Clinical Expression of Primary Ciliary Dyskinesia in Monozygotic Twins: Case Report

Primer Siliyer Diskinezinin Monozigotik İkizlerdeki Klinik Ekspresyonu: Olgu Sunumu

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ABSTRACT Primary ciliary dyskinesia is an autosomal recessively inherited disorder that describes a group of systemic diseases. The incidence ranges from 1/15 000 to 1/20 000 in live births. It is characterized by abnormal ciliary structure, impaired siliary function, defective mucociliary clearance, chronic middle ear, sinus, lung disease, and infertility. Fifty percent of primary ciliary dyskinesia is defined as Kartagener's syndrome characterized by bronchiectasis, sinusitis, otitis media, and situs inversus totalis. In our article, we evaluated 5-years-old monozygotic twins -submitted to our clinic because of recurrent respiratory problems- by clinical, ultrastructural analysis and imaging findings. We presented these cases because of relative rarity of Kartagener's syndrome and the different clinical expressions of primary ciliary dyskinesia among the monozygotic twins. We also emphasized the difficulties in the diagnosis of primary ciliary dyskinesia and discussed via the literature. To our knowledge, our patient is the first reported in literature in which Kartagener's syndrome has been found in only one of the monozygotic twins.

Key Words: Kartagener syndrome; twins, monozygotic

ÖZET Primer siliyer diskinezi otozomal resesif kalıtımla geçen bir grup sistemik hastalığı tanımlamaktadır. Hastalık 15 000-20 000 canlı doğumda bir görülür. Anormal siliyer yapı, siliyer fonksiyon bozukluğu, defektif mukosiliyer klirens, kronik orta kulak, sinüs, akciğer hastalığı ve infertilite ile karakterizedir. Bu hastalık grubunun %50'sini bronşektazi, sinüzit, otitis media ve situs inversus totalis kliniğini içeren Kartagener sendromu oluşturur. Makalemizde 5 yaşında, tekrarlayan solunum yolu problemleri ile başvuran monozigotik ikizleri klinik, ultrastrüktürel analiz, görüntüleme bulguları ile değerlendirdik. Bu olguları Kartagener sendromu'nun nadir görülmesi ve monozigotik ikizler arasındaki Primer siliyer diskinezinin farklı klinik ekspresyonlarını saptamamız nedeniyle sunduk. Primer siliyer diskinezi tanısındaki zorlukları vurguladık ve literatür bilgisi ışığında tartıştık. Bildiğimize göre olgumuz, literatürdeki Kartagener sendromunun monozigotik tek bir ikiz eşinde tanımlandığı ilk olgudur.

Anahtar Kelimeler: Kartagener sendromu; ikizler, tek yumurta

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Primary ciliary dyskinesia (PCD) is an inherited systemic disease, characterized by specific ultrastructural defects of cilia that are associated with impaired ciliary motion and mucociliary clearance. Children present with a history of chronic productive cough and a combination of chronic and recurrent respiratory infections, including rhinitis, sinusitis, otitis media and recurrent pulmonary infections. Situs inversus occurs in approximately %50 of patients with PCD. The triad of bronchiectasis,

chronic sinusitis and sinus inversus totalis is called as Kartagener Syndrome (KS).[1,2] It is defined firstly by Mares Kartagener in 1933.[3] In 1933, Bjorn Afzelius showed movement disorders in cilia by electron microscopically and called as "immotile cilia syndrome".[4] Subsequent studies demonstrated that the cilia are often motile, but their beat is not coordinated and effective. In 1981, Sleigh called the syndrome as "primary ciliary dyskinesia" to distinguish from acquired cilia dysfunctions such as viral infection and toxic agents.[5,6]

CASE REPORTS

CASE 1

A 5-year-old female (identical twin) was admitted to our hospital with complaints of frequently pyrexia, dyspnea, expectorating, persistent cough and easily vomiting. She was born at 36 weeks, at 2800 grams, and no evidence of respiratory distress was seen after birth. She had breastfed for three months, operated adenoidectomy and tonsillectomy. Her mother had allergic rhinitis diagnosis. No consanguinity was described in family history.

On physical examination, her weight was 17.5 kg (25-50 centile), and her height was 110 cm (50-75 centile). Postnasal drip and chronic otitis media on the right, rhonchi in the lungs were found. Cardiac apex beat and sounds at the right side. The appearances of the monozygotic twins were seen in Figure 1.

