

Congenital alveolar proteinosis

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ABSTRACT

Pulmonary alveolar proteinosis is recently described as a rare cause of lung dysfunction and respiratory distress in term neonates. In several cases, a deficiency or insufficiency of surfactant protein B (SP-B) has been caused by a frame shift mutation in the gene encoding SP-B. Three siblings with congenital pulmonary alveolar proteinosis showed clinical and radiological evidence. Histopathological and immunohistochemical studies in the last sibling revealed deficiency of SP-B, one of the group of 3 specific lipoproteins that reduce the surface tension between air and liquid interface within pulmonary alveoli, suggesting a gene associated illness.

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Pulmonary alveolar proteinosis (PAP) is a rare disease entity characterized by an excess production and accumulation of insoluble amorphous material composed of phospholipid and lipoprotein complexes, within the alveoli. These results in impaired gas exchange at the alveoli with progressive hypoxemia. Of the 4 children born to a healthy young couple of consanguineous marriage, only the first born male child has survived and is normal. Parents are first degree related cousins. The maternal and paternal grandfathers of the cases were brothers (**Figure 1**). Case reports of the remaining 3 siblings are presented. All 3 neonates presented with symptoms of severe, persistent and progressive fatal respiratory distress that appeared either at birth or a few hours after delivery. Diagnosis of PAP was established only in the last sibling, and since the clinical course and outcome of the earlier 2 siblings were similar, a retrospective diagnosis of congenital PAP, that is genetically determined is hypothesized. It is surmised that the patients possibly had a genetic disorder of surfactant protein-B deficiency (SP-B), leading to this disease entity, which may be referred to as "congenital alveolar proteinosis" (CAP).

Congenital alveolar proteinosis though a rare entity of severe respiratory distress during neonatal period its incidence is not known. The CAP may account for approximately 1% of all infant death within 6 months of life. Due to lack of adequate facilities for diagnosis, the entity seems to be having underestimated incidence in the Kingdom of Saudi Arabia.

Case Reports. Sibling 2 was a pre-term female baby, approximately 30 weeks gestation, with birth weight of 1000 gms. The baby had an apgar score of 2 and 4 at one and 5 minutes. The neonate was in respiratory distress with grunting and feeble cry, and poor air entry bilaterally. She was put on mechanical ventilator. Radiological examination of the chest was carried out initially revealed diffuse ground glass appearance of both lung fields. Follow up chest x-ray showed no radiological improvement with persistence of the uniform haziness and no aeration. Clinically, the condition deteriorated and the baby died after 4 hours.

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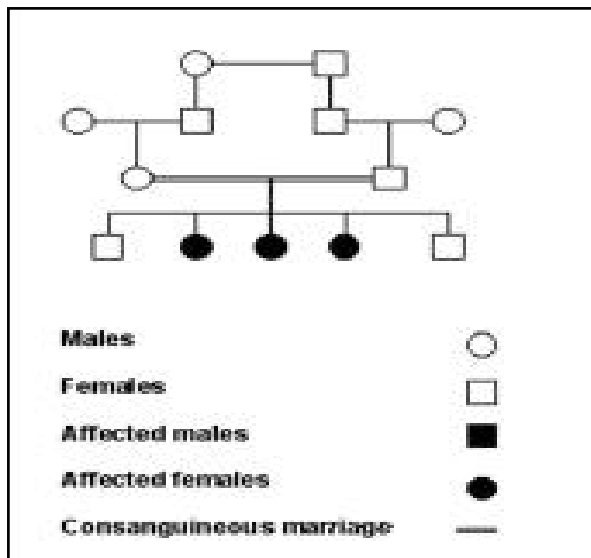


Figure 1 - Showing the family tree of the affected sibling.

