Recent Trends in Diagnosis And Management Of Immotile Cilia Syndrome

By

Dr. Ola Mostafa Abd El-kader

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Under supervision of

Dr. Samiha Samuel Wissa
Professor In pediatrics

And

Dr. Mohamed Badawy
Assistant Professor In Pediatrics
Faculty of Medecine
Cairo University

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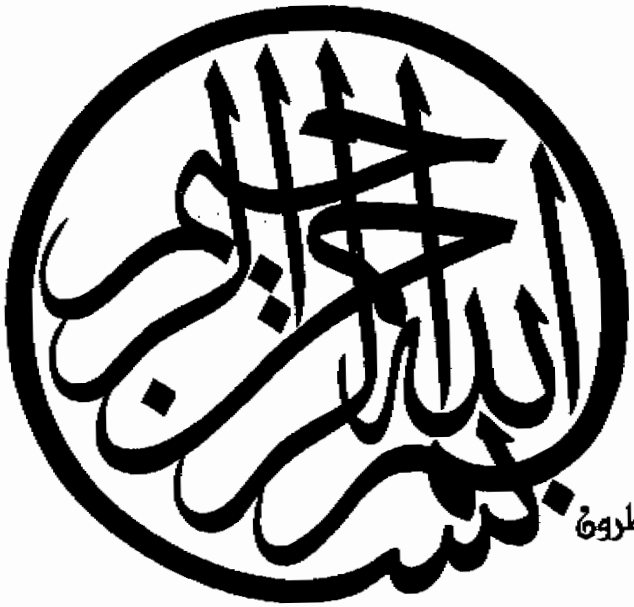

