Abnormal muscularization of intra acinar pulmonary arteries in two cases presenting as Sudden Infant Death (SIDS).

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ABSTRACT

Abnormal muscularization of acinar arteries is the hallmark of persistent pulmonary hypertension of newborn (PPHN), an uncommon disease with high rate of morbidity and mortality. PPHN presents with signs of respiratory distress immediately following birth. We herein report two cases presenting as a witnessed sudden unexpected death in the late neonatal period (SUDI), preceded by respiratory deterioration and in whom the presence of abnormal muscularization of the acinar pulmonary arteries was reminiscent of PPHN. The significance of this report is twofold; to increase the awareness amongst pediatricians and pathologists of this feature that can present in some cases of SUDI/Sudden Infant Death Syndrome (SIDS), and to highlight the importance of performing a thorough autopsy in order to identify the abnormality.

Keywords: acinar arteries, autopsy, persistent pulmonary hypertension of newborn, SIDS, sudden unexpected death in infancy.
Persistent pulmonary hypertension of newborn (PPHN) is a severe and well-established pulmonary disorder characterized by a failure of the pulmonary circulation to successfully adapt from fetal to extra-uterine life. It has an incidence rate of about 2 per 1000 live birth (1). Affected newborns are typically term or late preterm and commonly develop symptoms of respiratory distress and severe hypoxemia almost always immediately after birth (2-5).

Clinically, neonates with PPHN have elevated pulmonary artery pressure with evidence of right-to-left shunt and invariably require supplementary oxygenation and mechanical ventilation. Without proper diagnosis and prompt treatment, the mortality rate of PPHN is high and survivors of PPHN carry with them various long-term functional impairments (4).

The histological hallmark of PPHN is the muscularization of the small pulmonary arteries with abnormal extension of vascular smooth muscle into the small, normally non-muscularized intra-acinar arteries (4).

We herein report two cases of sudden unexpected death in infancy (SUDI) presenting in the late neonatal period in whom the presence of muscularization of intra-acinar arteries in the lung was reminiscent of the histological features of PPHN. Each case underwent a coronial autopsy examination at our institution as part of the overall investigation into the sudden unexpected death of an infant (SUDI) (6). Whist the first case had non-suspicious nature of death circumstances; the second one was initially related to an allegation of physical abuse.

**CASE REPORT**

**Case 1**

A 4 weeks-old female child presented to the Emergency Department of a district hospital with a two-week history of increasingly smaller volume of feeds associated with
episodic non-projectile vomiting. Two days prior, she became increasingly breathlessness with grunting. At the Emergency Department, she appeared unwell with shortness of breath and tachycardia with a heart rate of 170 beats per minute. On further inspection, she was noticed to have subcostal recession and intermittent grunting which, upon further enquiry, had been present for few days but not known by the parent to be abnormal. Her skin was mottled in appearance and the extremities were cold.

There were no signs of rashes, injuries or any marks found on her body. Her respiratory rate continued to increase with increased grunting until a subsequent cardiac arrest. She was pronounced dead following unsuccessful active resuscitation.

Her antenatal history was unremarkable. She was born through a Cesarean section at 38 weeks of gestation for maternal gestational diabetes. She was apparently well without any health or growth concerns. She has never been admitted to hospital since being discharged after birth.

A coronial post-mortem examination was requested by the local coroner as part of the overall investigation into SUDI. At autopsy, she appeared well-cared for with neither external dysmorphology nor suspicious injuries detected over the body. Her weight was 3880 grams (25th to 50th percentile). The rest of her developmental parameters were appropriate for the age. The internal examination revealed bilateral pleural effusion and ascites of 30 ml. There were few surface petechiae seen over of the thymus and pericardium. The heart appeared enlarged but with no structural abnormality. See Table 1. The ductus and the foramen ovale were closed. The lungs were congested and edematous. The presence of bilateral pleural effusions, ascites, enlarged heart with dilated right atrioventricular chambers was thought to be secondary to acute heart failure (the
ventricular wall thickness was not available in the post mortem report). The examination of
the rest of the internal organs was unremarkable.

Case 2

A healthy male neonate was born at term naturally after a normal pregnancy. He was
the first child in the family and had no health concerns since birth. On the 12th day of his
life, whilst on a journey back home from a pre-arranged hearing test, he appeared to be
struggling to breathe and off-color. His condition was progressively worsened and
required admission to a nearby hospital. He continued to deteriorate and subsequently
arrested and required active resuscitation. Despite efforts at resuscitation, he
succumbed to his illness on the same day of hospital admission. Initial examination
performed at the Emergency Department as part of overall sudden unexpected death
investigation revealed unexplained swelling at the back of head that raised the suspicion
of non-accidental injury causing or contributing to death. A forensic autopsy was
subsequently arranged, jointly performed by both pediatric and forensic pathologists.