Sibling 3 was the third baby to the same parents, it was a female, full term normal delivery with birth weight of 3100 gms. The neonate was normal at birth with an apgar score of 7 and 9 at one and 5 minutes. She developed symptoms of respiratory distress one hour after birth. She became lethargic, grunting with plenty of oral secretions. Initial x-ray chest showed a fine granular pattern of both lung fields with normal heart. Mechanical ventilation was begun, with intermittent endotracheal tube aspiration that revealed frothy white mucoid material and did not show any growth of pathogens on culture. Clinical improvement was satisfactory and follow up chest x-ray showed remarkable improvement over the next 48-72 hours. The neonate could not be weaned off the ventilator due to its inadequate respiratory effort. A short course of hydrocortisone 10 mg/kg/day was given for 3 weeks with a tapering dosage, showed transient improvement clinically and radiologically. Regular physiotherapy with pulmonary lavage used to improve the PaO₂ and saturation. Unfortunately, the child continued to have a progressive course of waxing and waning that paralleled with the accumulation of secretions. Clinical and radiological improvement was noted after the aspiration of the copious secretions only to be followed by a deterioration in clinical state with re-accumulation of secretions. On 95th day, the baby developed *Pseudomonas* infection and succumbed on the 97th day. The final clinical impression was chronic respiratory distress, the cause for which remained unexplained. Unfortunately, autopsy permission was declined.

Sibling 4 was a female delivered normally with birth weight of 2600 gms. The neonate was normal

at birth with an apgar score of 8 and 10 at one and 5 minutes. She became tachypneic at approximately 8 hours after birth and developed grunting, cyanosis and indrawing with low PaO₂ requiring mechanical ventilation. At this point, the chest x-ray showed good aeration of both lungs. She had a clinical course similar to the earlier sibling with alveolar arterial gradient of more than 400 mm Hg. She had a high lactate dehydrogenase (LDH) of 1489 IU/L, and serum protein of 4.4 gms/dl. Follow up chest x-ray 48 hours after birth revealed fine granular appearance of both lung fields. The baby continued to have progressive course with inadequate respiratory effort and developed reticular pattern of lung changes radiologically. Regular chest physiotherapy with pulmonary lavage used to improve the PaO₂ and saturation. In view of the previous siblings' similar neonatal problems, a clinical suspicion of PAP was entertained. The material obtained by tracheal aspirate was proved to be PAS positive.

Since the baby's condition was deteriorating and there was no hope for recovery, needle biopsy of the lung was performed on 25th day, and open lung biopsy was carried out on 28th day. Unfortunately, the baby developed pneumothorax, became critically ill and died the following day. Immuno-staining of lung tissue showed marked reduction of SP-B in alveolar cells. Compared to the previous sibling, on review, this had a more severe clinical course and it was difficult to maintain PaO₂ more than 50 mm Hg with FiO₂ 80-100%.

Discussion. Pulmonary alveolar proteinosis was first reported by Rosen *et al*¹ in 1958. Pulmonary surfactant is heterogenous mixture of phospholipids and protein secreted into the saccular or alveolar organelles, known as lamellar bodies as early as 24 weeks of gestation. Three apoproteins (SP-A, SP-B, SP-C) identified in pulmonary surfactant and fourth lecithin such as glycoprotein has been isolated. Surfactant protein-A is a glycoprotein and plays an important role in surfactant metabolism and host defense. Surfactant protein-B and SP-C are low molecular weight hydrophobic protein, which increase the rate of adsorption of phospholipids into the air liquid interface. The fourth SP-D function and regulation is not known yet. Hence, inherited deficiency of specific surfactant proteins lead to respiratory disease in neonates. The siblings described in this and previous report had the characteristic clinical and histopathological features of CAP with specific deficiency of SP-B. This supports the hypothesis that an inherited deficiency of SP-B was the cause of respiratory disease in these infants. Earlier studies have demonstrated the importance of SP-B in surfactant functions but the exact mechanism of

