoplasia of the right lung with sequestration (n = 1) and persisting left superior caval vein (n = 1). The diagnosis of scimitar syndrome was prenatally suspected in six of these 15 fetuses. All of these fetuses were delivered alive, and in all cases the diagnosis of scimitar syndrome was made during the first week after birth. For the remaining patients, the diagnosis of scimitar syndrome was made during the neonatal period in 38 patients, before 6 months in 32 patients and between 6 months and 2 years in 26 patients, representing 34%, 29% and 23% of the whole cohort, respectively.

Anatomy of the scimitar syndrome and associated defects

The anomalous pulmonary venous drainage of the right lung was total in 99 patients and partial (one or two right pulmonary veins) in 12 patients. Sixty-four patients had an associated CHD requiring surgical repair (58%), and 34 (31%) had one or more extracardiac malformations. The scimitar vein was stenotic in 13 patients at diagnosis, and the connection to the systemic veins was abnormal in six patients for at least one right pulmonary vein. The systemic venous return was abnormal in 19 patients. Seventy-three patients (66%) had systemic supply to the hypoplastic right lung. The right
pulmonary artery was smaller than the left in 104 patients (absent or occluded in seven), and was normally sized in seven patients.

**PH at diagnosis**

Seventeen patients had normal pulmonary artery pressure on echocardiography (median age at diagnosis 6.2 months). Four of 17 had an associated CHD, and 5 of 17 had systemic supply to the right lung that was closed percutaneously in one and neglected in four. All were asymptomatic except for a patient with tetralogy of Fallot.

Ninety-four patients had right and left heart catheterization. Thirty had normal pulmonary pressure (median age at heart catheterization 6.5 months). Of those, seven of 30 had a CHD, and 21 of 30 had systemic supply to the right lung that was closed in 13 of them.

Sixty-four patients had PH at heart catheterization; 50 of the 64 had CHD, and 47 of the 64 had systemic supply to the right lung that was closed in 39 of them.

**Table 1** shows the different types of PH at diagnosis. In addition to the different types of PH, 20 neonates were considered to have associated persistent PH of the newborn (PPHN).

Using the Panama and WSPH clinical classifications for PH, we attempted to identify the different contributors or co-morbidities causing PH in our whole cohort of patients and in patients with PH [11, 12]. Scimitar syndrome is itself part of both classifications, and is considered either as a single cause in the Panama classification or as part of the fifth group of the WSPH classification, included in complex CHDs. Results are shown in **Tables 2 and 3, Figs. 1 and 2**.
Table 2  Contributors to pulmonary hypertension adapted from the Panama classification [11].

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of patients</th>
<th>% of whole cohort (n=111)</th>
<th>% of those with PH (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prenatal or developmental PHVD</td>
<td>45</td>
<td>41</td>
<td>70</td>
</tr>
<tr>
<td>1.2. Associated with fetal pulmonary vascular maldevelopment</td>
<td>45</td>
<td>41</td>
<td>70</td>
</tr>
<tr>
<td>1.2.1. Associated with fetal pulmonary hypoplasia</td>
<td>22</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>1.2.1.c. Congenital diaphragmatic hernia</td>
<td>10</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>1.2.2. Associated with fetal lung growth arrest/maldevelopment</td>
<td>23</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>1.2.2.e. Pulmonary artery abnormalities (absent/occluded right pulmonary artery)</td>
<td>6</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>2. Perinatal pulmonary vascular maladaptation (PPHN)</td>
<td>20</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>2.1. Idiopathic PPHN (with no trigger other than scimitar syndrome)</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>2.1. Idiopathic PPHN (with no trigger other than scimitar syndrome and systemic supply to the right lung)</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2.2. PPHN associated with or triggered by:</td>
<td>13</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>2.2.3. CHD</td>
<td>7</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>2.2.4. Congenital diaphragmatic hernia</td>
<td>6</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>3. Paediatric heart disease</td>
<td>55</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>3.1. Systemic to pulmonary shunts</td>
<td>38</td>
<td>34</td>
<td>59</td>
</tr>
<tr>
<td>3.4. Paediatric PHVD associated with congenital abnormalities of the pulmonary arteries/veins</td>
<td>20</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>3.5. Pulmonary venous hypertension caused by congenital left heart inflow or outflow disease</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>6. Multifactorial PHVD associated with multiple congenital malformations/syndromes</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>6.1. Syndromes with CHD</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>7. Paediatric lung disease</td>
<td>14</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>7.4. Chest wall and spinal deformities</td>
<td>9</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>7.5. Restrictive lung diseases</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>10. PHVD associated with other system disorders</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10.1. Paediatric portal hypertension</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10.1.1. Congenital extrahepatic portocaval/portosystemic shunt</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

CHD: congenital heart disease; PH: pulmonary hypertension; PHVD: pulmonary hypertensive vascular disease; PPHN: persistent pulmonary hypertension of the neonate.

