

Ciliopathy with Special Emphasis on Kartageners Syndrome

Ashfaq Ul Hassan*, **Ghulam Hassan****, **Sajad Hamid Khan**, **Zahida Rasool*****, **Afeera Abida******
SKIMS Medical College, Srinagar; **College of Medicine Qassim University; *University of Science & Technology, Awantipora Kashmir, ****Resident Medicine, Ohio, USA*

Abstract:

Cilia are hair-like structures extending from the cell membrane, perform diverse biological functions. Primary defects in the structure and function of sensory and motile cilia result in multiple ciliopathies. The most prominent genetic abnormality involving motile cilia is primary ciliary dyskinesia (PCD) or Kartageners syndrome. PCD is a rare, usually autosomal recessive, genetically heterogeneous disorder characterized by sino-pulmonary disease, laterality defects and male infertility. One of the important components of cilia is the Dynein. Ciliary ultrastructural defects are identified in approximately 90% of PCD patients and involve the outer dynein arms, inner dynein arms, or both. Diagnosing PCD is challenging and requires a compatible clinical phenotype together with tests such as ciliary ultrastructural analysis, immunofluorescent staining, ciliary beat assessment, and/or nasal nitric oxide measurements. Increased understanding of the pathogenesis will aid in better diagnosis and treatment of PCD. The aim of the article is to present the basic defect involved in the etiology of this interesting syndrome.

Key Words: Ciliopathy, Situs Inversus, Laterality defect, Primary ciliary dyskinesia, Axoneme

Correspondence:

*Professor Ghulam Hassan
HoD, Anatomy
College of Medicine
Qassim University
PO Box: 6040, Almlaida-51432
Al-Qassim, Saudi Arabia*

Introduction

Ciliated columnar epithelia move mucus and other substances via cilia, and are found in the upper respiratory tract, the Fallopian tubes, the uterus, and the central part of the spinal cord. Mucociliary clearance is an important primary innate defense mechanism that protects the lungs from deleterious effects of inhaled pollutants, allergens, and pathogens. Ciliated columnar epithelium lines the lumen of the uterine tube, where currents generated by the cilia propel the egg cell, toward the uterus. Cilia are also involved in maintaining left–right axis during embryogenesis.

The movement of chromosomes during mitosis occurs on a bipolar, microtubule-based protein machine, the mitotic spindle. It has long been proposed that poleward chromosome movements that occur during prometaphase and anaphase A are driven by the microtubule motor cytoplasmic *dynein*, which binds to kinetochores and transports them toward the minus ends of spindle microtubules. Results show that dynein inhibitors disrupt the alignment of kinetochores on the metaphase spindle equator and also interfere with kinetochore and chromatid to pole movements during anaphase A. Thus, dynein is essential for poleward chromosome motility throughout mitosis in *Drosophila* embryos.⁽¹⁾ Mutations of Dynein genes encoding motility proteins which are components of sperm tails, and cilia in the respiratory and the reproductive tracts results in inhibition of vital functions.⁽²⁾

Cilia are classified according to their microtubule components as 9+2 and 9+0

Disruption of 9+2 cilia, which move mucus across respiratory epithelia, leads to rhinitis, sinusitis and bronchiectasis. Approximately half of the patients with primary ciliary dyskinesia (PCD) have situs inversus, providing a link between left–right asymmetry and cilia.

9+0 cilia at the embryonic node are also motile and involved in establishing left–right asymmetry. Most 9+0 cilia, however, act as antennae, sensing the external environment. Defective 9+0 cilia of principal cells of the nephron cause cystic diseases of the kidney. In the rods and cones of the retina, photoreceptor discs and visual pigments are synthesized in the inner segment and transported to the distal outer segment through a narrow 9+0 connecting cilium; defects in this process lead to retinitis pigmentosa. Although the function of primary cilia in some organs is being elucidated, in many

other organs they have not been studied at all. It is probable that many more cilia-related disorders remain to be discovered.⁽³⁾

Among the ciliary abnormalities are found: Changes in the structure of the microtubules, uncoordinated ciliary movements caused by the absence of inner or outer or both dynein arms and abnormalities of the kinetosomes and/or rete ridges.

In patients with ciliary dyskinesia bronchitis occurs early in life (during infancy) and usually has a recurrent tendency, so that bronchial biopsy is frequently undergone for diagnostic purposes

It has also been noted that Degenerative disorders of motor neurons include a range of progressive fatal diseases such as amyotrophic lateral sclerosis (ALS), spinal-bulbar muscular atrophy (SBMA), and spinal muscular atrophy (SMA). Although the causative genetic alterations are known for some cases, the molecular basis of many SMA and SBMA-like syndromes and most ALS cases is unknown. It has been noticed that missense point mutations in the cytoplasmic dynein heavy chain result in progressive motor neuron degeneration in heterozygous mice, and in homozygote's this is accompanied by the formation of Lewy-like inclusion bodies, thus resembling key features of human pathology. These mutations exclusively perturb neuron-specific functions of dynein.⁽⁴⁾

Kartageners Syndrome

Primary ciliary dyskinesia (PCD), also known as immotile ciliary syndrome or Kartagener Syndrome (KS), Afzelius' syndrome, Kartagener's triad, Siewert's syndrome, Dextrocardia-bronchiectasis-sinusitis, primary ciliary dyskinesia is a rare *autosomal recessive genetic disorder* characterised by Sinus Inversus, Bronchiectasis and infertility classically.

