

Case Report

KARTAGENER'S SYNDROME – A RARE CASE SERIES IN FEMALE PATIENTS

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ABSTRACT

Kartagener's syndrome is a rare autosomal recessive genetic disorder consists of situs inversus, chronic sinusitis, and bronchiectasis with primary dysfunction in the ciliary motility. The defective movement of cilia leads to recurrent respiratory tract infection and infertility. We hereby report two cases of this rare entity in the female patients who were presenting with recurrent respiratory tract infections and on investigation found to have Kartagener's syndrome. Although, there is no specific treatment, failure to recognize this condition may subject the patient to unnecessary repeated admissions and multiple unnecessary investigations and irrelevant treatment. The need for a high index of suspicion to make an early diagnosis in such patients so that whenever possible, options for timely treatment may be offered and genetic counselling is provided.

Keywords: Bronchiectasis, Sinusitis, Situs Inversus, Ciliary Dysmotility

INTRODUCTION

Kartagener's syndrome is one of the larger groups of ciliary motility disorders group called as primary ciliary dyskinesias (PCDs). It is an autosomal recessive genetic disorder, comprising a triad of situs inversus, bronchiectasis and sinusitis. This condition was described for the first time by Siewert in 1904, therefore some people call it siewert syndrome but the details of the condition were given by Manes Kartagener's in 1933 and it is commonly known as Kartagener's syndrome and reported four cases along with it 1933 (Arunabha *et al.*, 2014).

The estimated prevalence of PCD is about 1 in 30,000 though it may range from 1 in 12,500 to 1 in 50,000 (Arunabha *et al.*, 2014). In KS, the genetic defect leads to impaired ciliary motility which causes recurrent chest, ear, nose, throat and sinus infections, and infertility. Early diagnosis is important for the preservation of pulmonary function, quality of life, and increase in life expectancy in this disease.

CASES

Case 1

A 25 year old female came to chest OPD with complaints of recurrent cough with expectoration, head ache for 1 month. History of multiple similar episodes for past 9 years. On General examination patient is anaemic with grade 2 clubbing. Local examination of the paranasal sinus shows tenderness over the bilateral frontal and maxillary sinuses. Systemic examination shows apical impulse heard at right 5th inter costal space at mid clavicular line instead on left side. On chest percussion, cardiac dullness was elicited in right precordium. Hepatic dullness was elicited on the left side with a tympanic note on the right side. On auscultation, fine coarse crepitation heard over bilateral infra mammary, infra axillary and infra scapular area with heart sounds being best heard on the right hemi thorax. Chest X-ray postero-anterior (PA) view [Figure 1] revealed cardiac apex and aortic arch on the right side, suggesting dextrocardia and bilateral para cardiac cystic bronchiectatic changes and the hepatic shadow was seen on the left side and gastric fundus on the right side suggestive of situs inversus totalis. CT-Paranasal sinuses [Figure 2] shows mild diffuse mucosal thickening of the all the para nasal sinuses suggestive of pan-sinusitis. CT-scan thorax plain [Figure 3,4,5] was done which showed features of dextrocardia with right sided aortic arch and bilateral cystic and tubular bronchiectasis. Upper abdomen cuts section shows complete situs inversus with hepato-biliary system on the left side and spleen, gastric fundus and splenic flexure on right side with a raised right dome of diaphragm.

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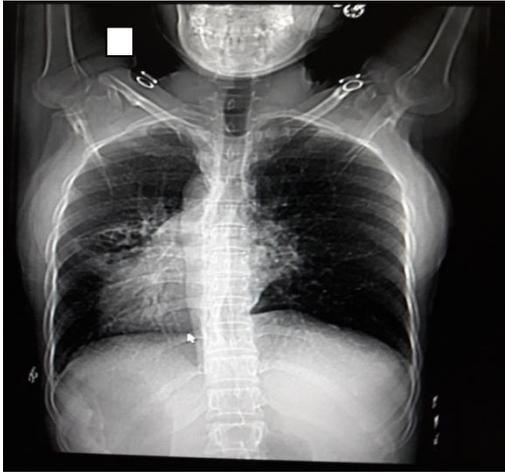