Outcome

Eighty-two of 111 patients were alive after a median follow-up of 15.7 years (range 2.4–32 years) (Fig. 3). Forty-four of 47 patients (93%) with normal pulmonary pressure at diagnosis were alive at last follow-up, with normal pulmonary pressure on echocardiography. The three deaths occurred in patients with tetralogy of Fallot (two postoperative deaths [one Fallot with anomalous left coronary artery from the pulmonary artery and absent right pulmonary artery] and one from severe restrictive respiratory failure). Twenty-six of 64 patients with PH died at a median age of 4.1 months. The causes of deaths were related to PH in 19 of 26 patients: 13 of these 19 deaths occurred during the postoperative course after surgery for the associated CHD (four in the operating room [Fallot left coronary atresia in one; Fallot with pulmonary atresia in one; hypoplastic left heart syndrome in one; coarctation with anomalous left coronary artery from pulmonary artery in one] and nine had refractory PH in intensive care, associated with respiratory failure in six cases [right bronchus atresia in one; bilateral lung hypoplasia in one; severe arteriolitis at autopsy in four, with available lung pathology]); and six of the 19 deaths were associated with refractory PH (three associated with respiratory failure, one complicated with fatal haemoptysis, two compassionate care in neonates). The non-PH-related deaths were of extracardiac origin in five patients (pulmonary infection in two [horseshoe lung in one, right bronchus atresia in one], enterocolitis in one, stroke in one, rejection after heart transplantation in one) and postoperative in two patients who had normal pulmonary pressure at time of death.

The proportions of deaths in patients with one, two or more than two causes of PH were 11 of 24 (46%), eight of 23 (35%) and seven of 17 (41%), respectively (difference not statistically significant).
Table 3  Contributors to pulmonary hypertension according to the World Symposium on Pulmonary Hypertension classification [12].

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of patients</th>
<th>% of whole cohort((n = 111))</th>
<th>% of those with PH((n = 64))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pulmonary arterial hypertension</td>
<td>60</td>
<td>54</td>
<td>94</td>
</tr>
<tr>
<td>1.1. <strong>&quot;Idiopathic-like&quot;</strong> pulmonary arterial hypertension</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1.4. Associated with:</td>
<td>55</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>1.4.4. CHD</td>
<td>54</td>
<td>49</td>
<td>84</td>
</tr>
<tr>
<td>1.7. PPHN</td>
<td>20</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>2. PH caused by left heart disease</td>
<td>17</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>2.4. Congenital/acquired left heart inflow/outflow tract obstruction</td>
<td>17</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>3. PH caused by lung diseases and/or hypoxia</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>3.5. Developmental lung diseases</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>5. PH with unclear and/or multifactorial mechanisms</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>5.4. Complex CHD—segmental PH</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

CHD: congenital heart disease; PH: pulmonary hypertension; PPHN: persistent pulmonary hypertension of the newborn.

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Figure 3. Flow-chart of the study population and outcomes. cath: catheterization; echo: echocardiography; PH: pulmonary hypertension.

At last follow-up, 30 of 38 survivors (79%) among patients with PH at diagnosis had normal pulmonary pressure on echocardiography and/or at right heart catheterization. For the majority of these patients, normalization of pulmonary pressure was obtained by the repair of the CHD and/or embolization of systemic supply. Only six patients received sildenafil during the postoperative course, which was stopped after a mean delay of 4.2 months. Eight patients are alive with PH: three with Eisenmenger syndrome; one with postoperative pulmonary arterial hypertension after ventricular septal defect closure; two with postcapillary PH (mild residual stenosis of the repaired scimitar vein in one and occlusion of the scimitar vein in the other); one with PH associated with congenital diaphragmatic hernia; and one with "idiopathic-like" pulmonary arterial hypertension. Five of eight patients receive targeted treatment for pulmonary arterial hypertension at last follow-up; all are in World Health Organization functional class I–II, except
Discussion