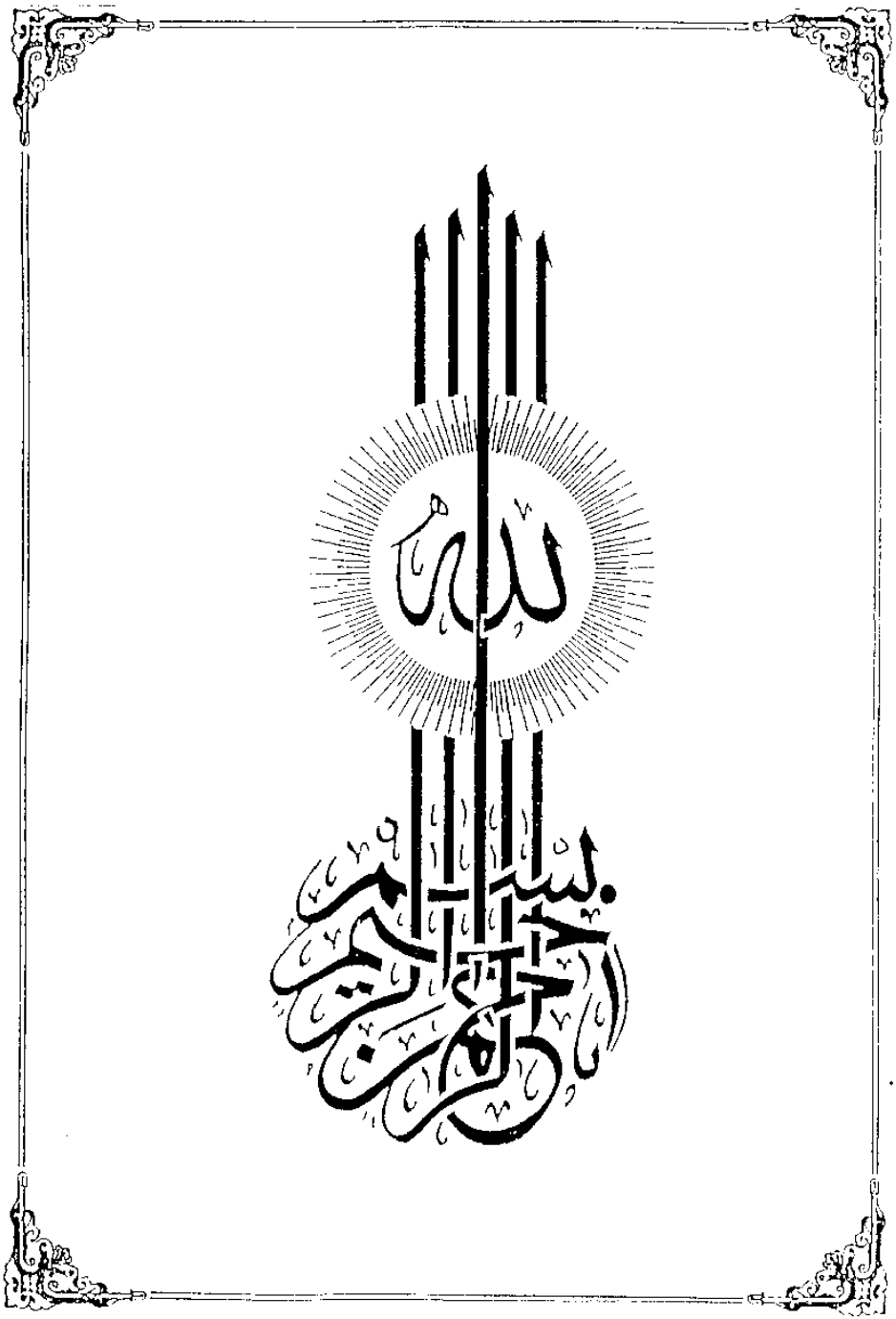

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LIST OF ABBREVIATIONS

AMMD : Aerodynamic Mass Median Diameter .

ATPASE : Adenosine Triphosphatase .

CBF : Ciliary Beat Frequency .

CF : Cystic Fibrosis .

CT : Computerized Tomography .

DNA : Deoxyribo Nucleic Acid .

ECG : Electro Cardio Gram .

FESS : Functional Endoscopic Sinus Surgery .

HLA : Human Leukocytic Antigen .

HLT : Heart - Lung Transplantation .

ICS : Immotile Cilia Syndrome .

KS : Kartagener's Syndrome .

MCT : Mucociliary Transport .

MT : Microtubule .

NO : Nitric Oxide .

PCD : Primary Ciliary Dyskinesia

PE : Pressure Equalization .

PPB : Part Per Bilion .

PMNS : Polymorphnuclear leukocytes .

RP : Retinitis Pigmentosa .

SOM : Secretory Otitis Media .

SVC SYNDROME : Superior Vena Cava Syndrome .

US I : Usher Syndrome Type I

Contents

INTRODUCTION

Sites of ciliated epithelia :

Ciliated epithelia appear in a number of tissues in mammals. Both the upper and lower air ways and the mucosa of the middle ear and eustachian tube are lined by a ciliated epithelium. In males, ciliated epithelium occurs on the ductuli efferentes on the border between the testis and the epididymis, in females the endometrial lining of the cervix and oviducts are populated by a lining of ciliated cells. Ciliated cells also appear in the ependyma of the brain. At these sites the primary function of the ciliated cells appears to be the clearance of debris and the transport and circulation of cells and fluids. The inside of the cornea is mono ciliated, that is each cell carries a single cilium **(Afzelius, 1981, - Carson and Collier, 1988).**

Modification and specialization of cilia are associated with sensory organs among mammals. Olfactory cells possess modified cilia having a normal microtubular configuration but without dynein arms. Also, hair cells of the vestibular organ each possesses a Kinocilium, a single long, rigid, non motile cilium. The eye most likely represents the highest specialization of the cilium seen in higher vertebrates with inner and outer segments of the rod cells being linked by a highly modified cilium. Spermatozoa are the only cells among higher vertebrates possessing true, albeit modified flagella, their function being the locomotion of the male gamete to the ovum for fertilization **(Carson and Collier, 1983).**

The cilium : Function and Structure :

Mucociliary clearance plays an important role in the lung defence mechanism, to clear the air way mucosa from inhaled particles, bacteria and cellular depris. This transport function is dependent on the beat frequency and coordination of cilia, rheological properties of periciliary fluid and mucus secretion **(Kobayashi et al, 1990).**