The laboratory findings showed a leucocyte count of 8.00/mm^3, erythrocyte sedimentation rate 3 mm/h, serum C-reactive protein 0.07 mg/dl. Alcohol acid resistant bacilli, tuberculin skin test, epidermal prick test was found as negative and the sweat chloride test was 43 mEq/L. Pulmonary function tests; forced vital capacity (FVC): 90%, forced expiratory volume (FEV_1): 105%, FEV_1/ FVC: 92%, maximal expiratory flow measurements (MEF_{25-75}): 86% and showed reversibility. In sputum culture, haemophilus influenzae grew. Bilateral paracardiac localized irregular infiltrative opacity was seen on anteroposterior chest radiography, heart and gastric fundus air were on the right (Figure 2). Decreased aeration in the left maxiller sinus

FIGURE 1: The photo of the monozygotic twins.
(See color figure at http://www.turkiyeklinikleri.com/journal/turkiye-klinikleri-journal-of-case-reports/1300-0284/tr-index.html)

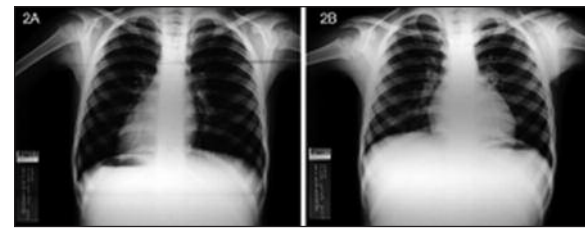

FIGURE 2: A: Anteroposterior chest radiography of twin 1 showing heart and gastric fundus air on the right, **B:** Anteroposterior chest radiography of twin 2.

and mucosal thickening at baseline were seen in Water's X-Ray. Dextrocardia, situs inversus and bronchiectasis were identified on thoracic high-resolution chest tomography (Figure 3). Dextrocardia was noted on echocardiography. Situs inversus totalis, liver in the left, spleen in the right, was noted on upper abdominal ultrasound.

Human leucocyte antigen (HLA) tissue groups of twins were 100% compatible, and on antenatal ultrasound single amniotic sac was seen. Ciliary dysmorphology were seen on the electron microscopical investigation of material taken by nasal brushing in a non-infective period (Figure 4). In reflux scintigraphy, findings were compatible with gastroesophageal reflux.

CASE 2

A 5-year-old female patient (identical twin) was admitted to our hospital due to recurrent upper respiratory tract infection. On physical examination, her weight was 17.5 kg (25-50 percentile), and her height was 110 cm (50-75 percentile); oropharyn-

geal hyperemia was identified. Serum immunoglobulin and subgroups were in normal ranges. Alcohol acid resistant bacilli, and epidermal prick test were negative and the sweat chloride test was 30 mEq/L. Heart and gastric fundus air were seen at the left at the anteroposterior chest radiography (Figure 2). No pathological finding was identified on the high-resolution chest tomography, echocardiography and upper abdominal ultrasound. Ciliary dysmorphology was not determined in the repeated electron microscopical investigation of material prepared by nasal brushing. The comparison of monozygotic twins findings were presented in Table 1.

Informed consents were obtained from the patient's parents.

DISCUSSION

PCD is a widely encompassing clinicopathological term describing rare disorders such as KS, immotile cilia syndrome, ciliary dysmotility, and primary orientation imperfections that are outcomes of a congenital deficiency of ciliary function. Kartagener's Syndrome is characterized by the triad of bronchiectasis, sinusitis, and situs inversus. Nasal polyps, olfaction disorders, recurrent otitis, hearing loss, male infertility due to sperm immotility, obstructive lung disease, duodenal atresia, and cornea anomalies are apparent in KS.[7]

TABLE 1: The comparision of monozygotic twins findings.

	Twin 1	Twin 2
Otitis media	+	-
Sinusitis / Recurrent upper respiratory tract infection	+	+
Bronchiectasis	+ (mild)	-
Situs inversus totalis	+	-
Echocardiography	Dekstrokardia	Normal
Abdominal ultrasound	Situs inversus totalis	Normal
Ciliary dysmorphology	+	-

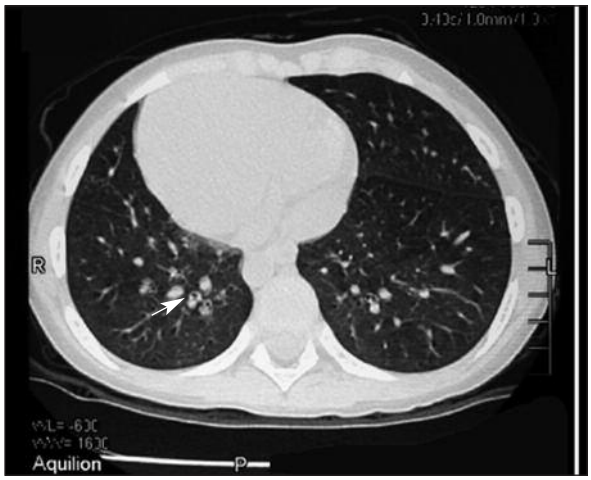

FIGURE 3: High resolution chest tomography scan of twin 1 demonstrating dextrocardia, situs inversus and mild bronchiectasis (white arrow).

