SCIE DOI: 10.14744/scie.2024.56244
South. Clin. Ist. Euras. 2024;35(4):378-383

Original Article

Clinical and Demographic Characteristics of Patients Diagnosed with Primary Ciliary Dyskinesia with CCDC40 Homozygous Mutation

Mine Yüksel Kalyoncu,[1] Ela Erdem Eralp,[2] Merve Selçuk,[2] Şeyda Karabulut,[2] Neval Metin Çakar,[2] Ceren Ayça Yıldız,[2] Müge Merve Akkitap Yiğit,[2] Eda Esra Baysal,[2] Fulya Özdemircioğlu,[2] Almala Pınar Ergenekon,[2] Yasemin Gökdemir,[2] Bülent Karadağ[2]

[1]Department of Pediatric Pulmonology, Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye
[2]Department of Pediatric Chest Diseases, Marmara University Faculty of Medicine, Istanbul, Türkiye

Submitted: 31.10.2024
Revised: 14.11.2024
Accepted: 15.11.2024

Correspondence: Mine Yüksel Kalyoncu,
Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye
E-mail: mineeyuksell@gmail.com

Keywords: CCDC40 mutation; high-speed video microscopy; nasal nitric oxide; primary ciliary dyskinesia.

ABSTRACT

Objective: Primary ciliary dyskinesia (PCD) is a rare genetic disorder caused by defective ciliary function, resulting in chronic respiratory infections and other systemic issues. CCDC40 encodes a protein crucial for assembling and functioning ciliary dynein arms, vital for ciliary movement. Mutations in CCDC40 can significantly exacerbate PCD symptoms. This study analyzed the clinical and demographic profiles of pediatric patients with PCD due to homozygous CCDC40 mutations.

Methods: A retrospective analysis was conducted of 13 patients at the Marmara University Division of Pediatric Pulmonology, focusing on their demographics, clinical symptoms, high-speed video microscopy (HSVM) findings, nasal nitric oxide (nNO) levels, PICADAR scores, sputum culture results, and respiratory function tests. Statistical analyses were performed using the SPSS software.

Results: The cohort had a median age of 17 years (25–75p, 11.5–21.5 years), with typical onset of symptoms at birth and a median diagnostic delay of 7 years (25–75p, 2–13.5 years). Notably, 84.6% of patients had consanguineous parents. The common symptoms included recurrent cough (100%), bronchiectasis (92.3%), and rhinosinusitis (92.3%). The median PICADAR score of the patients was 8 (25–75p, 5–11.5), and the median nasal NO value was 17.3 nl/min (25–75p, 7.7–114.5). HSVM analysis revealed immotile cilia and abnormal movement patterns in 53.8% and 30.7% of patients, respectively. Sputum cultures identified Haemophilus influenzae (92.3%) as the predominant pathogen.

Conclusion: The results highlight the importance of early diagnosis and intervention in managing PCD, particularly for those with CCDC40 mutations who may experience more severe respiratory complications than other genetic variants.

INTRODUCTION

Primary ciliary dyskinesia (PCD) encompasses a group of rare, genetically diverse, clinically variable disorders characterized by defective ciliary function. The global prevalence of PCD is estimated to be approximately 1 in 10,000 individuals.[1] Ciliary dysfunction results in impaired mucociliary clearance, which predisposes affected individuals to chronic infections of both the upper and lower respiratory tracts.[1] Beyond respiratory symptoms, PCD is associated with additional systemic manifestations, including laterality defects, male infertility, and hydrocephalus, in rare instances. To date, more than 50 genes have been implicated in PCD.[2]

At least 12% of PCD cases are attributed to defects in the inner dynein arm (IDA) and microtubular disorganization (MTD). The vast majority of these cases result from mutations in CCDC39 and CCDC40.[3] CCDC40 encodes a protein essential for the assembly and function of ciliary dynein arms, structures responsible for cilia movement.[4] Mutations in this gene typically result in a loss of ciliary motility, leading to severe clinical manifestations of PCD.

Around 50% of the individuals affected by CCDC40 mutations show defects in laterality, while male patients also experience infertility caused by immobile sperm tails with structural abnormalities.[5,6]

This study aimed to examine the clinical and demographic profiles, diagnostic procedures, and respiratory function measurements in subjects with homozygous mutations in the CCDC40 gene associated with PCD.