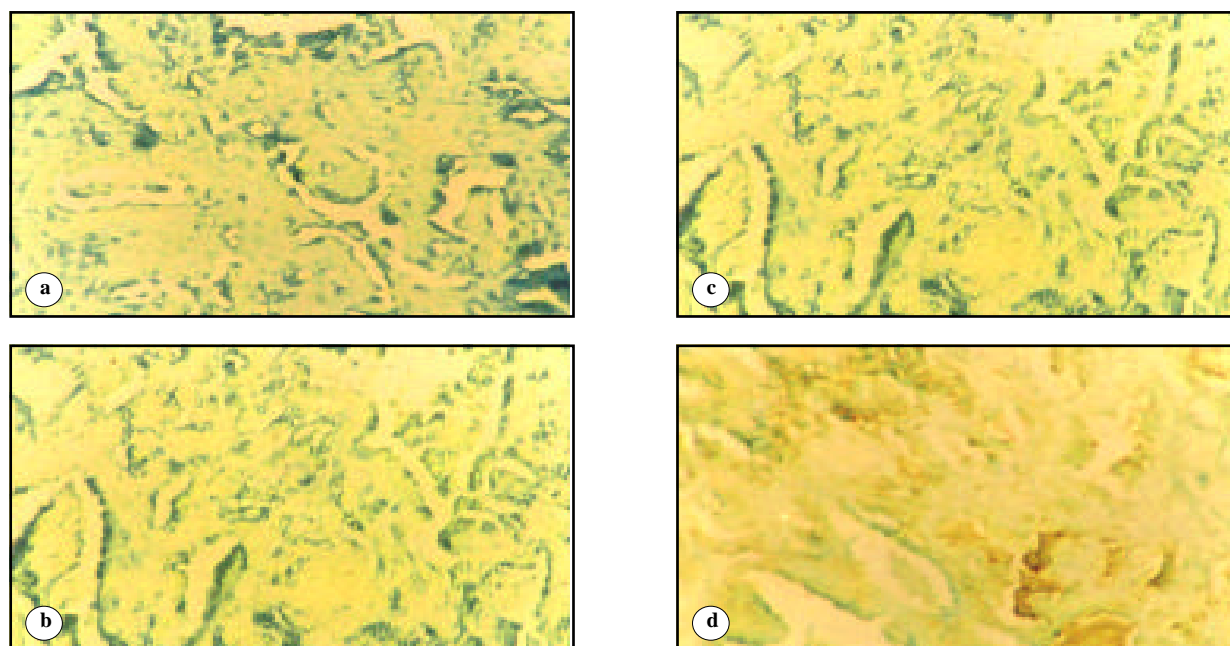


Figure 2 - Immunostaining showing (a) normal, (b) marked reduction in surfactant protein-B within alveolar cells, (c) Increased staining for surfactant protein-C and (d) Altered pattern of surfactant protein-A staining. Most of the staining is confined to the proteinaceous material and desquamated cells.

histopathological changes in alveolar proteinosis due to SP-B deficiency is not clear. Dr. Noguee in his earlier study has noted the absence of SP-B messenger-ribonucleic acid in his patient's lungs. Infants with SP-B deficiency studied in this and earlier report developed respiratory failure in spite of increased amount of SP-C. Surfactant protein-B is essential for tubular myelin formation. Previously reported cases have revealed the absence of tubular myelin supporting the hypothesis that those infants were deficient in SP-B.³ Evidence of incidence of CAP within families suggests a genetic defect as the cause of this disease in newborn infants. Earlier reports traced the pathology in 4 separate families. The diagnosis of CAP was not made until the birth of a second affected infant in each family. In the present study, suspicion of possible CAP as the cause of persistent respiratory distress in the last sibling was aroused only after going through the records of similar clinical course in the earlier 2 siblings. Subsequently, investigations to establish the diagnosis by positive PAS staining of tracheal aspirate and lung biopsy for changes of PAP were initiated. Immunohistochemical staining for surfactant apoproteins was also carried out, which established the diagnosis of SP-B deficiency. Hematoxylin and eosin staining of lung tissue showed extensive smooth muscle hypertrophy and extensive alveolar type II cell hyperplasia. Abundant plump alveolar macrophages filling many of the air spaces were seen. Some air spaces had granular eosinophilic proteinaceous material with

desquamated cells within them, changes were suggestive of alveolar proteinosis. Immunostaining of lung tissue showed marked reduction of SP-B immunostaining in alveolar cells, increased staining for SP-C and an altered pattern of SP-A staining, with most of the staining being confined to proteinaceous material and desquamated cells (**Figure 2a, 2b, 2c & 2d**). Biochemical assays for the proteins on lung fluid aspirate and lung phospholipid profile were not carried out.