Figure 1: Chest X Ray Shows Dextro-Cardia with Bilateral Para-Cardiac Bronchiectasis with Liver on Left Side, Spleen and Stomach on Right Side

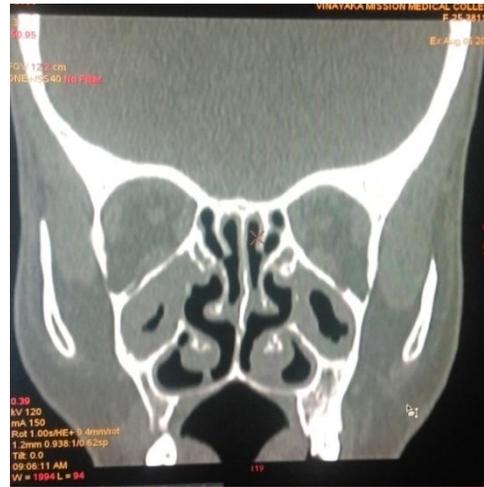


Figure 2: CT Para-Nasal Sinus Coronal Section Diffuse Soft Tissue Opacification of Bilateral Maxillary Sinus



Figure 3: CT Thorax Sagittal Section Lung Window Shows Bilateral Para-Cardiac Bronchiectasis

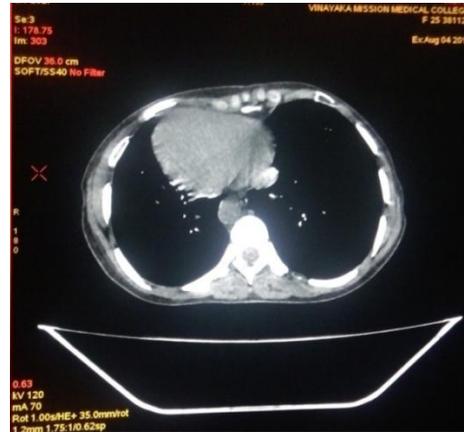


Figure 4: CT Thorax Mediastinal Window Shows Dextro-Cardia with Right Sided Aortic Arch



Figure 5: CT Upper Abdominal Section Shows Liver on Left Side, Spleen and Stomach on Right Side

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Case 2

A 12 year old female child came to paediatric OPD with complaints of recurrent cough with expectoration, headache for 6 month with a history of multiple similar episodes for past 5 years. On General examination patient was found normal. Systemic examination showed apical impulse heard on right side. Patient was referred to USG (Figure 6, 7) ultrasound showed spleen, seen in the right side and liver seen in the left side. IVC and hepatic veins were seen in the left side.



Figure 6



Figure 7

Water Views of the PNS (Figure 8) showed diffuse radio-opacification bilateral maxillary and frontal sinus. Frontal chest radiograph (Figure 9) showed dextrocardia with bilateral peri-hilar prominent bronchial markings.

