International Journal of Contemporary Pediatrics
Rajanna C et al. Int J Contemp Pediatr. 2023 Aug;10(8):1352-1356
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20232261

Case Report

Primary ciliary dyskinesia: a rare case of CCNO mutation

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Received: 31 May 2023
Revised: 04 July 2023
Accepted: 10 July 2023

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ABSTRACT

Primary ciliary dyskinesia (PCD) is a heterogenous inherited disorder characterized by impaired ciliary function. Clinical manifestations include respiratory distress in newborn, bronchiectasis, repeated lower respiratory tract infections, rhinosinusitis, otitis media, left- right laterality defects and infertility. Estimated frequency of PCD is 1 in 12,000-20,000 live births, prevalence in children with repeated respiratory infections is 5%. The diagnosis is often delayed even if characteristic findings are present as the tests available for diagnosis is limited. 14-year-old adolescent female, second born child to a consanguineously married couple with history of repeated respiratory tract infections, diagnosed outside as uncontrolled bronchial asthma, with history of nasal polyps, presented with delayed puberty and short stature. On examination child was noted to have proportionate short stature with SMR of Tanner stage 1, with normal systemic examination. High-resolution computed tomography (HRCT) done was suggestive of mild bronchiectasis. Child was evaluated for short stature. In order to rule out diseases associated with ciliary dysfunction; clinical exome sequencing was sent which showed Primary ciliary dyskinesia secondary to homozygous mutation of CCNO gene which was autosomal recessive. Primary ciliary dyskinesia with CCNO is a rare presentation which can have situs solitus. It was first reported in 2014. In children presenting with bronchiectasis and delayed puberty one should think of suspect ciliary dysfunction. In the absence of situs inversus, one can still suspect PCD secondary to various other mutations.

Keywords: Primary ciliary dyskinesia, CCNO mutation, Situs solitus, Short stature, Delayed puberty

INTRODUCTION

Cilia are minute hair like organelles found on surface of various organs in the human body. Cilia have varied functions depending on the structural types viz., motile cilia (motor), primary cilia (sensory) and nodal cilia (Figure 1).[1] Ciliopathies are the disorders of cilia. Advanced genetic studies have assisted in understanding the dysfunctions of cilia. Primary ciliary dyskinesia (PCD) is one such disorder of motile cilia.[2]

Primary ciliary dyskinesia is a rare genetically inherited autosomal recessive disorder affecting the upper and lower respiratory tract (MIM 244400).[3] It is a chronic disorder characterized by impaired ciliary function leading to chronic sinopulmonary disease, persistent middle ear effusions, laterality defects, and infertility. Though exact prevalence is not known, estimated frequency of PCD is 1 in 10,000 to 1 in 20,000 live births.[4,5] Its prevalence in children with repeated respiratory infections has been estimated to be as high as 5%.

Currently, there are 33 known genes associated with PCD.[6] Specific genes code for each part of ultrastructure of cilia, mutation of which leads to defect of corresponding structure. CCNO gene involved in centriole maturation and amplification is crucial for biogenesis of cilia. CCNO mutation leads to reduced number of motile cilia ending in impaired mucociliary clearance.[1]

As the symptomatology overlaps with a number of other chronic airway diseases, diagnosis is usually delayed

during which period the patient suffers from the complications. Hence, early diagnosis plays an important role. Here is a case of 14-year-old adolescent female admitted in our hospital presenting with delayed puberty and short stature.

CASE REPORT

14-year-old adolescent female presented with complaints of delayed puberty. She is the second born child of consanguineously married couple. She was term born with appropriate weight for gestational age. No significant antenatal, perinatal and postnatal history was noted. She had recurrent productive cough with accompanying wheeze and occasional dyspnea suggestive of lower respiratory tract three to four times annually. Upon physical examination, she had growth retardation. She was also operated twice for nasal polyps. She was diagnosed as asthma and treated with inhalers. She frequently required hospitalisation for her symptoms. Even at 14 years of age, she continued to have symptoms of acute respiratory illness 3-4 times a year. Currently the parents were apprehensive about her not attaining puberty.