The hypothesis of CAP is advocated solely based on the similarity of the clinical course of the earlier 2 siblings in this study. Further, of 3 neonates affected in this family, sibling 2 was premature (30 weeks gestation) and had symptoms of respiratory distress at birth and died 4 hours after delivery. It could well be that the cause of respiratory distress was not necessarily PAP. However in sibling 3, since the clinical course was similar to the fourth sibling studied, the possibility of CAP appears high. This study differs from the earlier report that there is a history of consanguinity and all affected siblings were females. Whether these observations have any bearing on this disease needs to be seen. The lone surviving child of this couple was the first born male child who is normal. There was no history of such occurrence in their families. Sporadic cases of neonatal alveolar proteinosis have been reported earlier in literature, raising the possibility of the existence of non-hereditary forms of this disease.² Pulmonary alveolar proteinosis was thought to be a condition of uncertain etiology. It has been

described as a disease due to mutations in the SP-B gene. So far, 2 "disease causing mutations" have been recognized. The gene for SP-B is located on chromosome 2. The disease is transmitted as autosomal recessive. Both males and females are equally affected.

Every newborn infant has a chance of 1 in 4 being affected. Noguee et al in their studies, have identified the genetic mutation as 121 in S 2.⁵ But the preliminary genetic study of this family indicated that this is not the causative mutation. Further work is in progress for the identification of the mutation. Mother has given birth to another female baby (fifth sibling) who has not shown any signs of respiratory distress and has remained normal.

It is concluded that, with genetic defect of surfactant apoprotein being established as the cause of congenital alveolar proteinosis genetic counseling is mandatory for the parents, describing the possible outcome of their next offspring. However, as there is a possibility of non PAP cause of respiratory distress in these siblings, given the history of this defect in an earlier sibling, the next born neonate needs investigation for congenital PAP by biochemical assay of proteins on lung fluid aspirates (bronchoalveolar lavage) and immunohistochemical study for surfactant lipoproteins.⁶ In this study similar to previous studies, it was noted that periodic pulmonary lavage may help to prolong shortly the survival time of these affected neonates. Given the uniformly fatal outcome of CAP, it remains to be seen if future research would

formulate an exogenous surfactant extract supplement (such as Survanta) that would modify the course of this disease.

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References

1. Rosen SH, Castleman B, Liebow AA. Pulmonary Alveolar Proteinosis. *N Engl J Med* 1958; 258: 1123-1124.
2. Moulton SL, Krous HF, Merritt TA, Odell RM, Gangitano E, Cornish JD. Congenital pulmonary alveolar proteinosis: failure of treatment with extracorporeal life support. *J Pediatr* 1992; 120: 297-302.
3. Noguee LM, de Mello DE, Dehner LP, Colten HR. Brief report: deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. *N Engl J Med* 328: 406-410.
4. Noguee LM. Personal Communication, Dec, 1993.
5. Noguee LM, Murphy AM, Dietz HC, Gamier G, de Mello DE, Colten HR. Mutations in the Pulmonary Surfactant Protein-B (SP-B) Gene in Neonates with Total Respiratory Disease: Proceedings of the International Conference, American Thoracic Society; 1994 May 22-25; Boston, Massachusetts, USA. Boston (MA): American Thoracic Society; 1994.
6. Martin RJ, Coalson JJ, Rogers RM, Horton FO, Manous LE. Pulmonary Alveolar Proteinosis: The Diagnosis by Segmental Lavage. *Am Rev Respir Dis* 1980; 121: 819-825.