British Paediatric Orphan Lung Diseases (BPOLD)

Name of Disease:

Pulmonary alveolar proteinosis (PAP)

Clinician:

Prof. Matthias Griese
Childrens´ Hospital, University of Munich, Lindwurmstr 4a, 80337 Munich, Germany

Clinical details:

Definition

In Pulmonary Alveolar Proteinosis abnormally high levels of surfactant accumulate in the alveoli causing problems with gas exchange. The condition can be primary or secondary.

Causes

Many causes lead to pulmonary alveolar proteinosis, i.e. persistent and substantial increase in surfactant pool size.

- **Autoimmune PAP** is the most frequent form, is caused by autoantibodies against granulocyte–macrophage colony-stimulating factor (GM-CSF) and may occur in children, but is mainly found in adults
- Mutations in the **alpha-chain of the receptor for GM-CSF** are a form of congenital PAP, manifesting during infancy and childhood
- Mutation in the genes of the surfactant proteins B (**SFTPB**) or C (**SFTPC**) are also associated with PAP during early life and present as interstitial lung diseases
- **Niemann-Pick Type C2** disease may present as PAP
- **Lysinuric protein intolerance** with SLC7A7 mutations
- Secondary PAP develops in association with conditions involving functional impairment or reduced numbers of alveolar macrophages. These conditions include inhalation of **inorganic dusts** like silica or titanium, some forms of **leukaemia** (myeloic, myelodysplastic syndrome), **immunosuppression** related to organ transplantation, **infections** (especially Pneumocystis)
- **Idiopathic** PAP are those forms where none of these causes can be identified

Clinical Presentation and Diagnosis

Neonates:
Mostly mature neonates (due to rarity of disease it is unlikely to occur in a premature infant, but not excluded), sometimes gradual onset, but most frequently rapid onset of chronic tachy- and dyspnoea, hypoxemia, respiratory distress not explained by cardiac diseases, infections, localised pulmonary or systemic diseases that may affect the lungs. Exclude Niemann-Pick Type C2 disease. Consanguinity or preious cases in family history should be investigated.

Children:
Exercise intolerance, gradual onset of progressive dyspnoea, little productive cough, weight loss,

BPOLD is funded by the University of Edinburgh Research and Development Fund

fatigue, bacterial pulmonary infections. Diffuse crackles, clubbing.

Low oxygen saturation, initially with exercise only. Hypoxemia, with normal CO2 most of the times on blood gases, sometimes LDH increased.

Chest x-rays bilateral alveolar filling, often symmetrical (bat-wing sign), on CT bilateral diffuse ground-glass opacity, smooth septal thickening in affected areas, with patchy or geographic distribution

If old enough for lung function testing: restrictive pattern, reduced diffusion capacity for CO (not very helpful for diagnosis).

Lysinuric protein intolerance, Niemann-Pick disease C2 and secondary PAP due to myeloic leukaemia or myelodysplastic syndrome, immunosuppression and infections must be excluded.

investigations
Stepwise approach to investigation:

Low oxygen saturation, initially with exercise only. Hypoxemia, with normal CO2 most of the times on blood gases, sometimes LDH increased.
Chest x-rays bilateral alveolar filling, often symmetrical (bat-wing sign), on CT bilateral diffuse ground-glass opacity, smooth septal thickening in affected areas, with patchy or geographic distribution
If old enough for lung function testing: restrictive pattern, reduced diffusion capacity for CO (not very helpful for diagnosis).
Lysinuric protein intolerance, Niemann-Pick disease C2 and secondary PAP due to myeloic leukaemia or myelodysplastic syndrome, immunosuppression and infections must be excluded.

Neonates:
Mutational analysis for SFTPB and SFTPC mutations when the above signs and symptoms are present after the exclusion of other causes. After other genetic causes for such chronic conditions are excluded (eg mutations in ABCA3 transporter or TTF1 gene), **lung biopsy** may be necessary for the diagnosis of the conditions, including PAP. Diagnostic bronchoalveolar lavage is not helpful in this situation to establish the diagnosis.

Children:
Bronchoalveolar lavage with the macroscopic appearance of whitish lavage fluid and the characteristic cytology pattern on the slides (PAS stain positive) may be diagnostic. **Thoracoscopic or open lung biopsy** is diagnostic. Have the lung tissue investigated by a reference pathologist, experienced in pediatric pulmonary pathology.

In children older than 8 years **anti-GMCSF autoantibodies** in serum should be studied.
In all patients with the established diagnosis of PAP the cause of the disease should be investigated by **genetic** analysis of the alpha-chain of the GMCSF receptor and if possible by **functional analysis** of the GMCSF signal transduction chain.

> Evidence gap: The very rare nature of this condition and recent development of novel investigations and potential treatments require international collaborative research efforts.

Course

The clinical course of PAP is unpredictable, and can be associated with progressive deterioration and death, long term stability or spontaneous remission. Death may occur because of progressive respiratory failure and/or in association with increased susceptibility to infection (bacterial, viral and fungal).

Treatment

Therapeutic whole lung lavage is the established and successful treatment option. As it is technically demanding, especially in small children or infants, it should preferentially be done in centres very experienced with this technique.

GMCSF injections or inhalations have been successfully done only in some adult patients with autoimmune PAP; if such antibodies can be demonstrated in children and whole lung lavage is not possible for very strong reasons, such children might be included in experimental protocols.

Lung transplantation is an option for those with end stage disease.

> Evidence gap: An assessment of GMCSF antibody levels in children may enable new treatment modalities.

Useful references:

Suzuki T, Sakagami T, Rubin BK, Nogee LM, Wood RE, Zimmerman SL, Smolarek T, Dishop MK, Wert SE, Whitsett JA, Grabowski G, Carey BC, Stevens C, van der Loo JC, Trapnell BC. Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. J Exp Med. 2008 Nov 24;205(12):2703-10.

Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003 Dec 25;349(26):2527-39

Griese M, Brasch F, Aldana VR, Cabrera MM, Goelnitz U, Ikonen E, Karam BJ, Liebisch G, Linder MD, Lohse P, Meyer W, Schmitz G, Pamir A, Ripper J, Rolfs A, Schams A, Lezana FJ. Respiratory disease in Niemann-Pick type C2 is caused by pulmonary alveolar proteinosis. Clin Genet. 2010.

Latzin P, Tredano M, Wüst Y, de Blic J, Nicolai T, Bewig B, Stanzel F, Köhler D, Bahuau M, Griese M. Anti-GM-CSF antibodies in paediatric pulmonary alveolar proteinosis. Thorax. 2005 Jan;60(1):39-44.

Web links:

Prof. Matthias Griese; Very interested in PAP in neonates and children
www.ped-pneumology.de
Anti-GMCSF antibodies in serum and lavage
Sequencing of the alpha-chain of GM-CSF-receptor in blood
Functional assay for GMCSF-receptor signal transduction chain in blood

The EU PAP website
Research and Information webpage

The US PAP (Pulmonary Alveolar Proteinosis) Foundation)
Information for families and patients

BPOLD is funded by the University of Edinburgh Research and Development Fund