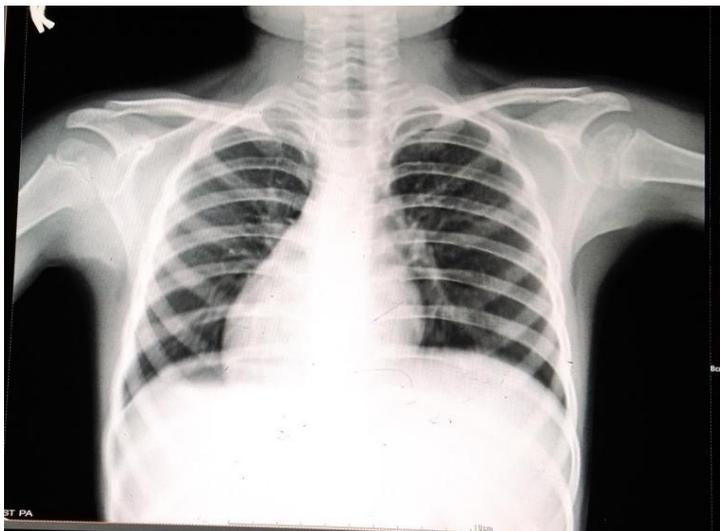


Figure 8

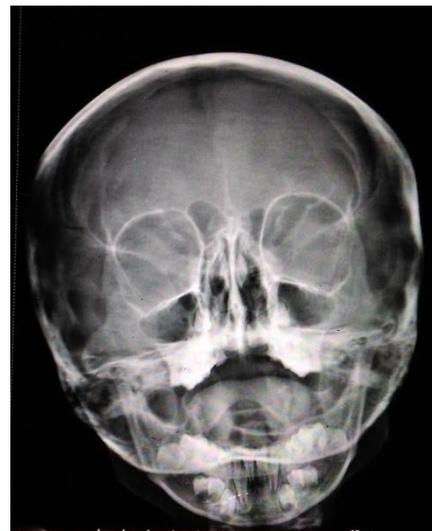


Figure 9

DISCUSSION

Who is Kartagener?

Kartagener's was a physician in Zurich in 19th century who was interested in cardio-respiratory disorder, he was born in 7 January 1897 in Galezian, Czechoslovakia, and he migrated to Switzerland in 1916 and obtained his medical qualification in 1924, in addition to cardio-respiratory interest he had good knowledge in biochemistry and mathematics, Association bronchiectasis, recurrent episodes of sinusitis

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and situs inversus had been recognised by Sievert 3 decades earlier, but the name was given by Kartagener's.

Pathophysiology

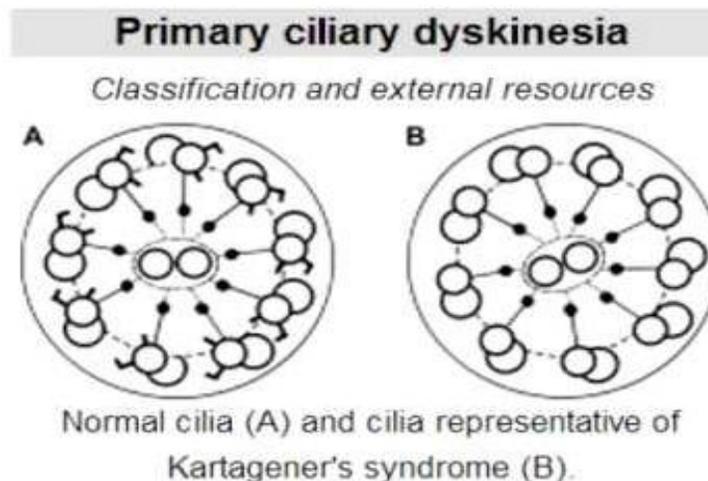
Patients with Kartagener's syndrome have lack of ciliary activity which facilitates bacterial activity and predisposes sinus and bronchus to infection. Absence or shortening of the dynein arm, that is responsible for the coordinate bending of the cilia is seen in 50% of cases (Burgess *et al.*, 2003). Impaired cell motility seen during embryogenesis results in situs inversus. It has been proposed that normal ciliary beating is necessary for visceral rotation during embryonic development. In patients with PCD half of the patients will have situs inversus i.e. will because of KS and the other half normal situs because of random rotation (Bali *et al.*, 1999). In rare cases no structural ciliary abnormality is detectable even though ciliary function is abnormal and the clinical syndrome is typical (Heron and Murphy, 1980; and Schidlow and Katz, 1983).

Patients with Kartagener's syndrome may have either situs solitus i.e dextrocardia only or situs inversus totalis where all the viscera are on the opposite side, including left sided appendix (Jonsson *et al.*, 1982). It is associated with mutation in genes, mainly affecting DNAI1 on 17 chromosome 9p21-p13, DNAH5 14 chromosome 5p15-p14 and DNAH11 on 18 chromosome 7p21 which results in numerous defects including structural 19 abnormalities of the dynein arms, radial spokes, and microtubules of the cilia (Pifferi *et al.*, 2001; Blouin *et al.*, 2000; Bent and Olearczyk, 2007).