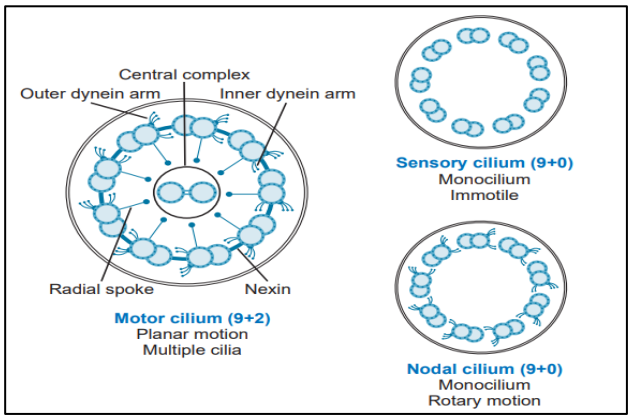


Figure 1: Structure of cilia.

On examination, child was hemodynamically stable, anthropometry showed underweight, proportionate short stature and height was below the mid parental height percentile. Sexual maturity by Tanner staging was 1, with no signs of pubarche and thelarche. No deformities or facial dysmorphisms noted. Blood counts with peripheral blood smear showed microcytic hypochromic anaemia. Radiological evaluation with x-rays to assess bone age showed features corresponding to chronological age (Figure 3). Hormonal studies were done- TSH, LH, FSH were within normal limits. Chest X-ray showed situs solitus and no laterality defects were noted (Figure 4). Chest X-ray did not show features of tuberculosis. Echocardiography was done for complex congenital heart diseases and none were found. Ultrasonography abdomen and pelvis showed normal female internal genital, with small sized uterus and ovaries were well visualized. As the patient had recurrent attacks of lower respiratory tract involvement, nasal polyps and was underweight, a disorder of mucociliary clearance was suspected and hence clinical exome sequencing was sent for. Reports showed this rare mutation of CCNO gene (Figure 5).

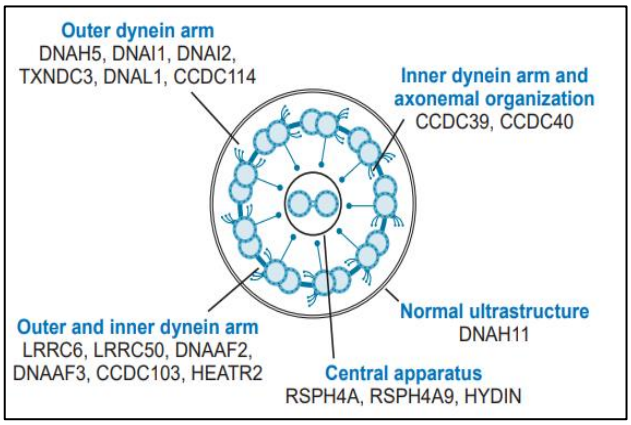


Figure 2: Ciliary ultrastructure with genes involved.

The girl is being followed up in our hospital with regular growth monitoring. She is being given supportive therapy like nutrition enrichment, physiotherapy, symptomatic treatment for acute respiratory infections.

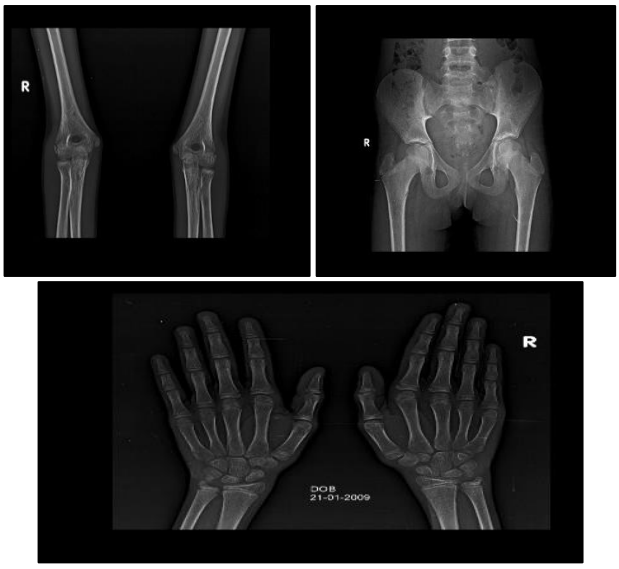


Figure 3: X rays for bone age determination.