MATERIALS AND METHODS

Study Design and Population

This retrospective study was conducted at Marmara University Pediatric Pulmonology Division and included patients diagnosed with CCDC40 homozygous PCD. The patient data were collected from medical records from (1999–2024), including demographic, clinical, and respiratory function test results, high-speed video microscopy (HSVM) findings, nasal nitric oxide (nNO) levels, and sputum culture results. Ethical approval was obtained from the Marmara University Ethics Committee (Protocol No:18.10.2024.1333), with informed consent waived due to the retrospective nature of the study. The Declaration of Helsinki was always followed.

Inclusion and Exclusion Criteria

Patients with a confirmed diagnosis of CCDC40 homozygous PCD based on genetic testing and complete clinical data were included. Individuals with incomplete clinical, laboratory, or genetic data were excluded from the analysis.

Data Collection

Demographic information such as age, gender, and age at diagnosis was collected. Clinical data including chronic cough, recurrent respiratory infections, sinusitis, bronchiectasis, otitis media, dextrocardia, and fertility status were retrospectively extracted from medical records.

Respiratory Function Tests

Pulmonary function was assessed using spirometry, measuring parameters such as forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio.[7] These results were compared with predicted values based on age, gender, and height.[7] Pulmonary function data were retrieved from patient records and analyzed for trends in disease severity.

PICADAR Questionnaire

Patients were interviewed and scored for probable PCD using the PICADAR questionnaire.[8,9] PICADAR, a scoring tool with seven predictor variables, assigns integer values (1–4) to each clinical factor's presence based on regression coefficients. A threshold of 5 points optimized sensitivity (0.90) and specificity (0.75).[9] The maximum score of 14 indicated a 99.80% likelihood of PCD. Scores of 10 or higher showed a 92.6% probability, while scores of 5 or more indicated an 11.10% chance of PCD.[9]

Immunofluorescence Analysis

Respiratory epithelial cells were obtained via transnasal brush biopsy (Cytobrush Plus; Medscand Medical, Malmö, Sweden), suspended in RPMI medium, and air-dried on glass slides at the outpatient clinic of Marmara University.[10] The samples were then sent to the University of Münster's IF Laboratory for analysis. IF analysis involved treating cells with 4% paraformaldehyde, 0.2% Triton X-100, and 1% skim milk, followed by incubation with primary antibodies for 3-4 hours and secondary antibodies for 30 min at room temperature.[10]

Antibodies targeted proteins of the ODAs (DNAH5) and nexin-dynein regulatory complex (GAS8) in the ciliary axoneme. Double labeling was performed using monoclonal mouse anti-DNAH5 and polyclonal rabbit anti-GAS8 (HPA041311) primary antibodies at 1:500 dilution and Goat Anti-mouse Alexa Fluor 488 and anti-rabbit Alexa Fluor 546 secondary antibodies at 1:1000 dilution. Hoechst 33342 (Sigma-Aldrich) stained the cell nuclei.[10] Confocal images were captured with a Zeiss laser scanning microscope (Axiovert 200 LSM510 META) and processed using Zeiss LSM510 software.

High-Speed Video Microscopy Analysis

Nasal epithelial cells were collected using nasal brushing.[11] Participants were excluded if they had used nasal steroids or decongestants within four weeks or exhibited acute respiratory tract infection symptoms during that period. The ciliated cells were transferred to RPMI 1640-Medium at 37°C and maintained using a heater plate (Tpi-TSX, Tokyo, Japan).

HSVM with Sisson-Ammons Video Analysis software (SAVA, MI, USA) measured ciliary movement frequency.[11] Measurements were taken with an inverted phase-contrast Nikon Eclipse TS100 microscope (Nikon, Japan) using a 40x objective and a digital high-speed video camera (Basler acA1300-200um, Germany). Digital image sampling was 640×480 pixels at 120-150 frames per second (fps). Recordings lasted one minute with 15-second intervals. Both the top and side views of the ciliary beat were analyzed in real time and slow motion.[11]

Ciliary beat patterns (CBP) were categorized as 'normal,' 'virtually immotile,' 'stiff beating with reduced amplitude,' 'circular gyrating motion,' and 'ciliary beat frequency'.[11] The HSVM results were compared to clinical symptoms and other diagnostic features.