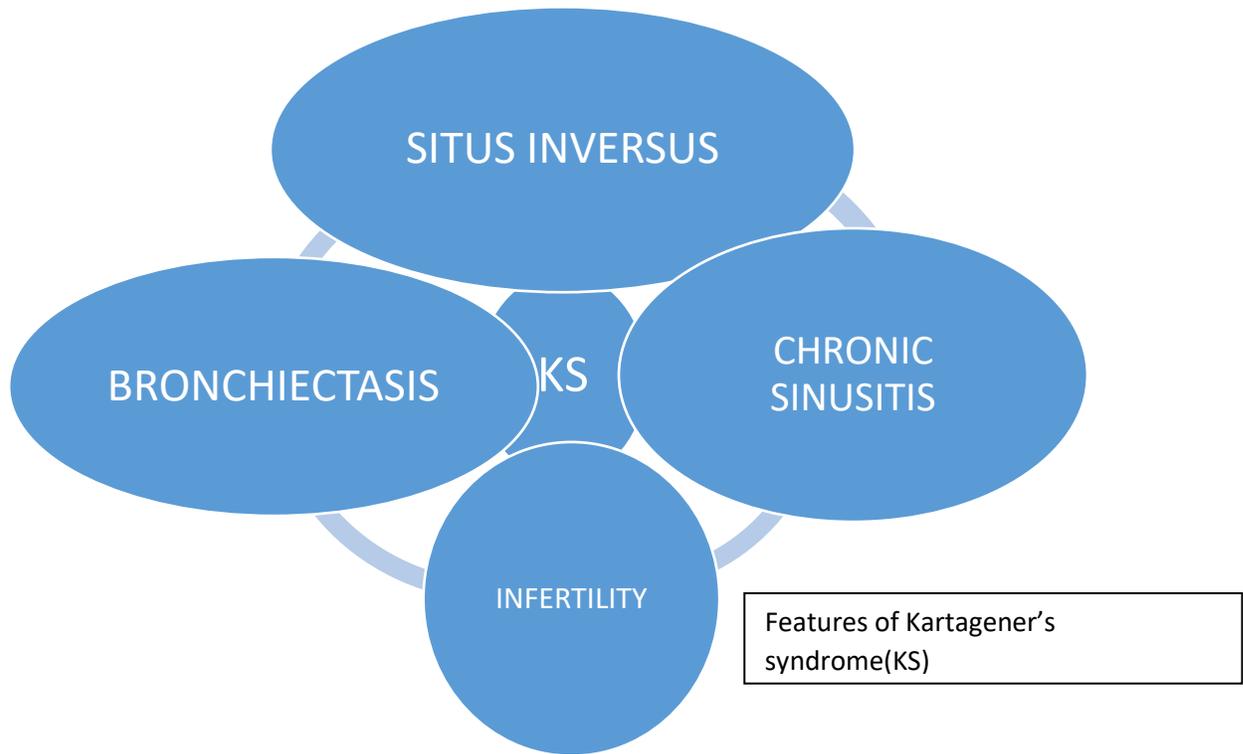
Normal Functions of Cilia is necessary During Development to Ensure Proper Rotation of Developing Organs in the Chest and Abdomen. In Bronchus Respiratory Clearance of Microorganism and Dust Particles. In Testis Motility of Sperms in Vas Deferens. In Uterus Motility of Ovum in Fallopian tube.

Each ciliated cell gives rise to approximately 200 cilia that vary in length from 5 to 6 mm and decrease in size as the airway becomes smaller. Patients with primary ciliary dyskinesias exhibit a wide range of defects in ciliary ultra structure and motility, which ultimately impairs ciliary beating and mucociliary clearance. The most common effect, first described by Afzelius (1976), is a reduction in the number of dynein arms, which decreases the ciliary beat frequency. Sturgess *et al.*, (1979) described how the radial spoke, which serves to translate outer micro tubular sliding into ciliary bending, was absent in some patients with primary ciliary dyskinesias.