Symptoms and signs are dyspnoea, productive cough, recurrent respiratory infections, colds, bouts of pneumonia, rheumatoid arthritis, renal abnormalities, turriccephaly, heart defects, malformations of renal vessels, anomalous subclavian artery, dextrocardia, and other abnormalities. Palpitation, otitis media, nasal speech, conductive hearing loss, anosmia, clubbing of fingers.⁽⁵⁾

Efforts to standardize the clinical criteria for the diagnosis of Kartagener's Syndrome have centered on Dextrocardia, Ciliary beat frequency of less than 10 Hz/s, Mean cross-section dynein arm count of less than 2.

If the patient does not have dextrocardia, the identification of primary ciliary dyskinesia becomes the mainstay of diagnosis. Genetic testing ultimately may become the principal means of establishing this diagnosis.⁽⁶⁾ There may be pulmonary artery obstruction *and* maldevelopment of the great arteries.

The symptoms mentioned are caused by an abnormal morphology of bronchial cilia and sperm tails, which can be demonstrated by electron microscopy. The dynein arms normally attached to the nine micro tubular doublets and providing a normal ciliary movement are lacking.

Situs Inversus in Kartagener's Syndrome

It is assumed that during early embryonic life ciliary beats in the growing embryo determine the type of laterality. When ciliary movements are absent laterality may develop fortuitously, thus affecting a situs inversus in about half the affected cases. The numerical evaluation of pedigrees from the literature supports this assumption.

Development of asymmetry along the left-right axis is a critical step in the formation of the vertebrate body plan. Disruptions of normal left-right patterning are associated with abnormalities of multiple organ systems, including significant congenital heart disease.^(7,8) Position of the viscera (heart, lungs, liver, spleen and bowels) is defined very early in embryogenesis. Normally, an asymmetry exists between the left and the right side of the human body, as the liver is on the right and the spleen on the left side. However, defects in asymmetry may occur during embryogenesis and there is a spectrum of malformations ranging from reverse asymmetry (situs inversus) to a complete lack of physiologic asymmetry (situs ambiguous). Amazingly, interplay between motile and sensory cilia is required for determination of left-right axis in early vertebrate development. Several recent breakthroughs indicate that cilia direct left-right asymmetry by signaling within the embryonic node soon after anterior-posterior and proximal-distal axes are established. The node is a transiently appearing, bowl-like structure within the midline notochord containing an

elegant cilia-powered apparatus. In the center of this bowl are cells with a single motile cilium (moving in an unusual vertical motion) that generate vectorial flow to transmit a signal received by primary cilia on the periphery. These sensory cilia bend in response to flow and generate a calcium-dependent response. This response triggers a program resulting in a left-sided, asymmetric heart and asymmetric patterning of visceral organs. Thus, left-right axis formation depends on proper node cell differentiation and cilia function. Accordingly, failure in node cilia function can result in randomization of left-right axis (half have situs inversus).

The recognition of situs inversus is important for preventing surgical mishaps that result from the failure to recognize reversed anatomy or an atypical history. For example, in a patient with situs inversus, cholecystitis typically causes left upper quadrant pain, and appendicitis causes left lower quadrant pain. A trauma patient with evidence of external trauma over the ninth to eleventh ribs on the right side is at risk for splenic injury. If surgery is planned on the basis of radiographic findings in a patient with situs inversus, the surgeon should pay careful attention to image labeling to avoid errors such as a right thoracotomy for a left lung nodule.

Infertility in Kartagener's Syndrome

Infertility is common, due to defective ciliary action in the fallopian tube in affected females or diminished sperm motility in affected males.

In Kartagener's syndrome (KS), primary defects of the ciliary axoneme cause dyskinetic ciliary motion. Because ciliary motion is an important factor in normal ovum transport, ciliary dyskinesia may cause infertility. On the other hand, the existence of some ciliary activity, albeit abnormal, may account for fertility in some women with KS. Biopsies of tubal mucosa were obtained at laparoscopy for ovum recovery during an in-vitro fertilization cycle. Ciliary activity, measured by laser light-scattering spectroscopy, was detected in all tubal specimens; however the majority of regions sampled showed no activity. In active regions, beat frequency ranged from 5 to 10 Hz, approximately 30% of normal.

- Electron microscopy showed similar morphological *defects in* tubal mucosa.

- The number of cilia per cell was approximately 20% of normal.
- The major ultrastructural abnormality was an absence of the central microtubules.

