the CaO. Although a change in FiO will only have a small effect on the CaO, and hence oxygen delivery, an increase in the inspired fraction of oxygen from 0.21 to 1 will translate into an approximately 10% increase in CaO. Given that the CaO is a mathematical combination of the CO and CaO, this will lead to modest increases in total oxygen delivery. At a constant VO2, this will result in an increase in the PVO2 and therefore affect the AaD0. This theoretical view has been confirmed by Douglas et al. The effect of positive end-expiratory pressure (PEEP) on the increase in AaD0 as the FiO increased, has not been directly examined. When the effect of PEEP on the Qs/Qt was examined, conflicting results were reported. One study demonstrated that PEEP prevented the increase in Qs/Qt as the FiO was increased while another failed to confirm this observation. First impressions suggest that the stabilising effect of PEEP should overcome the tendency of alveoli to collapse. One can, however, speculate that the alveoli with the lower ventilation-perfusion ratios (lower alveolar volume) are the least compliant and will therefore only benefit at a later stage of PEEP application, compared with the more compliant alveoli which will absorb the early PEEP. If this speculation is correct, then the alveoli with low ventilation-perfusion ratios at risk of collapse during denitrogenation are the alveoli that will benefit the least from PEEP. Also, PEEP could impede cardiac output and have an effect via the decrease in PVO2.

Data from this study seem to indicate that the commonly used indices do not accurately reflect the Qs/Qt of the injured lung. Also, the FiO, had an effect on some of these indices. The so-called less invasive indices should therefore be applied with the necessary circumspection and comparison should, at least, be made at a similar FiO2.

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Congenital syphilis associated with persistent pulmonary hypertension of the neonate — a clinicopathological case study

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Although more common in underdeveloped and developing countries, congenital syphilis occurs among all social groups. The spectrum of the disease varies from stillbirths and asymptomatic infected liveborn infants to overt syphilis-associated multisystem involvement. Apart from the classic clinical manifestation, unfamiliar disorders have been reported to occur in association with congenital syphilis.

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These include neonatal intestinal obstruction with or without ileal perforation, non-syndromic paucity of intrahepatic bile ducts and necrotising funisitis. Recently, Spear et al. described the first (to our knowledge) case of persistent pulmonary hypertension of the neonate (PPHN) with respiratory failure, associated with congenital syphilis. We report a neonate who presented with congenital syphilis-associated PPHN and superimposed intra-uterine hypoxia, illustrating the varying spectrum of clinical circumstances in which congenital syphilis should be a diagnostic consideration.

Case history

The patient, a male infant weighing 2 520 g, was the product of a 38 weeks’ gestation in a 34-year-old gravida 9, para 8 woman. The mother did not attend antenatal clinics and presented on the day of delivery in active labour. On examination, abdominal palpation revealed a singleton breech presentation. The cervix was 3 cm dilated and the membranes were intact. External fetal heart rate monitoring showed a basal heart rate of 150/min with extremely poor beat-to-beat variability of less than 5/min. Repeated late decelerations occurred. A lower uterine segment caesarean section was performed, yielding an infant with Apgar scores of 2 and 6 at 1 and 5 minutes, respectively. No meconium was noted. The placenta appeared large and weighed 700 g. The infant was intubated and ventilated. The initial physical examination revealed a hydropic and pale-looking infant. His abdomen was distended because of ascites and hepatosplenomegaly. Widespread skin desquamation and a truncal petechial rash were evident. Decreased capillary filling time, weakly palpable pulses, hypotension (blood pressure 40/19 mmHg) and active bleeding via the endotracheal tube were observed. Neurological findings included a depressed level of consciousness and generalised intermittent tonic seizures.

The initial chest radiograph (Fig. 1) showed interstitial lung involvement, right upper lobe opacification and an increased cardiothoracic ratio (0.64). The initial arterial blood gas analysis on a FiO2 of 1.0 revealed the following: pH 7.17, partial arterial carbon dioxide pressure (PaCO2) 5.5 kPa, partial arterial oxygen pressure (PaO2) 7.0 kPa, bicarbonate 16 mmol/l, and an arterial-alveolar PO2 ratio (a/APO2) of 0.07. (The a/APO2 ratio reflects the degree of compromise in arterial oxygenation and the ratio in a healthy baby is > 0.75.) The full blood count revealed a white cell count of 35 x 10^9/l (neutrophils 18%, lymphocytes 66%, monocytes 6%, eosinophils 4%, band cells 2%, basophils 2%, metamyelocytes 2%); the haemoglobin concentration was 8.9 g/dl; the mean corpuscular volume (MCV) was 120 fl; and platelet count 43 x 10^9/l. The liver enzyme values were as follows: aspartate aminotransferase (AST) 287 U/l, alanine aminotransferase (ALT) 45 U/l, lactate dehydrogenase (LDH) 1 931 U/l and alkaline phosphatase 372 U/l. The C-reactive protein level was 31 mg/l.