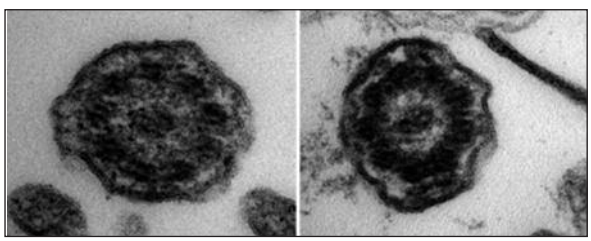

FIGURE 4: Ciliary dysmorphology (Removed characteristic 9+2 microtubular structure of cilia cells, microtubular adhesion and disorganization) were seen on the electron microscopical investigation of material prepared by nasal brushing.

Primary ciliary diskinesia is often diagnosed later in childhood due to its presumed rarity, and the technical expertise required for ciliary ultrastructural analysis necessary for diagnosis.[8] In the study made in 89 children with PCD by Gain et al., lung disease and bronchiectasis seen in the late childhood or adolescent.[9] Although our patient is 5-year-old yet, otitis media, sinusitis, situs inversus totalis and bronchiectasis were determined.

Primary ciliary dyskinesia is diagnosed by demonstrating structural disorders in cilia by electron microscopically, with the suspicious clinical findings. Toxic agents in the air and viral infections also change ciliary structure, especially its function.[10,11] Thus, repeated biopsies are required in suspicious cases. In our case, ciliary dysmorphology determined on the repeated electron microscopic investigation of respiratory cilia from nasal scarification. In the other identical twin, neither PCD findings nor ciliary dysmorphology was found despite the repeated ultrastructural investigation.

Primary ciliary dyskinesia is a phenotype with recognised clinical variability. Noone et al. re-

ported situs solitus in the one of the female monozygotic twin with PCD and situs inversus totalis in the other one.[12] The determination of KS and situs inversus totalis in the one of our monozygotic twins and the absence of PCD and organ lateralization in the other one have seen for the first time in the literature. In monozygotic twin females, different phenotypic findings -especially in the X-linked inherited diseases- may occur as a result of unequal X chromosome inactivation, or unequal inheritance of a genetically based factor in early embryonic stage. However certain reason is unknown yet.

In most families, PCD appears to be transmitted by an autosomal recessive trait but autosomal dominant or X-linked recessive inheritance patterns were demonstrated.[13,14] However, a specific genetic inheritance model does not show situs inversus, randomly inherited. In the presence of ciliary motility disorders, helical rotation of organs normally from the right to the left is randomly, and this is causing to the asymmetric heart and visceral organ development in the intrauterine term.[15] Primary ciliary dyskinesia is likely to be a genetically heterogeneous disorder. Blouin et al. performed a genome-wide linkage search to 31 multiplex PCD families, and no major locus for the majority of the families was identified. They suggested the potential genomic regions for PCD loci were localized on chromosomes 3p, 4q, 5p, 7p, 8q, 10p, 11q, 13q, 15q, 16p,17q and 19q. Primary ciliary dyskinesia families with a dynein arm deficiency and situs inversus provided suggestive evidence for linkage to chromosomal regions 8q, 16pter, and chromosomal regions 8q, 19q, respectively.[16] Consistently, Meeks et al. showed a conclusive evidence for a PCD locus on chromosome 19q.[17] Shortly after the heavy chain type axonemal 11 (DNAH 11) gene mutations and relationship with situs inversus, and ciliary dyskinesia demonstrated.[18] Mutations of axonemal human dynein heavy chain gene (DNAH5) and axonemal dynein intermediate chain gene (DNA11) were also identified in patients with PCD.[19]

In our case recurrent respiratory tract infection, otitis media, sinusitis and situs inversus totalis were identified, and ciliary structure disorder was demonstrated by electron microscopically. Interestingly, although recurrent upper respiratory tract infections and sinusitis were observed in the monozygotic identical twin of our case, otitis media, situs inversus totalis, and ciliary structure disorder were not determined. There were a few numbers of KS cases in monozygotic twins in the literature, and in these cases, both identical twin have same diagnosis. We presented these cases because of relative rarity of KS and the different clinical expressions of PCD among to the monozygotic twins.

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