European Management Platform for Childhood Interstitial Lung Diseases

COOPERATION

Proposed Best Practice Checklist:

Genetic testing for interstitial (diffuse parenchymal) lung diseases in children (chILD)

Usually rare, inherited interstitial lung diseases are associated with various characteristic clinical situations. Here we outline some to guide the selection of genetic tests to confirm this suspicion.

Neonate, mature or almost, unclear respiratory distress syndrome (RDS) or primary pulmonary hypertension, radiological evidence for diffuse parenchymal lung disease, exclusion of infection, cardiac, metabolic or other causes of diffuse lung disease, age 10 days or older. If there is a positive family history inherited diseases are more likely.

What test should be performed?

Sequential testing for SFTPB (first 121ins2, then rest of the gene) and ABCA3 are done; if negative, SFTPC mutations should be sought. Additionally high TSH (hypo-thyroidism), abnormal muscle tone or movements suggest testing for brain–thyroid–lung syndrome (TTF1). Additional extra-pulmonary organ involvements like cardiac, gastrointestinal, genitourinary anomalies suggest alveolar-capillary dysplasia (ACD) and mutations in FoxF1 and TBX4 might play a role. However frequently ACD may be isolated and only a minority of cases are caused by FoxF1 or TBX4 haploinsufficiency.

Infant, toddler, child or adolescent with suspected chronic diffuse parenchymal lung disease from history, clinical condition, chest imaging, and lung function testing.

What test should be done?

Ideally before going to lung biopsy, genetic analysis of SFTPC and ABCA3 should be done. If there is also evidence for hypo-thyroidism or neurological abnormalities, including muscular hypotonia or choreoathetosis, TTF1 mutations should be sought. If the clinical situation is urgent, and it is likely genetic results may be delayed, a lung biopsy may be performed at the same time as taking genetic samples

Infant, toddler, child or adolescent with suspected alveolar proteinosis, i.e. hypoxemia with or without exercise, characteristic milky bronchoalveolar lavage fluid and chest CT. If there is a positive family history inherited diseases are more likely.

What test should be done?

Genetics for GMCSF-Ra. In infants and toddlers, alveolar proteinosis may be caused by mutations in SFTPC, NPC2, ABCA3 genes.

Neonates, infant, toddler, child or adolescent with suspected pulmonary hypertension from history, clinical condition and echocardiographic/hemodynamic parameters.

What test should be done? Ideally before going to lung biopsy, genetic analysis of BMPR2, SMAD9, ENG and ALK1 should be done.

The interpretations of the results from genetic testing may not be straightforward if novel variations are found which have not been associated with lung diseases earlier. Great caution and long term follow up within a structured register are necessary to determine their pathogenic role.