Primary Ciliary Dyskinesia

Alternative Names
- PCD
- Ciliary Dyskinesia, Primary
- Immotile Cilia Syndrome
- ICS
- Polynesian Bronchiectasis
- Cilialy Dyskinesia, Primary, 1
- CILD1
- Immotile Cilia Syndrome 1

WHO International Classification of Diseases
Diseases of the Respiratory System

OMIM Number
242650

Mode of Inheritance
Autosomal Recessive

Gene Map Locus
9p21-p13

Description
Primary ciliary dyskinesia is a recessively inherited group of heterogeneous disorders that result from a primary defect in the structure or function of cilia resulting in altered mucociliary transport in the respiratory tract. The disease is not common and has an incidence of approximately 1:15,000 to 1:30,000 in the white population. Several structural abnormalities such as dynein arms defects, radial spoke defects or peripheral microtubules transposition have been described.

The symptoms of primary ciliary dyskinesia are present from birth, but there is a significant variation in both the severity of symptoms and the age at which the condition is diagnosed. Signs begin in the infant with recurrent sinopulmonary infections (chronic cough with bronchorrhea, chronic rhinosinusitis or chronic secretory otitis media). The lungs, nose, middle ear and sinuses are primarily affected as they rely on the coordinated, effective beating of cilia to remove secretions. In addition, ciliary defects affect flagella of spermatozoa, causing infertility in males. Infertility is one of the situations where the disease is diagnosed in males, but also in females in whom the risk of ectopic pregnancy is increased. About 50% of all patients affected with primary ciliary dyskinesia have laterality defects such as situs inversus (Kartagener's syndrome).

The prognosis of the disease depends on the severity of the respiratory involvement. Recurrent pulmonary infections lead to bronchiectasis with chronic respiratory failure in 1/3 of cases. There is no aetiological treatment of primary ciliary dyskinesia, but when diagnosed early, management can be optimized.

Molecular Genetics
Primary ciliary dyskinesia is genetically a heterogeneous condition that is caused by mutations in the DNAI1, DNAH5 and DNAHI1 genes located on human chromosomes 9p, 5p, and 7p, respectively. These genes encode a dynein arm intermediate chain (DNAI1) and two heavy chain proteins (DNAH5, DNAHI1), which are all structural components of the outer dynein arm. Mutations in these genes account for only a number of disease cases and possibly other loci can be linked to the disease. Particular interest is directed to the 19q13.4 locus identified in a group of families from Saudi Arabia [See also: Epidemiology in the Arab World > Saudi Arabia > Meeks et al. (2000)].

Epidemiology in the Arab World

Jordan
[See: Palestine > Al-Shroof et al., 2001]
Palestine
Al-Shroof et al. (2001) reported a large family that lived in refugee camps in Jordan with ciliary dyskinesia syndrome associated with hydrocephalus and mental retardation in 3 generations. There were nine individuals; four male siblings have been diagnosed as having mental retardation, and a maternal uncle was believed to have been similarly affected. The parents of the four affected siblings were first-degree cousins and had 15 offspring. Chromosome analysis of the family showed a normal karyotype. Electron microscopy of the nasal cilia from three affected siblings showed features of primary ciliary dyskinesia. The ultrastructure of nasal cilia in three patients showed disorientation of the central tubules and absence of inner dynein arms in some of the tubules. Computed tomographic scans of the brains of all four affected siblings showed hydrocephalus. Relevant clinical and laboratory features ruled out the possibility that the familial mental retardation observed in their patients could be because of hormonal disturbances, metabolic storage diseases, and chromosomal abnormalities. Accordingly, Al-Shroof et al. (2001) postulated that the recurrent pulmonary infections and hydrocephalus in their large Jordanian family were likely related to ciliary dyskinesia, which appeared to follow an autosomal recessive mode of inheritance. They also suggested that the unusual presentation of ciliary dyskinesia, hydrocephalus, and mental retardation may represent a new syndrome.

Qatar
Abdul Wahab et al. (2001) reported two siblings with primary ciliary dyskinesia born to a consanguineous Qatari family. The first case was a 6-year-old Qatari girl with history of chronic productive cough, chronic serous otitis media, and nasal discharge. From the first month, she had frequent episodes of wheezing and numerous episodes of presumed upper and lower respiratory tract infections. There was no family history of cystic fibrosis or immune defects, but there was a positive family history of asthma in her cousins. At the age of seven years, light and electron microscopy of nasal epithelial cells showed ciliary aplasia confirming the diagnosis of primary ciliary dyskinesia. The brother of the first case presented with respiratory distress at age of two hours and examination showed a chest recession and bilateral crackles. Within the first 6 months of life, he was admitted several times because of persisting wheezing, chronic cough, and upper airway obstruction. He also had two episodes of otitis media.

Saudi Arabia
El-Sayed et al. (1997) described the clinical profile of 16 patients (nine males and seven females) with primary ciliary dyskinesia. All children (11 patients) had bilateral otitis media with effusion. Of the five adults, three had tympanosclerosis; one had bilateral cholesteatoma; and one patient had bilateral keratitis obturans in combination with tympanosclerosis. Hearing improvement and a dry ear was achieved in all the children treated by tympanostomy tube insertion. El-Sayed and colleagues suggested that otitis media is a prominent feature of this disorder and that most subjects suffer from protracted bilateral otitis media with effusion throughout childhood.

Meeks et al. (2000) conducted linkage analysis in eight affected subjects from four families from Saudi Arabia. All patients had a similar ultrastructural phenotype of absent outer dynein arms. Over 300 microsatellite markers were typed and excess homozygosity was identified on chromosome 19q. High density mapping data further restricted the candidate region to 19q13.3-qter. Haplotype analysis in the candidate region confirms linkage in two of the families and non-linkage in the other two.

United Arab Emirates
Stannard et al. (2004) reported three siblings from a consanguineous family of Arabic descent from the United Arab Emirates. The family also had four unaffected children. The affected siblings included a female who developed a wet-sounding cough shortly after birth and had repeated hospital admissions for persistent chest infections. The second sibling was a 4-year-old boy who had a 2-year history of a wet-sounding cough and rhinorrhoea since infancy. The third sibling was a male reviewed at age of 8 months and had respiratory difficulties from birth and was admitted to a special care baby unit shortly after birth. The results of the nasal ciliary biopsies in these three children support the diagnosis of primary ciliary dyskinesia due to a defect of the central microtubule pairs. It is of interest that the ciliary beat pattern in these siblings was circular. This is the beat pattern seen not only in cilia with a transposition defect but also in primary nodal cilia that are found on the ventral surface of the embryonic node. Stannard and colleagues proposed to name this ultrastructure of ciliary dyskinesia as central microtubular agenesis.

References
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Ghazi O. Tadmouri: 30.11.2004