The infantile form of scimitar syndrome has a high risk of death, mainly associated with PH and the presence of an associated CHD. These characteristics clearly define a different disease from that in older children and adults [5,7]. The different causes of PH in scimitar syndrome have already been well described, and include the respective roles of left-to-right shunting from the anomalous pulmonary venous connection, systemic arterial supply to the lung, associated cardiovascular defects, restriction of the pulmonary vascular bed because of pulmonary hypoplasia, with subsequent volume overload of the contralateral lung, pulmonary venous obstruction and the high prevalence of PPHN in this condition [1,13]. The infantile form of scimitar syndrome is clearly a condition at risk of PH, but it is difficult to recognize a predominant pathophysiological mechanism or to describe typical histopathological findings or, as yet, to describe management strategies. In 2018, the WSPH Pediatric Task Force aimed to further capture specific paediatric features in the WSPH clinical classification, while preserving the main core of the classification [12,14]. Indeed, PH presenting in neonates is often associated with developmental vascular abnormalities, and is currently classified as PH associated with lung disease and/or hypoxia [15]. However, distinct childhood forms of PH are not completely comparable to adult WSPH group 3 PH, because the impact of PH on the immature and developing lung is recognized as a major factor influencing outcomes in children [16]. Along the same lines, the PH related to cardiac anomalies in scimitar syndrome is not unambiguous, with variable contributions of left-to-right shunting, elevated wedge pressure and segmental PH [17]. For this reason, scimitar syndrome has been added to the fifth group of the WSPH classification, which includes clinical conditions with unclear or multifactorial mechanisms for PH [12]. Accordingly, the Panama classification, which defines a much larger group of conditions responsible for PH, mentions scimitar syndrome in different subgroups [11].

Our results show that PH in scimitar syndrome is indeed multifactorial in the majority of cases, as two thirds of patients with PH had two or more causes of PH, and one fifth had more than two causes. However, when we tried to identify the different contributors to PH, we observed that the role of the underlying CHD was predominant; indeed, it was present in >80% of the patients with PH. One of the prominent and distinguishing features of PH in infants is injury to the developing fetal and neonatal lung circulation [18]. The group of developmental (vascular) lung disorders has been designated to identify these features as a special subcategory within the WSPH classification group 3 PH [14]. Our haemodynamic data in most patients with PH showed that the role of increased pulmonary flow was the most important. This is demonstrated by the reversibility of PH in most patients after suppression of a cardiac left-to-right shunt or of a significant systemic supply to the right lung [19]. Nevertheless, the underlying pulmonary vascular developmental lung disease is attested by the high prevalence of PPHN in this series. We voluntarily isolated this item, as this diagnosis was mainly made on neonatal clinical history, e.g. transitory right-to-left shunt in children with ventricular septal defect. Still, it demonstrates...
that there is a perinatal pulmonary vascular maladaptation. Another argument for pulmonary vascular maldevelopment is the small group of patients with “idiopathic-like” PH who had no shunt or postcapillary PH. Accordingly, two patients had CHD without left-to-right shunt (one coarctation, one tetralogy of Fallot), and kept high pulmonary vascular resistances from the neonatal period [20, 21]. Similarly, three patients were considered as having Eisenmenger physiology, but, in fact, had no clinical evidence for significant left-to-right shunting [22]. Lung development is impaired at an early stage during fetal life in scimitar syndrome. Haworth et al. have shown that pulmonary arterial muscularity of the intra-acinar arteries, which in the normal lung have a major role in pulmonary neonatal adaptation, was increased in all parts of both lungs [13]. It remains unclear, however, why the lung vasculature should fail to adapt normally in only some patients with scimitar syndrome. The genetic background of paediatric PH appears to differ from that of adult PH, and accompanying genetic disorders, syndromes and growth abnormalities are frequent in children with PH. Recently, two genes, TBX4 and SOX17, have been identified as contributing to CHDs and PH [23, 24]. A genetic susceptibility could then partly explain the variability of PH features in patients with scimitar syndrome. Whether these contributors should be regarded as causally related, disease modifiers or bystanders is an additional piece in the multifactorial nature of PH in this condition.

Study limitations

A retrospective aspect is always a limitation, as clinical practice has changed and the outcome has certainly improved for the sickest patients. In addition, the different causes of PH in each patient could have been influenced by the practice and experience of the two investigators involved in this task. We did not have an exact assessment of pulmonary function or morphology in all patients, but we reported that lung function was impaired, even in the long term, in a large proportion of patients with scimitar syndrome [25]. We cannot describe the histopathology of the lungs in deceased patients to attempt to characterize the remodeling of their pulmonary arteries and veins.

Conclusions

We have shown here that scimitar syndrome is an archetypal example of multifactorial causes of PH, even if the role of an associated CHD is predominant to determine the prevalence of PH in the condition. Neonates with scimitar syndrome require accurate phenotyping that is needed to guide management and to predict outcome.

Sources of funding

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Disclosure of interest

The authors declare that they have no competing interest.

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