The clinical course was complicated by severe PPHN and status epilepticus. The PPHN was confirmed by two-dimensional echocardiography which showed right-to-left shunting across the ductus arteriosus, tricuspid insufficiency and an estimated pulmonary artery systolic pressure of 48 mmHg. The pulmonary arterial hypertension initially responded to hyperventilation-induced alkalosis. No tolazoline or exogenous surfactant was administered. Further treatment included penicillin, dopamine, intravascular volume expansion and a continuous bicarbonate infusion. The ventilatory course of the patient is depicted in Fig. 2. The ventilation index (VI1), the product of ventilator respiratory rate and peak inspiratory pressure partly reflects severe respiratory compromise (VI1 > 1 000) and our approach to ventilation in some patients with PPHN, i.e. hyperventilation (higher VI1) to induce an alkalosis in an attempt to reduce pulmonary vascular resistance with subsequent improvement in oxygenation (higher a/APO2 ratios). In Fig. 2, the effect of this approach on oxygenation is most evident at 18 hours of age. Despite attempts to stabilise the infant, the infant’s general condition continued to worsen. Pneumonia and necrotising funisitis were recently diagnosed. The patient was intermittently ventilated and no other effective therapy was available. On day 14, the patient died of respiratory failure with a PO2 of 12 kPa at an a/APO2 of 0.24.

Fig. 1. Admission chest radiograph showing a bilateral streaky infiltrative pattern with opacification of the right upper lung lobe with associated air bronchogram. The cardiothoracic index is increased.

Fig. 2. The ventilatory course of the infant during hyperventilation (VI1 = maximum inspiratory pressure (cm H2O) x respiratory rate).
there were marked fluctuations in oxygen saturations (depicted in the a/A ratio changes) which coincided with recurrent convulsions. The convulsions were resistant to all forms of treatment including phenobarbitone, phenytoin, continuous lignocaine infusion and pentothal. Ultrasonographic studies of the brain demonstrated bilateral subependymal intracranial haemorrhages without hydrocephalus or brain swelling. In the light of the severe respiratory compromise and status epilepticus it was decided to withdraw life support therapy. The patient died 37 hours after birth.

Autopsy showed lungs of normal macroscopic size. There was a slightly increased combined lung mass of 46.5 g. Histopathological examination of lung sections (Fig. 3) revealed pulmonary oedema, intra-alveolar haemorrhages, localised bronchopneumonia and a marked interstitial infiltrate of lymphocytes, plasma cells and macrophages associated with fibroblast proliferation and mild interstitial fibrosis. Close examination of the peripheral pulmonary arterioles within the inter-alveolar septa showed focal muscularisation with associated increased adventitial connective tissue. These changes were observed in numerous sections representative of all the lung lobes. Meconium aspiration, intravascular thrombi and abnormalities of the pulmonary veins were absent. No evidence of obliterative fibrosis as described in 'pneumonia alba' was present.

Fig. 3. The inter-alveolar septa are infiltrated by numerous macrophages, lymphocytes and plasma cells (inset) with associated fibroblasts and delicate fibrosis. Note the muscularisation of an intra-acinar arteriole (arrows)

Examination of the cardiovascular system revealed a patent foramen ovale and a ductus arteriosus. The brain showed no evidence of syphilitic involvement. A subependymal matrix haemorrhage without ventricular dilatation was present. Sections of the pancreas, hypophysis, epididymis, pharynx, submucosa of the small intestine, adrenals, kidneys and pericardium showed extensive interstitial fibrosis and inflammation. Extramedullary haematopoiesis was a prominent finding in the liver, spleen, myocardium, lungs, adrenals and pancreas. The placenta was unavailable for histological assessment.

Discussion
PPHN remains a challenging clinical problem. The incidence varies, but accounts for 1 - 4% of all neonatal intensive care unit admissions per year.11-12 The clinical syndrome is characterised by severe hypoxaemia due to right-to-left shunting of blood through the ductus arteriosus and/or foramen ovale. Symptoms usually appear soon after birth in affected full-term or post-term babies.13 However, in developing countries, babies with this condition tend to be of both lower birth weight and gestational age.14 PPHN was previously noted to occur equally frequently (50:50) with or without underlying lung disease. During the past 9 years, reports clearly show a shift towards a 25:75 ratio in favour of PPHN occurring in association with lung disease or cardiac anomalies.15 The change particularly seems to reflect increasing awareness of PPHN associated with diseases such as haemolytic disease and pneumonia caused by a variety of organisms.14-17