Development of cilia ***(ciliogenesis)*** takes place after replication and transformation of the cell centrioles to basal bodies. Cilia originate from basal bodies which also serve to anchor them to the cell. Cilia are long, thin, mobile projections from the luminal surface of the cell. Each cellcontainsapproximately 200 cilia* beating at 1000 min in organized waves of contraction **(Mygind, 1981) (Fig. 1).** On electron microscopy, cross- sectional structure of the central core ***(axoneme)*** of a respiratory tract cilium is highly ordered; nine peripheral pairs of microtubules surround a central microtubular doublet ***("9+2 pattern").*** Each peripheral pair of microtubules is connected to adjacent doublets by nexin links. Appended symmetrically to the comparable microtubule of each peripheral doublet are two hook like structures ***(inner and outer dynein arms).*** The dynein arms are made up of the protein dynein, which has ATP- ase activity, and are oriented in a colck wise direction. Surrounding the central pair of tubules is a sheath, and a series of radial spokes connect the central tubules to each of the outer doublets. The same anatomic features are evident in the tails of the spermatozoa.This characteristic structure is seen along most of the length of the axoneme with certain changes at the base and tail as shown in **Fig. 2.**

(*) There exists some doubt regarding the number of cilia percell. differences in the methods used and the mucosa studied may account for the discrepancies.

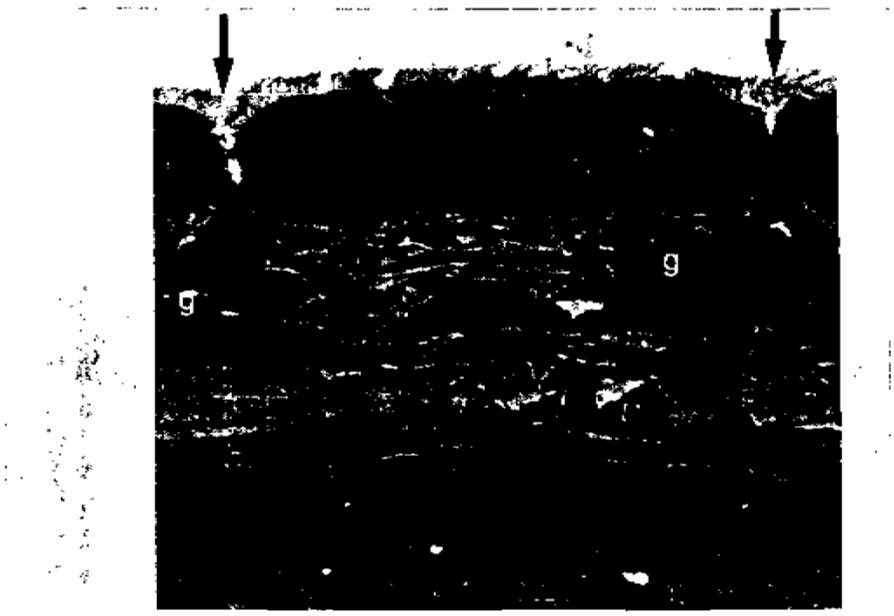


Fig. 1: The mucosa of the respiratory portion of the nasal cavity. The cilia of normal subject show cohesive wave form.

(Leeson et al, 1988).

