Sleep disordered breathing in an adult with cherubism

Cherubism is a rare disorder with bilateral enlargement of the mandible that regresses with time. Bone degrading osteoclasts and bone building osteoblasts function abnormally causing the changes. It is an autosomal dominant condition which manifests in early childhood by the age of 2–5 years, but later regresses with time. Airway obstruction occurs due to backward displacement of the tongue affecting respiration. An 18 year old male was referred to us for snoring. On inquiry the mother reported swelling of the lower face since childhood, which had progressed to its present size. The patient had difficulty in speech, mastication, and swallowing with mental retardation. The lower eyelids were retracted and his oral examination revealed gingival hypertrophy with most of the upper and lower teeth could not be visualised. Fine needle aspiration of the mandible revealed the presence of giant cells with fibrous tissue. A diagnostic biopsy of the mandible revealed the presence of non-caseating granulomas. Typical presenting symptoms include cough and dyspnoea in addition to skin and/or eye lesions. We report a case of sarcoïdosis presenting as upper extremity venous thrombosis.

A 39 year old woman presented with sudden swelling of the right upper limb and right side of the neck and face. She reported no cough, dyspnoea, chest pain, or systemic symptoms of fever or weight loss. She had no previous medical history, smoked 20 cigarettes daily, and was on an oral contraceptive pill (levonorgestrel, Schering Health Care Laboratories). On examination her body mass index was 31. She had extensive swelling of the right upper limb and right side of the neck and face. Her upper limb pulses were normal and she had no palpable lymphadenopathy. Full blood count, coagulation screen, electrolytes, renal function indices, and serum angiotensin converting enzyme levels were normal. Liver function tests and fasting cholesterol were mildly raised. Serum calcium and 24 hour urinary calcium levels were normal. Pulmonary function testing revealed normal spirometric parameters (FEV1 2.32 litres (85% predicted), FVC 2.97 litres (93% predicted), reduced carbon monoxide transfer factor at 15.7 mmol/min/mm Hg (62% predicted)). A plain chest radiograph showed slight widening of the superior mediastinum, and a computed tomographic (CT) scan showed thrombosis of the right brachiocephalic vein with enlargement of the axillary and mediastinal lymph nodes (fig 1). She underwent mediastinoscopy with biopsy of lymph nodes and histopathological examination revealed fibrosis and hyalinised granulomas consistent with sarcoïdosis. She was treated with low molecular weight heparin and intravenous steroids were continued as an outpatient. A thrombophilia screen performed 16 weeks after the thrombosis revealed normal protein C and S levels, normal antithrombin III levels, and testing for the lupus anticoagulant was negative.

This is the first report to our knowledge of sarcoïdosis presenting as upper extremity deep vein thrombosis, although a recent case reported in Thorax described a patient with tuberculous mediastinal lymphadenopathy associated with pulmonary artery occlusion.1 In addition to venous compression by enlarged lymph nodes, possible contributing factors in our patient include the use of the oral contraceptive pill, cigarette smoking and obesity, all of which have been associated with an increased risk of venous thromboembolic disease related to venous stasis and/or altered coagulation. Upper extremity thrombosis due to venous compression from enlarged mediastinal lymph nodes is usually associated with malignant lymphadenopathy. However, the present report shows that benign mediastinal lymphadenopathy, such as that associated with sarcoïdosis, also has the potential to cause venous thrombosis.

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Genotype-phenotype correlations in PCD patients carrying DNAHS mutations

Primary ciliary dyskinesia (PCD) is usually inherited as an autosomal recessive disorder. Affected individuals suffer from recurrent infections of the upper and lower respiratory tract due to reduced mucociliary clearance. Half of the affected offspring exhibit a complete situs inversus because of randomisation of left-right body asymmetry.1,2 The PCD phenotype results from axonemal abnormalities in cilia and flagella. Total or partial absence of dynein arms are found in 70–80% of PCD cases.3 PCD represents a heterogeneous group of genetic disorders. Distinct PCD loci have been mapped to chromosome 9p13-p21 (DNAH5), 19q13.3-qter and 5p15-p14, respectively.4,5 We identified DNAH5 as the gene responsible for PCD located on 9p. DNAH5 encodes a protein highly similar to the Chlamydomonas pdynein heavy chain.6 Mutants of the Chlamydomonas orthologue show a slow swimming phenotype and are characterised by axonemal abnormalities consisting of outer dynein arm (ODA) defects.7 This phenotype appears similar to that observed in a large Arab family
used to map the PCD locus. Sequence analysis of the DNAH5 gene in PCD patients with randomisation of left-right asymmetry identified mutations resulting in non-functional DNAH5 proteins.

The murine orthologue of human DNAH5, called Dnahc5, is predominantly expressed in the lung as shown by Northern blot analysis. During gastrulation expression is confined to the node, which explains the randomisation of left-right asymmetry in PCD. Mice with a targeted mutation in Dnahc5 display a phenotype highly similar to that observed in patients with PCD. Dnahc5 deficient mice develop respiratory symptoms due to reduced mucociliary clearance, and half of the affected offspring have complete situs inversus.

In order to gain insight into the development of the disease phenotype and the function of DNAH5, we have studied the expression of Dnahc5 in the murine respiratory tract in both embryonic and adult tissue of mice using section in situ hybridisation analysis as described previously. We found that Dnahc5 expression is confined to ciliated epithelial cells of the upper and lower airways (fig 1A–H). This expression pattern is consistent with the PCD phenotype of humans resulting from mutations in DNAH5 and mice with a targeted disruption of Dnahc5, respectively.

Our expression data strongly suggest that ultrastructural abnormalities resulting from DNAH5 mutations should be present in ciliated respiratory epithelia of the nasopharynx, the larynx, and the bronchi. Sampling of respiratory cilia at different sites of the airway should not therefore affect ultrastructural findings caused by DNAH5 mutations.

Individuals of different PCD families exhibit various degrees of respiratory symptoms. We hypothesised that the severity of the disease phenotype might correlate with the molecular nature of the DNAH5 mutation in a family. Ultrastructural analysis of respiratory cilia in three families carrying homozygous mutations of DNAH5 indicated such a genotype-phenotype correlation. Electron microscopic photographs of respiratory cilia from families F173 and F658 have been reported previously and were compared with ultrastructural findings of the UNC-7 family. Mutations causing premature translational termination of DNAH5 (1855NfsX5, 2814fsX1) result in a complete absence of all ODA in respiratory cilia (fig1I–K). In contrast, a splice site mutation predicting a loss of exon 75 (IVS74+1G>C) did not cause total absence of ODA. We semiquantitatively assessed ciliary axonemes from the affected siblings of UNC-7 for the presence of ODA in a blinded manner (n=36 cilia for one sibling, n=9 from the other). Both siblings had shortened stubby ODA compared with normal. Computer-aided quantitative measurement showed that 54% of the ODA were less than half the average length of ODA in normal subjects, which indicates partial ODA deficiency.

We provide evidence for the first genotype-phenotype correlation in PCD. DNAH5 mutations should be considered in individuals with total and partial absence of ODA.

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