Nasal Nitric Oxide (nNO) Measurement

Nasal nitric oxide levels were measured using a chemiluminescence analyzer following American Thoracic Society/European Respiratory Society standard guidelines.[12] Patients performed breath-holding or exhalation techniques while nNO was measured from one nostril.[12]

In patients suspected of PCD, nNO levels below 77 ppb, measured with a chemiluminescence NO analyzer during mouth breathing, exhibit over 95% specificity and sensitiv-

ity for PCD diagnosis.[12] nNO levels were compared with established normal ranges and between patients.

Radiological Assessment

Chest X-rays and high-resolution computed tomography (HRCT) scans were reviewed for all patients. Bronchiectasis severity and the presence of situs abnormalities (such as situs inversus) were noted.[13]

Sputum Culture Analysis

Sputum samples were collected from patients during routine clinical visits. The microbiological profile was analyzed by performing sputum cultures to identify bacterial pathogens, with particular focus on common PCD-associated organisms such as Pseudomonas aeruginosa (PA), Haemophilus influenzae, and Staphylococcus aureus (SA). The frequency of positive cultures and chronic colonization were evaluated in relation to clinical outcomes.

Statistical Analysis

All statistical analyses were performed using (statistical software, e.g., SPSS). Descriptive statistics were used to summarize continuous variables (mean±standard deviation) and categorical variables (frequencies and percentages). Comparative analyses of demographic, clinical, and functional characteristics were performed using Student's t-test for continuous variables and chi-square or Fisher's exact test for categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Thirteen pediatric patients with CCDC40 homozygous PCD constituted the cohort for the current analysis. Of all patients, 9 (69.2%) were females. The median patient age was 17 years (25–75p, 11.5–21.5 years). The median age of symptom onset was 0 years (25–75p, 0–0 years), and the median age at diagnosis was 7.0 years (25–75p, 2–13.5 years). No parent was diagnosed with PCD, whereas two siblings had PCD.

Approximately 84.6% of patients (11/13) exhibited parental consanguinity. All patients (13/13) presented with recurrent wet cough, 69.2% of patients (9/13) manifested otitis media, 92.3% of patients (12/13) demonstrated bronchiectasis, and 92.3% of patients (12/13) displayed rhinosinusitis. Sixty-one percent of patients (8/13) experienced neonatal respiratory distress, and 61% of patients (8/13) presented with situs inversus totalis. Clinical and demographic characteristics of the patients are presented in Table 1.

The median PICADAR score of the patients was 8 (25–75p, 5–11.5), and the median nasal NO value was 17.3 nl/min (25–75p, 7.7–114.5). Immunofluorescence (IF) analysis of respiratory biopsy specimens obtained from four patients revealed that two patients had an outer dynein arm (ODA) defect and two patients had an IDA and MTD defect, along with genetic tests.

High-speed video microscopy (HSVM) analysis revealed immotile cilia in 53.8% of patients (7/13) and abnormal

Table 1. Clinical and demographic characteristics of CCDC40 homozygous PCD patients

ID	Gender / Age (year)	Neonatal respiratory distress	Chronic rhinitis	Recurrent otitis and sinusitis	Situs inversus totalis	Bronchiectasis consanguinity	Parental	PICADAR (nl/dk)	Nno findings (37°)	HSVM
ID-1	F/26	-	+	-	-	+	+	3	36	immotile
ID-2	F/25	+	+	+	-	+	+	7	NA	immotile
ID-3	F/22	+	+	+	+	+	+	12	4	NA
ID-4	M/21	-	+	+	-	+	+	4	655	abnormal pattern
ID-5	F/17	+	+	-	+	+	+	11	22	immotile
ID-6	F/20	-	+	+	+	+	+	8	9	immotile
ID-7	F/16	+	+	+	-	+	+	8	305	abnormal pattern
ID-8	F/17	-	+	+	+	+	+	6	11	immotile
ID-9	M/15	+	+	-	+	+	+	11	0	abnormal pattern
ID-10	M/13	+	+	+	+	+	-	12	51	abnormal pattern
ID-11	M/10	+	+	+	+	+	+	12	13	NA
ID-12	F/7	+	-	+	+	+	+	11	NA	immotile
ID-13	F/6	-	+	+	-	NA	-	4	NA	immotile

NA: not available; F: female; M: male; Nno: Nasal Nitric Oxide; HSVM: High-Speed Video Microscopy Analysis.

movement patterns (stiff movements) in 30.7% (4/13) patients. HSVM sampling could not be performed in two patients because consent could not be obtained.