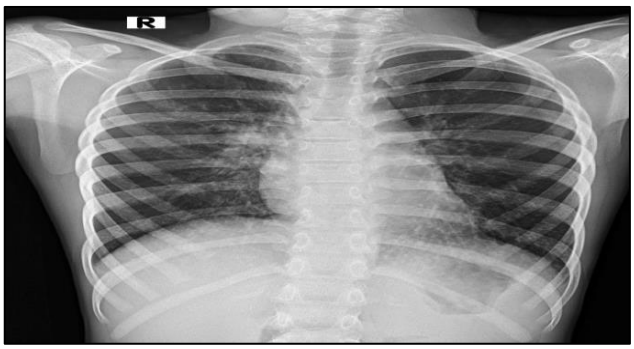
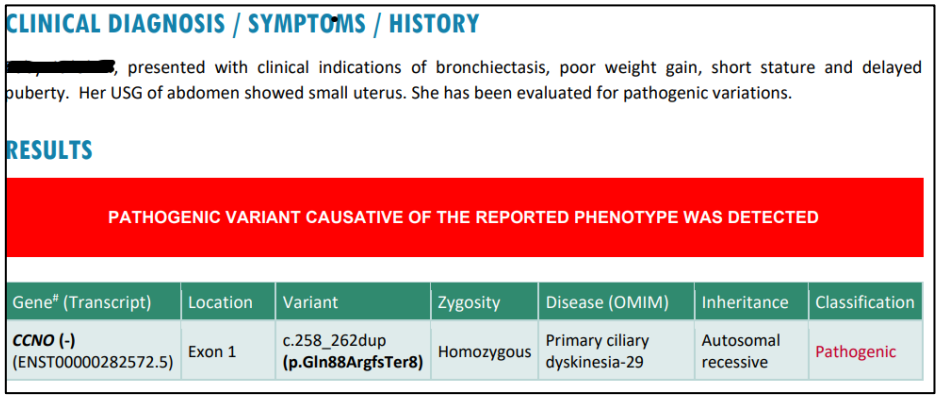


Figure 4: Chest X-ray showing emphysematous changes and normal laterality.



CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

[redacted], presented with clinical indications of bronchiectasis, poor weight gain, short stature and delayed puberty. Her USG of abdomen showed small uterus. She has been evaluated for pathogenic variations.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***CCNO* (-)** (ENST00000282572.5)	Exon 1	c.258_262dup **(p.Gln88ArgfsTer8)**	Homozygous	Primary ciliary dyskinesia-29	Autosomal recessive	Pathogenic

Figure 5: Clinical exome report of the patient.

DISCUSSION

Primary ciliary dyskinesia is a heterogenous group of disorder affecting the mucociliary clearance due to defective ciliary structure and function. PCD is inherited predominantly as autosomal recessive pattern, however few cases of autosomal dominance and x- linked inheritance are reported. Currently, there are 33 known genes associated with PCD.[6] To name a few, DNAH5, DNAI1, DNAI2, TXNDC3, DNAL1, CCDC114- encode proteins integrated in outer dynein arm. Similarly, CCDC39, CCDC 40 encode for inner dynein arm and axonemal organisation, LRRC6, LRRC50, DNAAF2, DNAAF3, CCDC103, HEATR2 encode for outer and inner dynein arm, RSPH4A, RSPH4A9, HYDIN encode for central apparatus. CCNO, MCIDAS encode for oligocilia (Figure 2).[1]

Ultrastructure of motile (motor) cilia shows central complex surrounded by microtubules in doublet organisation held dynein, nexin, and radial spoke.[7,8]

The formation of this complex structure involves several genes which when mutate results in PCD. Hence, it is important to diagnose by associating clinical phenotypes. Clinical symptoms of PCD includes respiratory problems – chronic sinusitis, otitis media, atypical asthma unresponsive to therapy, recurrent pneumonia, bronchiectasis, laterality defects- situs inversus, heterotaxy syndromes with complex congenital heart diseases, immotile sperm, male infertility, female subfertility, hydrocephalus to name a few. There is a definitive genotype-phenotype association.[9]

Gold standard test to assess the ciliary structure and its defects is the transmission electron microscopy of the curettage sample from nasal epithelium and endobronchial brushings. Diagnosis of the mutated genes can be done by clinical exome sequencing. More than 70% of the cases are accounted by bi- allelic mutations. PCD foundation in their consensus statement have also come up with diagnostic criteria.[10-12]

American thoracic society clinical guidelines for PCD has included four key clinical features: unexplained neonatal respiratory distress in a term infant, chronic wet coughing beginning at less than six months of age, chronic daily nasal congestion beginning at less than six months of age and abnormalities of organ left-right asymmetry. Two out of the four features are essential to make the diagnosis.[13] The other clinical features noted are chronic otitis media with middle ear effusion and subfertility of both males and females owing to dysmotility of sperm or fallopian tube cilia.