A recent study showed that heterotaxy (situs ambiguous or laterality defect other than situs inversus totalis) occurs with a prevalence of at least 6% and can be associated with complex congenital heart disease in PCD. Hydrocephalus occurs rarely in PCD, although a frequent feature in mouse models of PCD, suggesting that ependymal ciliary dysmotility has greater implications in mice. Retinitis pigmentosa, polycystic kidney disease, liver cysts and biliary atresia (all features of ciliopathies of sensory cilia) have been reported rarely in PCD (Jonsson *et al.*, 1982) suggesting that there may be overlap of diseases associated with defects in motile and sensory cilia.



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Clinical Features

Kartagener's syndrome is an autosomal recessive disorder with a triad of bronchiectasis, recurrent episodes of sinusitis and situs inversus. It is an entity of primary ciliary dyskinesia with an incidence of 1 in 20000–60000.

Females can present with subfertility due to sluggish movement of ova in the fallopian tubes, while males demonstrate infertility secondary to immotile spermatozoa.

Kartagener's syndrome can have variable presentations and severity due to its multisystem involvement and reversal of viscera orientation. There are currently no reliable noninvasive diagnostic methods for this disease and the correct diagnosis is often delayed by years, causing irreversible pulmonary damage with subsequent morbidity.

There was a 98% reduction of level of nasal nitric oxide concentration in patients with Kartagener syndrome compared to age-matched controls suggesting that nitric oxide measurements could be of help in the early diagnosis and hence management of the disease process. Early diagnosis and treatment is important to prevent long term sequel and morbidity associated with it. Genetic counseling, social, psychological and fertility issues should be addressed once it is diagnosed and help these patients to live with.

Kartagener's syndrome without morbidity and in a dignified way. Differential diagnosis is from cystic fibrosis (an inherited disorder), Young's syndrome, in addition to features of Kartagener's syndrome, has azoospermia.

Cystic fibrosis is a disorder affecting fluid secretion in exocrine glands and epithelial lining of GIT, respiratory system and reproductive system.

Kartagener's syndrome should be kept in mind in a patient presenting with:

1. Recurrent sinusitis and bronchiectasis.
2. Asthma like symptoms and signs responding poorly to conventional treatment.
3. Recurrent lower respiratory tract infections causing fever, sweating and weight loss, tempting the physician to give a trial of antituberculous drugs. From the preceding discussion, it is also clear that those patients with Kartagener syndrome having situs inversus totalis will present with left sided appendicitis if

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they develop this problem at some stage in their lives. Having situs inversus totalis will present with left sided appendicitis if they develop this problem at some stage in their lives.

Most males are sterile, but many females have a lowered fertility. About 50% of the people affected with primary ciliary dyskinesia have situs inversus, so, they fit in the criteria for Kartagener's syndrome (Bent and Olearczyk, 2007).

Investigation

Nasal mucociliary clearance can be measured by the nasal saccharin transit time" test in which a saccharin pellet is placed on the anterior end of the inferior turbinate and the time taken for the subject to notice the taste is recorded. This test requires the patient's co-operation and is not reliable in children under 10 years of age. Nasal cilia are easily accessible, and can be obtained from the inferior turbinate without anesthesia by a non-invasive brush technique. Ciliary beat frequency can then be assessed by light microscopy and photometric techniques, and cilia fixed on electron microscopy (Cancan *et al.*, 1988).

Demonstration of abnormal ciliary movement needs electron microscopic studies of biopsies obtained from the nasal mucosa or trachea. However, these procedures are invasive and available only at specialized centers, therefore, the diagnosis of Kartagener's syndrome in this case was clinical, supported by imaging studies.