Five patients showed normal spirometry results, five had mild obstructive impairment, and two adult patients had severe small airway obstruction. The youngest patients in the obstructive impairment group were 10 and 13 years of age, whereas the remaining three were 17 years of age or older.

Successful collection of at least two culture samples was achieved in 12 patients. A pathogenic species was confirmed when identical pathogens were identified in a minimum of two cultured specimens from the same patient. Haemophilus influenzae was the most commonly isolated pathogen (n:12/13, 92.3%), followed by PA (n:5/13, 38.5%) and methicillin-resistant SA (n:2/13, 15.4%). Three of the 5 patients with PA were adults.

DISCUSSION

This study provides a comprehensive analysis of clinical, demographic, and diagnostic characteristics in patients with CCDC40 homozygous PCD. Our cohort consisted of 13 patients. The early onset of symptoms (median age: 0 years) and a median diagnostic delay of seven years reflect the diagnostic challenges associated with PCD. Diagnostic delays are commonly reported in PCD due to the nonspecific nature of early symptoms, such as neonatal respiratory distress and chronic cough, often attributed to other more common conditions.[14-16] Concurrently, the absence of a gold standard diagnostic test contributes to a delay in diagnosis.[8]

Consanguineous marriages were observed at a high rate in our cohort (84.6%), supporting the idea that CCDC40 mutations are associated with autosomal recessive inheritance, especially in populations with a high rate of consanguineous marriage.[16]

Clinical features including chronic wet cough, sinusitis, chronic middle ear disease, situs anomalies, and history of neonatal respiratory distress (NRD) are observed more frequently than in general patients.[15] Prominent clinical features included NRD (61%), early-onset persistent chronic cough (100%), rhinosinusitis (92.3%), and situs inversus totalis (61%). NRD and situs inversus totalis were also observed at slightly higher rates than reported in previous studies.[15] The higher ratio of situs inversus totalis may be due to CCDC40 being expressed specifically in the embryonic node and midline, which are important tissues controlling left-right patterning.[5]

The prevalence of NRD in PCD remains uncertain; it has been reported to vary considerably in the literature, ranging from 15% to 91%.[17] However, it is reported that these data are generally of poor quality.[18] In the large international dataset, including data from Türkiye, 55% of children with PCD had a history of NRD.[18] The increased NRD frequency in our patient cohort likely results from the more severe pulmonary symptoms linked to CCDC40 mutations. Literature case series have documented more severe NRD in PCD patients with this genetic variant.[19]

The PICADAR score, a predictive tool for low-resource settings, was used to evaluate the probability of PCD.[9] A score of 14 corresponds to a 99.8% probability of PCD, and a score of 10 corresponds to a probability of 92.6%.[9] In our cohort, all five individuals had a median score of ≥8, suggesting moderate clinical suspicion in this cohort, aligning well with the overall diagnostic presentation. Importantly, the consistently low nNO levels (median: 17.3 nl/min) reaffirm its utility as a reliable diagnostic marker for PCD, particularly in resource-limited settings where genetic testing may not be readily accessible.[15]

Immunofluorescence (IF) analysis has emerged as a valuable diagnostic tool for PCD, offering high specificity and rapid results compared to traditional methods.[20] In patients diagnosed with homozygous CCDC40-related PCD, IF examination revealed the absence of the inner dynein arm protein in both ciliary structures and spermatozoa.[14] In our study cohort, although IDA defects were observed in two patients, consistent with the literature, two patients exhibited ODA defects. Nevertheless, several studies have reported that the genes that primarily affect IDA are crucial for the assembly and localization of ODA.[21] Our findings may be related to this phenomenon.