At post-mortem examination, he appeared as a well-nourished and normally formed
neonate. His weight of 3655 gram (25-50th centile) and relevant external parameters
were appropriate for his age. There were generalized subcutaneous edema that was
more prominent over both eye lids and scrotum. There were no injuries detected over
the head, trunk and all four limbs. Full skeletal x-rays revealed normal bone remodeling
with no bony abnormalities or fractures of either remote or recent in nature.

Internally, the so-called suspicious head swelling appeared as a late-resolving cephalo-
hematoma in association with mild biparietal sub scalp edema, which was thought to be
further complicated by a perimortem coagulopathy. There were numerous petechiae on
the surface of the thymus, heart and lungs. The pericardium contained 22 ml of straw-
colored pericardial effusion. The heart was pale, enlarged and with a globous shape. It
was structurally normal but the cavities appeared dilated (the ventricular wall thickness
was not available in the post mortem report). The foramen ovale and the ductus
arteriosus were probe patent. The lungs were increased in weight and showed
congested parenchyma. See Table 1.

Histopathological findings and cause of death

In both cases, the histological examination of the lungs showed largely intact bronchial
and alveolar architecture except for marked congestion. The pulmonary vasculature was
abnormal at the level of intra-acinar arteries (Fig 1). These showed marked thickening of
the walls due to persistence of the smooth muscle, intimal proliferation and excess of
perivascular collagenous tissue (Fig 2) These changes were highlighted with elastic stain
and immunohistochemistry against alpha smooth muscle actin. A muscle coat was
present in the pre-capillary arterioles, within the alveolar unit, which under normal
development should not persist at this level. There were areas with prominent
lymphangiectasis with focal hemosiderosis in Case 1 and bilateral diffuse intra-alveolar
hemorrhage and dilated, congested veins in Case 2.

Bronchial arteries and bronchioles were patent and there was no evidence of
misalignment or alveolar capillary dysplasia, confirmed with CD34 immunostaining (not shown). There were no plexiform lesions or occlusion of the bronchial arteries. There was no evidence of an acute or chronic infection, veno-occlusive disease or infarction. Sections of the liver in Case 2 showed venous congestion with presence of extramedullary hematopoiesis, which was associated with presence of nucleated red cells precursors in the peripheral blood, in keeping with a degree of chronic hypoxia. Ancillary investigations performed in both cases which included metabolic, microbiology and toxicology analyses were unremarkable. In none of the cases a cause for secondary pulmonary hypertensive changes was identified. None of the cases had evidence of hypoxic ischemic encephalopathy, meconium or other aspiration.

DISCUSSION

In utero, the pulmonary blood flow is low due to a high pulmonary vascular resistance and the availability of shunts through the foramen ovale and the ductus arteriosus. This allows blood to bypass the pulmonary vascular bed. Following the first breath at birth, lung inflation and oxygenation lead to a dramatic fall in the pulmonary vascular resistance. In PPHN, such normal transition does not materialize so that pulmonary vascular resistance remains high. This results in diminished pulmonary blood flow and consequent hypoxemia (3, 4). PPHN is clinically suspected in neonates who present with symptoms and a signs of respiratory distress immediately after birth. It is a difficult and challenging condition to manage clinically and up until recently the mortality rate remains high (6,7). Although the clinical presentation in our cases did not match that of PPHN, the prominent medial thickness of the small arteries was so prominent in our cases and the fact that the witnessed death was preceded by prominent respiratory symptoms was puzzling.
An initial study from Naeye (8) described a group of SIDS babies that had 1.6 times as much muscle in their small pulmonary arteries as controls. According to the author (8), the excess of muscle was due to hypertrophy in two third of the cases, whilst it was attributed to hyperplasia of smooth-muscle fibres in the remaining cases. The author’s (8) hypothesized that this structural change is the result of chronic alveolar hypoxia. Williams et al (9) study on 15 consecutive SIDS and controls showed an extension of muscle in arteries not usually muscularized, as well as an increase in the percentage of medial wall thickness in some SIDS participants; therefore corroborating Naeye’s results (8). Krous et al (10) retrospectively compared the relative medial thickness in alveolar wall arteries, pre-acinar and intra-acinar arteries as well as the demographic, clinical and pathological features in 19 SIDS cases with 19 age-matched controls. All cases and controls in their study (10) were >28 days of age, whilst our cases were 12 and 28 days old. With reference to the intra-acinar arteries morphometry, Krous et al (10) showed that age was inversely correlated to the relative medial thickness for small intra-acinar arteries (p=.018) and that increasing relative medial thickness of pre-acinar and intra-acinar arteries correlated with increasing relative medial thickness of alveolar wall arteries, suggesting that increasing muscularization is seen in all categories of vessels with a stimulus sufficient to produce it in alveolar wall arteries.

Although SIDS and control groups in Krous et al study (10) did not differ for known clinical risk factors that would potentially expose them to hypoxia, the increased thickness of alveolar wall arteries had significantly more males and premature birth than the other groups. Interestingly, the heart’s weight in SIDS cases from Krous’ study (10) was normal, a significant difference with our 2 cases, where it was above the expected for the age (see Table 1).