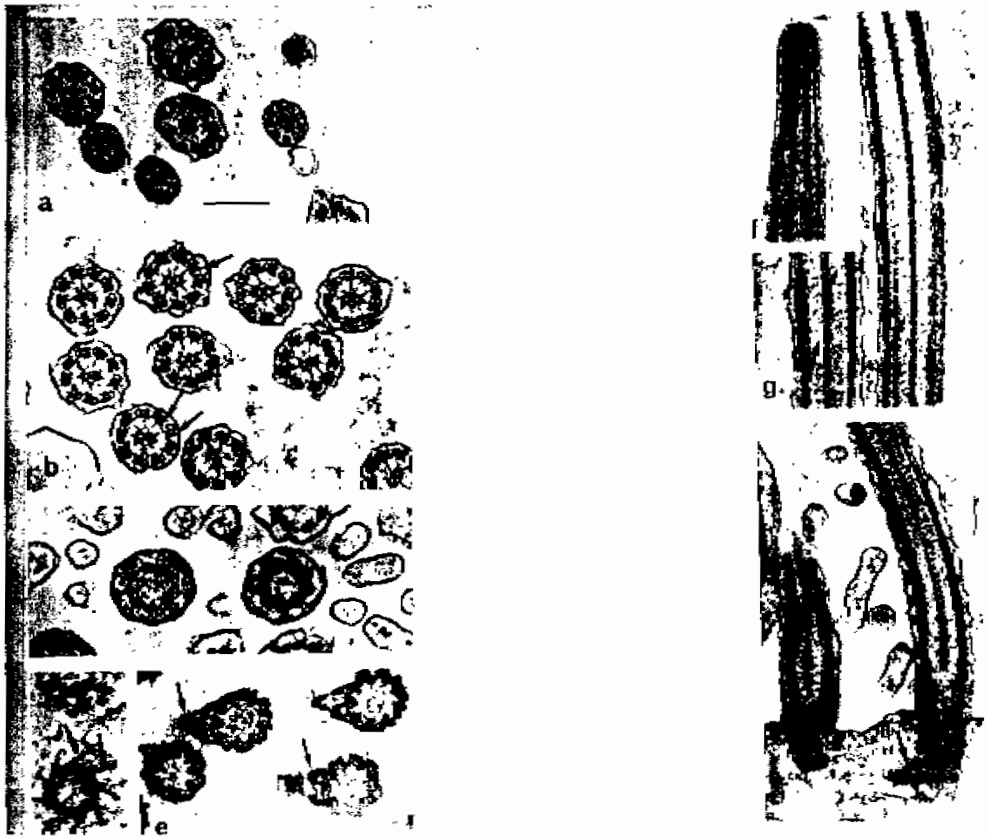


Fig. 2: Tansmission electron micrographs of Cross - Sectional (a - e) and longitudinal - sectional profiles (f - h) of cilia from normal humans showing normal structure and arrangement of microtubules. Near the tip of the cilia the 9 doublets are replaced by single peripheral microtubules (a). In longitudinal section, some fine projections are seen at the tip of the cilia (f, arrow). The (9+2) microtubular pattern is evident along most of the length of the axoneme with prominent dynein arms (b, small arrows), and distinct radial spokes. Radial spokes are also easily recognizable from longitudinal sections of cilia (g, arrows). The central pairs of microtubules are usually oriented in one direction (b). Near the base of the cilia the pair of microtubules begin to disappear, the doublets become connected to each other, and the microvilli begin to appear among the cilia (c). As the axoneme enters the cell body, the peripheral doublets become triplets (basal body), with alar sheets attaching to the triplets (d, arrows). Further below the insertion of cilia into the cell body, basal feet are seen projecting from the basal body, and they generally point to the direction of the effective ciliary beat (e., h., arrows). From Rossman et al, (1984).

It is important to know that, even in normal subjects there is a small percentage of abnormal cilia **(Fig. 3 - Table 1.).**

The rhythmic motion of cilia affecting mucociliary transport in the respiratory tract is produced by the linking via dynein arms of one pair of outer tubules to the adjacent doublet and the sliding of actin filaments of the microtubular pairs past each other, much as occurs with actin and myosin in muscle. The hydrolysis of adenosine triphosphate by the dynein ATP ase powers this reaction. Since the outer filaments are tied together by nexin links and tied to the central sheath by radial spokes, the sliding of the microtubule pairs is converted to a bending motion of the ciliary shaft. The direction of bending is detected by the relationship of the peripheral tubules vis-a-vis the central tubules. Coordinated bending of sheets of cilia on respiratory epithelial cells is necessary to move the overlying mucous blanket towards the larynx. This is made possible by orientation of central doublet pairs within 25° of each other **(Swartz, 1988).**

General Idea of the Immotile Cilia Syndrome :