HSVM plays a crucial role in diagnosing PCD.[22] Studies show that, when performed by experts, HSVM accurately detects PCD with high sensitivity and specificity, in line with multidisciplinary assessments and ERS guidelines.[22] In our patients' HSVM analysis, the majority exhibited immotile cilia or abnormal cilia movement patterns, thereby confirming the clinical diagnosis of PCD. The utility of HSVM, particularly due to its capacity for rapid result generation, was demonstrated through the identification of immotile cilia in 3 patients presenting with bronchiectasis and low PICADAR scores, without necessitating the delay associated with genetic testing.

PCD patients with CCDC40 mutations have been reported to show worse lung disease compared to those with ODA defects.[23] Respiratory function tests were normal in the younger age group of our patients, whereas obstructive and severe respiratory failure were observed in older patients. The spirometry findings, which showed normal to mild obstructive impairment in the majority of pediatric patients but more severe obstruction in adult patients, suggest progressive airway disease in PCD.[24]

In addition, although it is thought that the youngest ages of 10 and 13 years in our patients with obstructive impairment groups may be associated with poor lung function prognosis due to CCDC40 homozygosity, larger sample sizes are required to draw definitive conclusions. Furthermore, our findings indicated that pulmonary function in patients with PCD typically declines as they age, which aligns with existing research. This underscores the critical need for early detection and treatment to mitigate the

disease's progression.[23]

Primary ciliary dyskinesia patients are susceptible to recurrent bacterial infections due to impaired mucociliary clearance.[25] The most common pathogens in PCD airways include Haemophilus influenzae, SA, Moraxella catarrhalis, and PA.[25] In sputum cultures taken from our patient group, Haemophilus influenzae and PA were observed at high rates, similar to the literature where PA is more common in adult patients. Studies have not shown a correlation between persistent SA infection and declining pulmonary function in PCD patients.[26] Recent findings suggest that the prevalence of SA infection in pediatric and adolescent patients with PCD is between 35% and 46%.[27]

In our study, two adults with methicillin-resistant SA colonization had severe obstructive pulmonary function and concurrent PA colonization. Owing to the small sample size, a definitive causal link between methicillin-resistant SA and deteriorating respiratory function could not be confirmed, although the co-occurrence of methicillin-resistant SA and PA may have worsened the condition.

Conclusion

In conclusion, this cohort of CCDC40 homozygous PCD patients demonstrates a characteristic clinical phenotype, including early onset of symptoms, frequent respiratory infections, and progressive lung disease. The combination of clinical, functional, and genetic assessments proved essential for accurate diagnosis and management. Given the progressive nature of lung disease in PCD, particularly in adulthood, early diagnosis and aggressive management of respiratory infections and structural lung disease are crucial to improving long-term outcomes.

Ethics Committee Approval

The study was approved by the Marmara University Hospital Ethics Committee (Date: 25.10.2024, Decision No: 18.10.2024.1333).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: Y.G.; Design: A.P.E.; Supervision: B.K.; Materials: Ş.K., N.M.Ç.; Data collection &/or processing: C.A.Y., E.E.B.; Analysis and/or interpretation: F.Ö., M.M.A.Y.; Literature search: M.S.; Writing: M.Y.K.; Critical review: E.E.E.

Conflict of Interest

None declared.