Both animal studies and human case reports indicate that increased pulmonary vascular resistance occurs in association with Gram-negative organisms (Pseudomonas spp., Escherichia coli), group B Streptococcus, Pneumococcus and Ureaplasma urealyticum infections.14-17 In cases of neonatal sepsis it has been suggested that PPHN might be mediated or exacerbated by endogenous thromboxane A2 release. Urinary metabolite (dionorthromboxane B2) excretion was found to be consistently higher early in the course of pulmonary hypertension associated with sepsis, compared with hypertension without sepsis.16

Recently, Waites et al.17 described 5 babies who suffered from U. urealyticum pneumonia associated with PPHN. Four of the 5 infants also had other concomitant bacterial infections, including Staphylococcus epidermidis, Mycoplasma hominis and a Haemophilus species. Nevertheless, both U. urealyticum and M. hominis have been shown to produce phospholipases which may be involved in the pathogenesis of PPHN via the liberation of arachidonic acid and subsequent thromboxane.17

In some cases, the sequence of events resulting in clinical PPHN suggests that perinatal hypoxia could have been the underlying 'trigger'. It is possible that thromboxane, released as a result of hypoxia, may mediate both platelet aggregation and pulmonary hypertension.18 There are considerable data to show that the pulmonary vasculature undergoes extensive remodelling in cases of smooth-muscle cell hyperplasia and that there is an increase in connective tissue when it is exposed to chronic hypoxia.19 The pathogenesis of the cellular hyperplasia is unclear, but may involve vascular endothelial injury, smooth-muscle cell and fibroblast interaction.20,21

Pulmonary parenchymal involvement in infants with congenital syphilis is common and is a difficult problem to manage.21 In premature babies with syphilis, the lung disease indicates a combination of surfactant deficiency, lung immaturity, interstitial scarring and extramedullary haematopoiesis; it is slow to resolve. The pulmonary involvement in the present case demonstrated a combination of pathological findings of which lymphocyte, macrophage and plasma cell infiltration of the interstitium was the most prominent. In addition to this, and previously
unreported, excessive focal intra-acinar arteriolar muscularisation was shown. It is not clear from the present case whether asphyxia and/or syphilis infection per se led to the development of the pulmonary hypertension. The evidence that hypoxia played a role is convincing (late decelerations, low Apgar score, severe metabolic acidosis at birth, hypoxic ischaemic encephalopathy). A review of the records of 37 infants with congenital syphilis who were admitted to our neonatal intensive care unit (1984 - 1991) revealed no documented PPHN (unpublished data).

The role of chemical mediators of inflammation and fibroblast proliferation released by macrophages and lymphocytes in the neonatal lung in cases of congenital syphilis has not been studied. Apart from the role of hypoxia, no hypothesis adequately explains the pathogenesis of treponematid infection of the neonatal lung. Despite the evidence for an immunopathy's causing syphilitic placitis, we were unable to detect the typical vasculitic changes in the lung characteristic of a type III immunological reaction. It is therefore unclear what pathogenetic role non-organ-specific serum auto-antibodies, such as rheumatoid factor or circulating immune complexes, play in the development of lung disease in babies with syphilis.

Polymorphonuclear leucocytes infiltrate within 1 - 2 days following testicular injection of Treponema pallidum in rabbits. Serum immunoglobulin G is first detectable on day 3 and interleukin-2 (IL-2) is activated by day 4. T lymphocytes infiltrate and proliferate by day 6. Macrophages subsequently infiltrate infected tissues and phagocytose and secrete treponematid factors that kill and lyse T. pallidum in the presence of opsonic antibody. Recently suggested that T. pallidum stimulates IL-2 production, delayed-type hypersensitivity reaction and gamma interferon production (Th2 response) which up-regulate phagocytosis by macrophages. Subsequent overspill of prostaglandin E2 by macrophages interrupts the continued cycle of macrophage activity (through inhibition of T-helper cell synthesis of gamma interferon), eventually culminating in chronic infection. Macrophages also release several mediators that stimulate lung fibroblast proliferation. Of these fibronectin, platelet-derived growth factor and insulin-like growth factor 1 are implicated in fibroblastic conditions of the lung.

In summary, reviewing our previous experience with congenital syphilis as well as the present case, we have to conclude that the coexistence at birth of congenital syphilis and PPHN is a rare finding. This combination also appears to be poorly responsive to conventional therapeutic manoeuvres. Further research is warranted to clarify the potential role of inflammatory mediators, circulating immune complexes, vascular endothelial damage and prostanoid production in the pathogenesis of prenatally acquired syphilitic lung disease associated with PPHN, before the "great imitator" is definitely implicated as a cause of PPHN.

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