In an earlier study, Krous et al (11) had found no difference of either increased relative medial thickness or peripheral extension of medial smooth muscle in the small pulmonary arteries (including intra-acinar arteries) between 87 SIDS cases and 17 controls.
In the post-natal period the pulmonary circulation exhibits a much lower vascular resistance than the systemic one, and responds to stimuli such as partial oxygen pressure and alterations in blood differently. Hypoxemia dilates the systemic circulation, whereas the opposite is observed in the pulmonary arteries (12). The maintenance of high vascular resistance in the fetus is related to the pulmonary vasculature, reduced oxygen tension, reduced endothelial production of vasodilators (such as nitric oxide, prostacyclin and endothelial growth factor) and increased production of vasoconstrictive prostaglandins (12).

The development of excessive musculature in the intra-acinar vascular wall caused by remodeling has a crucial role in vasoconstriction and the increase in vascular resistance. Muscularization of normally non-muscularized peripheral vessels is the result of the release of endothelial vasoconstrictors, growth factors, matrix proteins and adhesion molecules as a cellular response to hypoxia (10, 13).

Although our cases fell under the spectrum of Sudden Unexpected Death in Infancy (SUDI), there shared some unusual findings: both died in hospital after a short history of unexplained respiratory deterioration: case 1 had been increasingly breathlessness with grunting for two days, and then presenting with shortness of breath and tachycardia and subcostal recession before arrest; case 2 suddenly struggled to breathe and died shortly after admission. Hypoxia-induced smooth muscle proliferation in pulmonary arteries requires several days (10), so at first sight it seems unlikely that the short lived respiratory symptoms in our cases had any influence in the muscularization of the intra-acinar arteries. However, on further questioning to the parents of Case 1, they had noticed that she had developed subcostal recession and intermittent grunting for few days (but not known this to be abnormal). In addition, the liver in Case 2 showed extramedullary hematopoiesis and there were numerous nucleated red cells in the peripheral blood. This later feature is a known marker of hypoxia and hypoxic mode of death (14,15). In consequence, it can be hypothesized that both our cases had been exposed to a degree of chronic hypoxia.
The findings in our two cases are in keeping with those of Naeye (8) and Williams (9) and discrepant with the earlier paper from Krous et al (11) although not significantly with the more recent study from this group (10). The discrepancy could be related to substantial differences between Krous et al (10,11) study population and our 2 cases; mainly: SIDS cases and controls in their study were > 28 days old (our 2 cases where 12 days and 28 days old); the heart’s weigh in their cases was normal (whilst it was increased in our 2 cases), and their cases had no evidence of chronic hypoxia or respiratory deterioration before death (whilst it was a relevant feature in our cases).

The diagnosis of SUDI/Sudden Infant Death Syndrome (SIDS) is a diagnosis of exclusion. In our institution, these cases are thoroughly investigated, with review of the circumstances of death and analysis of all relevant laboratory investigations which included radiology, toxicology, microbiology, cytogenetics and metabolic analyses (6). The autopsy of the first case was jointly performed by both pediatric and forensic pathologists as there was an allegation of non-accidental injury.

In summary, we describe two cases presenting as sudden unexpected neonatal death /SIDS in which the abnormal pulmonary vasculature was akin to that of PPHN.

Both cases showed respiratory deterioration before the witnessed SUDI and presented muscularization of the small pulmonary arteries with abnormal extension of vascular smooth muscle into the small, normally non-muscularized intra-acinar arteries (4). A study from Ohara et al (16) suggested that in PPHN these pathological findings may represent a pulmonary vascular bed that has been remodeled by the development of the muscular layer in utero. Thus, these abnormalities could have been the result of a variety of prenatal insults, including increased sensitivity to intrauterine hypoxia or stress leading to chronic vasoconstriction and secondary remodeling of the pulmonary circulation (16).
Further investigations are required in order to through address a potential role of these vascular abnormalities in some cases of SUDI/SIDS.

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REFERENCES


Figure 1: Case 1: a. Muscularization of intra acinar artery (Trichrome x 60) and b: normal age-matched control E: endothelial proliferation (trichrome x 60) and c: Perls stain showing prominent hemosiderin-laden macrophages filling the alveolar spaces indicating previous lung hemorrhage (x20).

Figure 2: Duplication of elastic lamina (Elastic van Giesson x40)
Table 1: Symptoms, heart and lung weights in case 1 and case 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Symptoms</th>
<th>Heart weigh (expected)</th>
<th>Lungs weigh (expected)</th>
<th>Lung/body ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28 days</td>
<td>2 weeks less feeding, vomits. 2 days’ breathlessness, grunting. Shortness of breath, tachycardia</td>
<td>36.45 g (21 ± 5)</td>
<td>87.97 (64±27)</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>12 days</td>
<td>Suddenly struggling to breathe. Respiratory arrest after admission</td>
<td>36.31 g (23±7)</td>
<td>98.68 (64±21)</td>
<td>0.02</td>
</tr>
</tbody>
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