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Review Article

Pulmonary interstitial glycogenosis

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Abstract

Pulmonary interstitial glycogenosis is a type of interstitial lung disease seen only in infants. It is characterised by the interstitium being expanded by poorly differentiated mesenchymal cells with abundant glycogen. The pathogenesis and the aetiology of the condition is not well known. It carries a more favourable prognosis than paediatric interstitial lung disease in general but morbidity may be associated with coexisting lung conditions.

Keywords: Paediatric intersititial lung disease, Pulmonary interstitial glycogenosis

Introduction

Interstitial lung disease (ILD) is a rare group of disorder in children. The prevalence is estimated to be 0.36 per 100,000 in the pediatric population ages 0-16.[1] It is even rarer in young infants but it is important to consider this group of disease in neonates and infants with persistent respiratory distress and oxygen dependency of unknown cause, together with radiological abnormalities. Interstitial lung disease that are more prevalent in infancy includes: (1) diffuse developmental disorder, (2) growth abnormalities reflecting deficient alveolarisation, (3) specific condition of undefined aetiology, and (4) surfactant disorders (Table 1).[2] Among them, pulmonary interstitial glycogenosis (PIG) is a type of interstitial lung disease uniquely seen in infancy, first described in 2002 by Canakis et al in seven cases.[3]

Clinical symptoms and signs

PIG usually presents within 24 hours after birth or early in the neonatal period with 4 weeks. It can occur in term babies as well as premature babies.[2-4] It has been reported in monozygotic preterm twins.[5] PIG was also reported in cases with congenital heart diseases and persistent pulmonary hypertension that is not responsive to inhaled nitric oxide.[6,7] It was also reported in children with hypertrophic cardiomyopathy.[8] Affected neonates or infants usually present with tachypnoea, intercostal insucking, and hypoxaemia requiring oxygen supplement. Some will require mechanical ventilation or non-invasive ventilatory support. The age of lung biopsy in past series was usually within 6 months, at most 10 months.

Radiological features

Imaging can be variable and non-specific in the diagnosis of PIG. Chest radiograph shows large volume lungs with a fine interstitial reticular pattern. This progresses rapidly to a coarse interstitial pattern with linear coarse opacities mixed with overinflated areas, worse at the lung bases. High resolution computerised tomography (HRCT) of the thorax shows linear reticular opacities, septal thickening, mixed with areas of overinflation and ground glass opacity.[4,9,10] In some of the patients who have undergone treatment HRCT showed scarring with patchy basal ground glass opacities.[3]

Histopathology

The most prominent feature is diffuse interstitial thickening, expanded by round- to spindle-shaped cells with pale cytoplasm. These cytoplasm contains masses of periodic acid-Schiff positive material suggestive of glycogen. The interalveolar septae shows minor component of inflammatory type cells but no signs of interstitial fibrosis. In the biopsies, the airways and blood vessels had no abnormalities.[3] Under electronic microscopy, the cytoplasm of these poorly and variably

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Table 1. Interstitial lung diseases that are more prevalent in infancy

Diffuse developmental disorders
Acinar dysplasia
Congenital alveolar dysplasia
Alveolar capillary dysplasia with misalignment of pulmonary veins
Growth abnormalities reflecting deficient alveolarisation
Pulmonary hypoplasia
Chronic neonatal lung disease
Related to chromosomal disorders
Related to congenital heart disease
Specific conditions of undefined aetiology
Neuroendocrine cell hyperplasia of infancy
Pulmonary interstitial glycogenosis
Surfactant dysfunction disorders
Surfactant protein B (SFTPB) mutations
Surfactant protein C (SFTPC) mutations
ABCA3 mutations
Histology consistent with surfactant dysfunction disorder without a yet recognised genetic aetiology
Pulmonary alveolar proteinosis
Chronic pneumonitis of infancy
Desquamative interstitial pneumonitis
Nonspecific interstitial pneumonia

differentiated interstitial cells looks empty or contained low contrast granular material indicative of glycogen. Electron dense, well-defined particles indicative of nonparticular glycogen will be seen in ultrathin section treated with tannic acid method or Periodic Schiff-Methenamine Silver. The other cell types found within the lung interstitium are usual ultrastructurally with no cytoplasmic glycogen, although occasional patches can be present in alveolar type II cells.

Pathogenesis

The aetiology and underlying pathogenic mechanism of PIG are unknown. There are doubts whether primary cause of PIG is isolated aberrant differentiation of pulmonary mesenchyme or if the presence of these cells reflects a secondary reaction to pulmonary insult or another disease entity. No one suggested that it is an inflammatory process. Deutsch et al found that 40% of 46 lung biopsies with principle diagnosis of lung growth abnormality also had patchy PIG changes.[2] In another review by Langston and Dishop, nearly 60% of infants with growth abnormalities had patchy PIG.[11] Onland's report of PIG in monozygotic twins may represent genetic aetiology. But this pair of twins suffered from twin-twin transfusion syndrome which may also indicate the presence of a reactive process.[5] As the PIG phenotype can be found in lung biopsies of children of all gestational ages, this suggests that the abnormality originates in utero.[12]

Treatment

For PIG, as in other paediatric interstitial lung disease, there is no consensus treatment guideline. Treatment is supportive. In some cases, symptoms resolve without any treatment. Intravenous pulse corticosteroid therapy was used (methylprednisolone, 10 mg/kg/day once a day for 3 days each month) in some patients for 6 up to 11 months with improvement in oxygenation and symptoms. The mechanism of steroid therapy is uncertain, similar to the uncertainty in the aetiology.

In contrast to other interstitial pneumonitis such as lymphocytic interstitial pneumonitis, PIG is not characterised by inflammation but dysmaturity of the interstitial cells. The effect of corticosteroid therapy is likely a result of the acceleration of the maturation process instead of the modification of the inflammation. In some patients, repeated biopsy specimen after treatment showed resolution of the pathology.[7] The use of high-dose steroid in cases with patchy PIG

in the setting of significant pulmonary growth abnormality is however not recommended in view of possible consequences on postnatal alveolarisation and neurodevelopmental outcomes.[13] Trial of hydroxycholoquine was also administered with no significant response.[3]

Prognosis

While the overall mortality of paediatric ILD is around 20%, the prognosis of PIG is more favourable. In the series by Canakis, 6 out of 7 of the infants survived. The exception was a 25 week premature baby with bronchopulmonary dysplasia. Death has also been reported in full term baby with PIG and pulmonary maturational arrest, with lung tissue showing dilated airways with lack of secondary septation.[12] Morbidity is increased when PIG is associated with other conditions. If the theory that PIG is a reactive process is true, the severity of the defect that "induces" the accumulation of abnormal mesenchymal cells, or the underlying injury, should predict the outcome rather than the presence of PIG alone. Prognosis is more dependent on the overall clinical picture than on the presence of PIG alone. Prognosis appears to be favourable in isolated or diffuse PIG. Hunter syndrome was diagnosed when a neonate with PIG reached the age of 3, indicating that careful follow-up of children with PIG is necessary.[10]

Conclusion

The understanding of the presentation, pathogenesis, aetiology and prognosis continue to evolve. Although PIG is rare, it may be underrecognised in neonates because histological examination is required to establish the diagnosis. It is important to consider interstitial lung disease and PIG in neonate with early onset respiratory distress and persistent symptoms / oxygen dependency, in the context of the appropriate radiological findings.

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