CCNO is one of the rarest and recently reported gene mutation involved in PCD, most associated with MCIDAS (multiciliate differentiation and DNA synthesis-associated cell cycle protein). The phenotype that differentiating from other mutations is the rapid progression, no laterality defects and subfertility.[14-16]

CCNO gene is located on chromosome 5q.11.2 and stands for CYCLIN O. CCNO gene mutations are inherited by autosomal recessive pattern.[17] It encodes for uracil DNA glycosylase. Function of CCNO lies in ciliogenesis, where it is involved in pathways that promote amplification and maturation of centrioles. PCD due to CCNO mutation was first described in 2014.[18]

Symptomatology of PCD depends on the dysfunction of the cilia in the related organ which affects the normal functioning. Prominent features noted are related to the upper and lower respiratory system. Severe cases present soon after birth as neonatal respiratory distress. Presence of dextrocardia, situs inversus or situs ambiguous indicates to a highly probable diagnosis of PCD.[19,20]

Later presentations in life shows symptoms involving the sinuses as chronic recurrent sinusitis, chronic middle ear infections, recurrent nasal polyps, lower respiratory infections with sputum production and decreased clearance of the same, recurrent wheeze leading to bronchiectasis.[21] Chronic infections affect the normal growth in the child leading to short stature, delayed puberty.[22] In the present case, she presented with repeated

respiratory symptoms. Her presentation was similar to a case report by Wang et al.[23]

She was treated with antibiotics and relieved of the symptoms earlier during the presentation. Later she had presentation of nasal polyps similar to a study by Boon.[21] She was operated for the same. Further as she grew older, she presented similar respiratory problems. She was investigated with several radiological investigations which was normal. She was diagnosed as asthma and was on treatment for the same. Symptomatically child was better with the treatment.

Presently she presented as short stature and delayed puberty. She was investigated for the same. Tuberculosis being more prevalent in our region was tested to be negative. Congenital heart diseases were ruled out with 2D echocardiography. Pulmonary function tests done was within normal and no parameter indicated asthma. HRCT done showed changes suggestive of mild bronchiectasis in bilateral lung fields. What made this different from other forms of PCD is that there is no situs inversus as noted in majority of PCD.

Early presentation and rapid worsening necessitating early diagnosis of this mutation, may be missed if not suspected. We had reached a stage with no answer. As quoted when we think of rare diagnosis, we are rarely correct. Yet it was decided to get clinical exome sequencing. Recurrent attacks of lower respiratory tract involvement, nasal polyps and underweight was leading to disorders of mucociliary clearance, cystic fibrosis being our first differential diagnosis. It was a long wait of 2 weeks after the adolescent was discharged that we received the report, which showed the rare mutation of CCNO gene (Figure 5). Our quest ended here explaining everything the girl underwent since toddler years. Incidence of PCD due to CCNO mutation is more than expected as per recent analysis.[24] Another prominent gene involved in cilia biogenesis is MCIDAS and bi allelic CCNO – MCIDAS mutations are noted. Reduced motile cilia in genitourinary organs is responsible for abnormal gamete transport and fertility problems.[25]

PCD has no proven treatment. The only aim is to facilitate mucociliary clearance by supportive therapy. Antibiotics for recurrent infections, bronchodilators though not very effective, myringotomy for chronic otitis media, endoscopic sinus surgery for refractory and severe nasal symptoms can be tried, benefits may be short lived or questionable.

Prognosis is variable depending on the rate of deterioration of respiratory functions.

CONCLUSION

Primary ciliary dyskinesia is a rare, heterogenous, inherited disorder characterized by impaired ciliary function leading to chronic sinopulmonary disease, laterality defects and subfertility. The classical disease form was the Kartagener's syndrome detected in 1933.[26,27] In the recent years, owing to advances in genetics, many cases with different phenotype- genotype combinations have been reported leading to increased understanding of the presentation of the condition. Progressive bronchiectasis and respiratory deterioration are noted at younger age, which can be prevented by early diagnosis and treatment. High index of suspicion is required and paediatricians should think of PCD in case of unresponsive, difficult to treat respiratory symptoms. Once diagnosed active surveillance with spirometry, chest CT imaging and sputum or oropharyngeal cultures at regular intervals is recommended.

ACKNOWLEDGEMENTS

Authors would like to thank patient and her parents.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Rajanna C, Karumbaiah PK. Primary ciliary dyskinesia: a rare case of CCNO mutation. Int J Contemp Pediatr 2023;10:1352-6.