The immotile cilia syndrome is a genetic disorder whose molecular lesion produces immotile or otherwise defective cilia. As a result of wide distribution of cilia, symptoms produced include sinusitis, otitis, chronic rhinitis, chronic or recurrent bronchitis, bronchiectasis, male sterility, corneal abnormalities and impaired olfactory function **(Swartz, 1988).** Although ciliary abnormalities are presumbly present before birth, affected neonates have normal birth weight. Growth and development usually progress within normal percentiles for age. Symptoms may appear in the form of respiratory distress in the neonatal period. However, in the majority of cases manifestations of respiratory disease may be recognized only in late infancy or early childhood. The severity of symptoms varies considerably **(Sturgess and Turner, 1983).** However, the long term

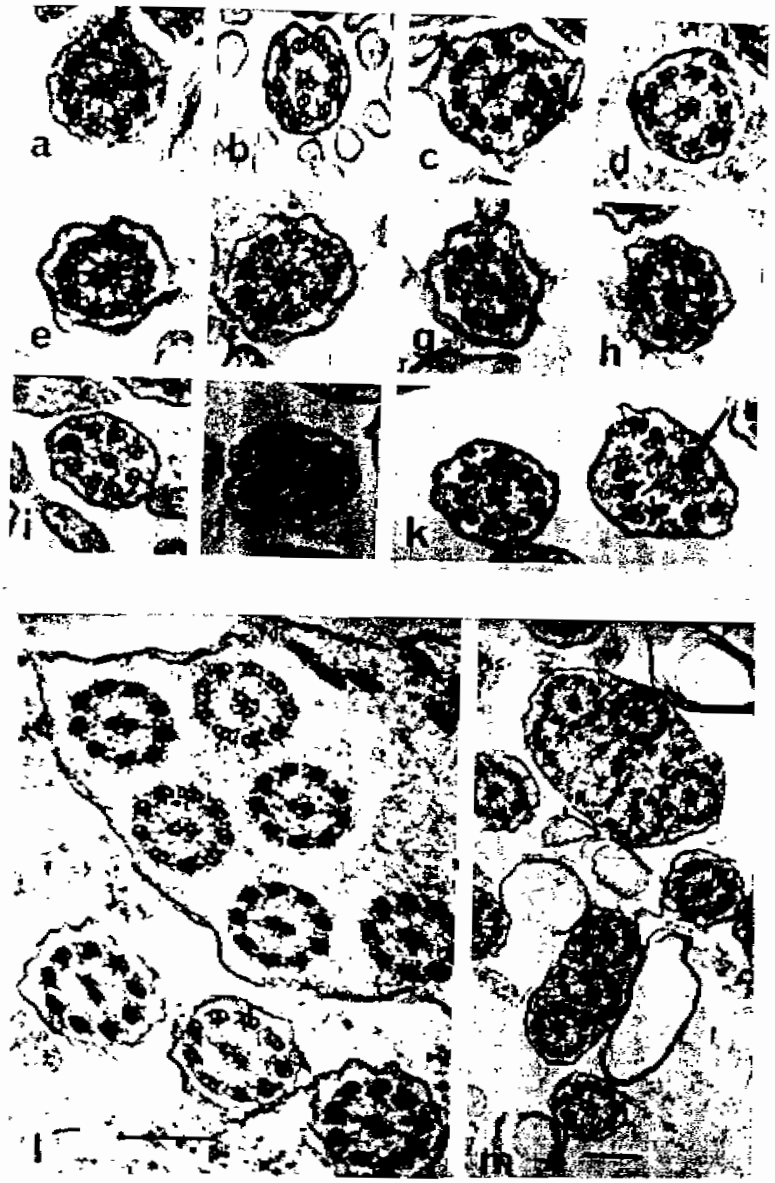


Fig. 3: Cross - Sectional profiles of cilia from normal humans showing abnormal structures. Extramicrotubular doublets can be found either outside (a) or inside (b) the 9+2 complex - Additional single microtubules can be found both outside (b - d) or within the 9+2 complex (e. and f.). In the case of the latter (e. & f.), the abnormality is classified as cilia having extra central microtubules.