Diagnosis of primary ciliary dyskinesia (PCD) lacks a "gold standard" test and is therefore, based on combinations of tests including nasal nitric oxide (n NO), high-speed video microscopy analysis (HSVMA), and genotyping and transmission electron microscopy (TEM). There are few published data on the accuracy of this approach. Combination testing was found to be a highly accurate approach for diagnosing PCD. HSVMA alone has excellent accuracy, but requires significant expertise, and repeated sampling or cell culture is often needed. TEM alone is specific but misses 21% of cases. nNO (≤ 30 nL·min⁻¹) contributes well to the diagnostic process. In isolation nNO screening at this cut-off would miss ~10% of cases, but in combination with HSVMA could reduce unnecessary further testing. Standardisation of testing between centres is a future priority (Jackson *et al.*, 2016).

List of Investigations for Diagnosing Kartagener's Syndrome

- Saccharin clearance - >1hr – significant
- Genetic testing - Dna i 1 & dna h 5
- Nasal no concentration - Reduced.
- Mucociliary clearance time - Decreased (5-20 mins)
- Ciliary beat frequency - Decreased (10-15 Hz)

Cystic fibrosis excluded by nasal nitric oxide concentration which is autosomal recessive inheritance which involves the mutation of CFTR gene (chromosome – 7). Clinical features includes chronic bacterial infection, bronchiectasis, exocrine pancreatic insufficiency, intestinal dysfunction - meconium ileus, abnormal sweat gland function, urogenital dysfunction. Investigation includes sweat chloride test >60 meq (diagnostic) with abnormal nasal potential difference and DNA testing

High Resolution CT Images Help in Assessment of Severity and Scoring of Bronchiectasis.

Score 0 indicates no evidence of bronchiectasis;

Score 1 mild bronchiectasis with bronchial dilatation two times the diameter of the accompanying blood vessel,

Score 2 moderate bronchiectasis with bronchial dilatation two to three times' vessel diameter

Score 3 severe bronchiectasis with bronchial dilatation more than three times vessel diameter.

The distribution pattern of bronchiectasis can be classified in each lobe as central, peripheral or diffuse with the presence or absence of peri bronchial thickening and mucus plugging. Lundberg *et al.*, (1994) conducted intranasal nitric oxide inhalation test on diseased and control subjects. There was a 98% reduction of level of nasal nitric oxide concentration in patients with Kartagener syndrome compared to age-matched controls suggesting that nitric oxide measurements (which are noninvasive and can easily be performed even in infants) could be of help in the early diagnosis and hence, management of the disease process.

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Several studies have demonstrated that nasal NO is extremely low (10-15% of normal) in PCD patients suggesting that nasal NO measurement may be a useful screening test for PCD. Because low nasal NO levels have been reported in a limited number of other disorders with overlapping clinical features (e.g., cystic fibrosis [7, 23, 25], pan bronchiolitis [26], and nasal polyposis [27]), confirmatory ciliary ultrastructure analysis and/or genetic mutation analysis are needed for a firm PCD diagnosis.

Treatment of this rare congenital disorder includes antibiotics, intravenous or oral, intermittent or continuous, and are used to treat upper and lower airway infections. Hemophilus influenzae and Staphylococcus aureus are the most common organisms (Bent and Olearczyk, 2007). Long-term low-dose prophylactic antibiotics may be necessary in children. Obstructive lung disease/bronchiectasis should be treated with inhaled bronchodilators, mucolytics, and chest physiotherapy. Influenza and pneumococcal vaccination should be encouraged. Lung transplantation and heart-lung transplantation have occasionally been tried in severe cases with some success (Otgün *et al.*, 2004; and Alvarez *et al.*, 2005).

Conclusion

Whenever there is a case of situs inversus look for sinusitis and bronchiectasis which can yield a diagnosis of Kartagener's syndrome. Early diagnosis and treatment is important to prevent long term sequel and morbidity associated with it. A noninvasive screening test should be devised for its early detection. Genetic counseling, social, psychological and fertility issues should be addressed once it is diagnosed and help these patients to live with Kartagener's Syndrome without morbidity and in a dignified way. Early diagnosis and treatment of associated complications of this rare syndrome significantly improves the quality of life and prognosis of the patients.

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