Electron microscopy demonstrated that the majority of cilia lacked dynein arms and radial spokes and that various defects of microorgans existed in the sperm. The most frequent defect was total defect of axoneme followed by defect of inner dynein arms in the sperm. These findings suggest an association between the structural abnormality of absent inner dynein arms and immotility of cilia and sperm in Kartagener's syndrome⁹

The Chest in Kartagener's Syndrome

Mucociliary clearance is an important primary innate defense mechanism that protects the lungs from deleterious effects of inhaled pollutants, allergens, and pathogens

The main consequence of impaired ciliary function is reduced or absent mucus clearance from the lungs, and susceptibility to chronic recurrent respiratory infections, including sinusitis, bronchitis, pneumonia, and otitis media. The cause of this disease lies in malfunctioning cilia. Cilia line the entire respiratory tract (lungs, nose, sinuses, and middle ear). Cilia defend these surfaces by moving any inhaled particles (e.g. bacteria) forward out of the lung, like a miniature escalator. Family studies make it easier to track genes and figure out which genes might be associated with disease. Preliminary studies have elucidated some genetic mutations associated with PCD⁽¹⁰⁾

In one study conducted examination of ciliary movement of the bronchus revealed immotility in all of the five patients examined. The ultrastructure showed ciliary Dynein arm defects in all patients. Histopathological examination of lung specimens obtained at autopsy or by video-assisted thoracoscopic surgery showed oblitative thickening of the walls of the membranous bronchioli with infiltration of lymphocytes, plasma cells and neutrophils, but most of the distal respiratory bronchioli were spared and alveolar spaces were overinflated. Pathologically, the diffuse centrilobular small nodules on the chest CT mainly corresponded to membranous bronchiolitis. Very few cases report demonstrating that the association of diffuse bronchiolitis might be one of the characteristic features of the lung in Kartagener's syndrome⁽¹¹⁾

Jonsson *et al.*⁽¹²⁾ described a 21-year-old man with recurrent sinusitis, bronchitis and otitis media, situs inversus viscerum including left-sided appendix with appendicitis at age 12, and a normal 4-year-old son. Electron microscopy of nasal and bronchial mucosa showed abnormal orientation of the basal processes of the cilia and absent dynein arms but completely normal sperm.

Eavey *et al.*⁽¹³⁾ found significantly fewer ciliary outer dynein arms in all 4 patients with full-blown Kartagener syndrome and in 2 of 5 patients with sinusitis and bronchiectasis but no dextrocardia. No changes were found in carriers or in any other persons studied. The count of outer dynein arms was consistent in a given individual.

Sturgess *et al.*⁽¹⁴⁾ analyzed 46 cases from 38 families: 20 males and 26 females. Situs inversus was present in 26. The ultrastructural change in respiratory tract cilia was deficiency in outer dynein arms (in 19), inner dynein arms (in 3), both inner and outer dynein arms (in 15), and radial spokes (in 5) and involved a microtubular transposition anomaly in 4. Segregation analysis was consistent with autosomal recessive inheritance. The finding of various structural defects suggests that there are several genetic determinants. Examination of paternal age and birth order gave no evidence of new dominant mutation.

Anomalies of the bronchial cilia were studied in 5 children with recurrent pulmonary infections. Case 1 had Kartagener's syndrome and an absence of the inner and outer dynein arms in most cilia, although a few shortened and even some normal arms could be seen. Cases 2 and 3 had unilateral bronchiectasis without family history of Kartagener's syndrome. Serial studies of the bronchial epithelium at times showed a bilateral lack of the inner dynein arms and a partial lack of outer arms. These abnormalities persisted in these 2 children after they had recovered from the acute pulmonary infection but disappeared after 6-8 months of antibiotic treatment. Cases 4 and 5 had recurrent pulmonary infections without bronchiectasis and many shortened outer dynein arms could be seen, but these anomalies disappeared after recovery. In all 5 children such architectural ciliary anomalies were present as megacilia, fused cilia, naked cilia, and completely disorganised axonemas. These architectural defects were particularly numerous in the children without bronchiectasis. Observations suggest that

anomalies of the bronchial ciliary microtubular system may not only be congenital but may also be acquired; this might well help to explain some cases of repeated respiratory tract infection and bronchiectasis.⁽¹⁵⁾

Ciliated bronchial or nasal epithelium from 20 Polynesian bronchiectatic patients was examined in an electron microscope. In all patients there was a partial or complete loss of dynein arms. Also, in many patients other ciliary abnormalities were present with a high proportion, often over 25%, of cilia affected. This contrasts with a control group where ciliary abnormalities were infrequent. Mucociliary clearance, measured by imaging 99mTc sulfide dust with a gamma camera, was either absent or markedly reduced in these bronchiectatic patients.⁽¹⁶⁾

Conclusion

It can be concluded that a defect in one micro ultrastructural component of cilia or the cilia itself can give rise to a wide variety of clinical symptoms of devastating consequences. A ciliary defect can present with more severe and more widespread variety of diseases which are not restricted to the symptomatology confined to the Kartagener's syndrome. The need of having a basic knowledge of Histology, Embryology along with knowledge of Medicine can act synergistically to boost the diagnostic capacity of any physician.

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