Among the peripheral doublets, occasionally a single microtubule is found instead of a doublet (g), or one of the 9 peripheral doublets is missing (h). Alternatively, the central pair of microtubules may be missing, with one or more peripheral doublets translocated towards the center of the cilia (i. & j.). Translocation of the microtubules can take place even with the central pair present (K, arrow). Compound or multiple cilia are found where two or more axonemes become enclosed by one cell membrane (l. & m.). The dynein arms and radial spokes are usually found in these cilia.

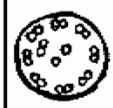
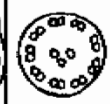
 % Normal Cilia	 % With Extra Peripheral MT.	 % With Missing peripheral MT.	 % With Translocated Peripheral MT.	 % Multiple Cilia.	 % With Extra Central MT.	 % With Missing Central MT.	 % With Translocated Central MT.	
95.2 ± 3.2	0.9 ± 1.7	1.3 ± 1.3	0.8 ± 1.1	1.0 ± 1.5	0.1 ± 0.2	0.4 ± 0.8	0.05 ± 0.2	Normal Non-Atopic 6.965 Cilia
96.9 ± 1.7	0.5 ± 0.7	0.8 ± 1.3	0.9 ± 0.8	0.5 ± 0.6	0.2 ± 0.2	0.2 ± 0.4	0	Normal Atopic 1.726 Cilia
97.2 ± 1.8	0.3 ± 0.2	0.7 ± 0.6	0.5 ± 0.4	0.5 ± 0.4	0.3 ± 0.07	0.7 ± 1.1	0.03 ± 0.07	Smokers 5.180 Cilia
96.00 ± 3.0	0.6 ± 1.4	1.1 ± 1.1	0.7 ± 0.9	0.8 ± 1.2	0.09 ± 0.2	0.5 ± 0.8	0.04 ± 0.1	Pooled Data 13.871 cilia Total Atypical 0.555 Cilia
	Total % of Peripheral MT Defects 2.6 ± 1.9.				Total % of Central MT Defects 0.6 ± 0.8.			

Table 1: Proportion of normal cilia and cilia with specific ultrastructural defects in the "healthy" population. Radial spokes and dynein arms were omitted in the above drawings of defective cilia in order to emphasize the specific abnormality evaluated. (Rossman et al, 1984).

prognosis for patients is relatively good, some patients living to an advanced age. Some patients over 35 years of age with this syndrome show on pulmonary function testing only mild to moderate airways obstruction. Exacerbations of infections tend to be more severe in late childhood and adolescence; in adult years, there may be an amelioration of symptoms **(Swartz, 1988).**

The criteria for diagnosis of the immotile cilia syndrome include: **(1)** clinical manifestations of recurrent and chronic upper and lower respiratory tract infections such as rhinitis, sinusitis, otitis, bronchitis and bronchiectasis; **(2)** absence or near absence of tracheobronchial or nasal mucociliary transport; **(3)** total or near total absence of dynein arms of the cilia in nasal or bronchial mucosa; rarely, ultrastructural axonemal defects other than absent dynein arms such as absent or defective radial spokes or transposition of a peripheral microtubular doublet to the center of an axoneme are associated with the syndrome; and **(4)** sterility in males associated with living but immotile spermatozoa with similar axonemal ultrastructural abnormalities. In women, reduced fertility is a feature as well. The term immotile cilia syndrome is generally used to describe this tetrad of clinical and laboratory findings associated with dynein deficient cilia. However, the term ciliary dyskinesia syndrome or dyskinetic cilia syndrome have been suggested as a result of the finding that the cilia in some patients with this syndrome, although anatomically abnormal, are in fact motile, albeit with abnormal motions **(Swartz, 1988).**

Diagnosis of the ciliary defects rests with the ultrastructural examination of the cilia in the transmission eletron microscope **(Sturgess and Turner, 1983)** obtained from mucosal biopsies of the nasal turbinates or the trachea. **(Escribano et. al, 1993).** It is recommended that 50 to 100 cilia with proper orientation should be studied before a diagnosis of immotile cilia syndrome is