REFERENCES

1. Wallmeier J, Nielsen KG, Kuehni CE, Lucas JS, Leigh MW, Zariwala MA, et al. Motile ciliopathies. Nat Rev Dis Primers 2020;6:77. [CrossRef]
2. Raidt J, Riepenhausen S, Pennekamp P, Olbrich H, Amirav I, Athanazio RA, et al. Analyses of 1236 genotyped primary ciliary dyskinesia individuals identify regional clusters of distinct DNA variants and significant genotype-phenotype correlations. Eur Respir J 2024;64:2301769. [CrossRef]
3. Antony D, Becker-Heck A, Zariwala MA, Schmidts M, Onoufriadis A, Forouhan M, et al. Mutations in ccdc39 and ccdc40 are the major cause of primary ciliary dyskinesia with axonemal disorganization and absent inner dynein arms. Hum Mutat 2013;34:462–72. [CrossRef]
4. Sui W, Hou X, Che W, Ou M, Sun G, Huang S, et al. Ccdc40 mutation as a cause of primary ciliary dyskinesia: A case report and review of literature. Clin Respir J 2016;10:614–21. [CrossRef]
5. Becker-Heck A, Zohn IE, Okabe N, Pollock A, Lenhart KB, Sullivan-Brown J, et al. The coiled-coil domain containing protein ccdc40 is essential for motile cilia function and left-right axis formation. Nat Genet 2011;43:79–84. [CrossRef]
6. Aprea I, Wilken A, Krallmann C, Nothe-Menchen T, Olbrich H, Loges NT, et al. Pathogenic gene variants in ccdc39, ccdc40, rsph1, rsph9, hydin, and spef2 cause defects of sperm flagella composition and male infertility. Front Genet 2023;14:1117821. [CrossRef]
7. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official american thoracic society and european respiratory society technical statement. Am J Respir Crit Care Med 2019;200:e70–88. [CrossRef]
8. Lucas JS, Barbato A, Collins SA, Goutaki M, Behan L, Caudri D, et al. European respiratory society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J 2017;49:1601090. [CrossRef]
9. Behan L, Dimitrov BD, Kuehni CE, Hogg C, Carroll M, Evans HJ, et al. Picadar: A diagnostic predictive tool for primary ciliary dyskinesia. Eur Respir J 2016;47:1103–12. [CrossRef]
10. Omran H, Loges NT. Immunofluorescence staining of ciliated respiratory epithelial cells. Methods Cell Biol 2009;91:123–33. [CrossRef]
11. Raidt J, Wallmeier J, Hjeij R, Onnebrink JG, Pennekamp P, Loges NT, et al. Ciliary beat pattern and frequency in genetic variants of primary ciliary dyskinesia. Eur Respir J 2014;44:1579–88. [CrossRef]
12. Collins SA, Gove K, Walker W, Lucas JS. Nasal nitric oxide screening for primary ciliary dyskinesia: Systematic review and meta-analysis. Eur Respir J 2014;44:1589–99. [CrossRef]
13. Rademacher J, Dettmer S, Fuge J, Vogel-Claussen J, Shin HO, Shah A, et al. The primary ciliary dyskinesia computed tomography score in adults with bronchiectasis: A derivation und validation study. Respiration 2021;100:499–509. [CrossRef]
14. Zhao L, Huang S, Wei W, Zhang B, Shi W, Liang Y, et al. Novel compound heterozygous ccdc40 mutations in a familial case of primary ciliary dyskinesia. Front Pediatr 2022;10:996332. [CrossRef]
15. Peng B, Gao YH, Xie JQ, He XW, Wang CC, Xu JF, et al. Clinical and genetic spectrum of primary ciliary dyskinesia in chinese patients: A systematic review. Orphanet J Rare Dis 2022;17:283. [CrossRef]
16. Kuehni CE, Frischer T, Strippoli MP, Maurer E, Bush A, Nielsen KG, et al. Factors influencing age at diagnosis of primary ciliary dyskinesia in european children. Eur Respir J 2010;36:1248–58. [CrossRef]
17. Goutaki M, Meier AB, Halbeisen FS, Lucas JS, Dell SD, Maurer E, et al. Clinical manifestations in primary ciliary dyskinesia: Systematic review and meta-analysis. Eur Respir J 2016;48:1081–95. [CrossRef]
18. Goutaki M, Halbeisen FS, Barbato A, Crowley S, Harris A, Hirst RA, et al. Late diagnosis of infants with pcd and neonatal respiratory distress. J Clin Med 2020;9:2871. [CrossRef]
19. Ghandourah H, Dell SD. Severe disease due to ccdc40 gene variants and the perils of late diagnosis in primary ciliary dyskinesia. BMJ Case Rep 2018;2018:bcr2018224964. [CrossRef]

20. Shoemark A, Frost E, Dixon M, Ollosson S, Kilpin K, Patel M, et al. Accuracy of immunofluorescence in the diagnosis of primary ciliary dyskinesia. Am J Respir Crit Care Med 2017;196:94–101. [CrossRef]
21. Hjeij R, Onoufriadis A, Watson CM, Slagle CE, Klena NT, Dougherty GW, et al. Ccdc151 Mutations cause primary ciliary dyskinesia by disruption of the outer dynein arm docking complex formation. Am J Hum Genet 2014;95:257–74. [CrossRef]
22. Rubbo B, Shoemark A, Jackson CL, Hirst R, Thompson J, Hayes J, et al. Accuracy of high-speed video analysis to diagnose primary ciliary dyskinesia. Chest 2019;155:1008–17. [CrossRef]
23. Davis SD, Ferkol TW, Rosenfeld M, Lee HS, Dell SD, Sagel SD, et al. Clinical features of childhood primary ciliary dyskinesia by genotype and ultrastructural phenotype. Am J Respir Crit Care Med 2015;191:316–24. [CrossRef]
24. Halbeisen FS, Goutaki M, Spycher BD, Amirav I, Behan L, Boon M, et al. Lung function in patients with primary ciliary dyskinesia: An ipcd cohort study. Eur Respir J 2018;52:1801040. [CrossRef]
25. Roden L, Gorlich D, Omran H, Peters G, Grosse-Onnebrink J, Kahl BC. A retrospective analysis of the pathogens in the airways of patients with primary ciliary dyskinesia. Respir Med 2019;156:69–77. [CrossRef]
26. Wijers CD, Chmiel JF, Gaston BM. Bacterial infections in patients with primary ciliary dyskinesia: Comparison with cystic fibrosis. Chron Respir Dis 2017;14:392–406. [CrossRef]
27. Maglione M, Bush A, Nielsen KG, Hogg C, Montella S, Marthin JK, et al. Multicenter analysis of body mass index, lung function, and sputum microbiology in primary ciliary dyskinesia. Pediatr Pulmonol 2014;49:1243–50. [CrossRef]

CCDC40 Homozigot Mutasyonu Olan Primer Siliyer Diskinezi Tanısı Almış Hastaların Klinik ve Demografik Özellikleri

Amaç: Primer siliyer diskinezi (PSD), silyer fonksiyonun bozulmasıyla karakterize nadir bir genetik hastalıktır ve silyer fonksiyon bozukluğu, kronik solunum yolu enfeksiyonlarına ve diğer sistemik sorunlara yol açar. CCDC40, silyer hareketten sorumlu olan dynein kollarının işlevi için gerekli bir protein kodlar. Bu genin mutasyonları, PSD'nin şiddetli klinik bulgularına neden olabilir. Bu çalışma, CCDC40 homozigot mutasyonları olan pediatrik PSD hastalarının klinik ve demografik özelliklerini retrospektif olarak incelemeyi amaçlamıştır.

Gereç ve Yöntem: Marmara Üniversitesi Pediatrik Pulmonoloji polikliniğinde takipli 13 hasta çalışmaya alındı. Hastaların demografik verileri, klinik semptomları, yüksek hızlı video mikroskopisi (HSVM) bulguları, nazal nitrik oksit (nNO) ölçümleri, PICADAR skorları, balgam kültürü sonuçları ve solunum fonksiyonu testleri retrospektif olarak incelenmiştir. İstatistiksel analizler SPSS yazılımı kullanılarak yapıldı.

Bulgular: Çalışma grubunun medyan yaşı 17 yıl (25–75p, 11.5–21.5 yıl) olup, semptom başlangıç yaşı medyan 0 yıl (25–75p, 0–0 yıl) idi. Tanıda medyan gecikme süresi 7 yıl (25–75p, 2–13.5 yıl) idi. Hastaların %84.6'sında akraba evliliği mevcuttu. Yaygın semptomlar arasında kronik balgamlı öksürük (%100), bronşektazi (%92.3) ve rinosinüzit (%92.3) saptandı. Hastaların median PICADAR skoru 8 (25–75p, 5–11.5), median nazal NO değeri ise 17.3 nl/dk (25–75p, 7.7–114.5) olarak bulundu. HSVM analizinde hastaların %53.8'inde immotil silyalar, %30.7'sinde ise anormal hareket paterni saptandı. Balgam kültürlerinde en yaygın patojen Haemophilus influenzae (%92.3) idi.

Sonuç: PSD'nin yönetiminde erken tanı ve müdahale önemlidir. Özellikle CCDC40 mutasyonları olan hastalar, diğer genetik varyantlara kıyasla daha şiddetli solunum komplikasyonları yaşayabilirler.

Anahtar Sözcükler: CCDC40 mutasyonu; nazal nitrik oksit; primer siliyer diskinezi; yüksek hızlı video mikroskopi.