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ORIGINAL ARTICLE

Developmental and behavioral problems in preschool-aged primary ciliary dyskinesia patients

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Abstract

Primary ciliary dyskinesia (PCD) causes a broad spectrum of disease. This study aims to explore the developmental, behavioral, and social-emotional aspects of preschool-aged children with PCD. Fourteen PCD, 17 cystic fibrosis (CF) patients and 15 healthy subjects were enrolled. Developmental features of the participants were evaluated with Ages and Stages Questionnaire. Parents of participants filled out the Child Behavior Checklist (CBCL). The number of children screened positive for developmental delay was statistically higher in the PCD group. Higher numbers of children with PCD were screened positive for developmental delay in communication and problem-solving domains. Delay in fine motor skill domain was more common in children with PCD and CF compared to healthy subjects. There was no difference among the three groups in terms of gross motor and personal-social development. None of the children in all three groups was shown to have social-emotional problems. In CBCL, patients with CF had higher internalizing problem scores. Externalizing and total problem scores did not differ between the three groups. However, among PCD patients, children with developmental delay on more than one domain had higher externalizing and total problem scores.

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Conclusion: The current study revealed that positive screening for developmental delay is more common in preschool-aged PCD patients compared to patients with CF and healthy children.

What is Known:
- *Intelligence scores of school-aged PCD patients are similar to healthy subjects despite their higher internalizing problem scores on Child Behavior Checklist (CBCL).*
- *School-aged PCD patients exhibit higher hyperactivity and inattention findings.*

What is New:
- *Positive screening for developmental delay in communication, problem-solving and fine motor skills is more common in preschool-aged PCD patients.*
- *Preschool-aged PCD patients screened positive for developmental delay in more than one domain have higher externalizing and total problem scores on CBCL.*

Keywords Primary ciliary dyskinesia · Developmental delay · Behavioral problems · Social-emotional problems

Abbreviations

AAP	American Academy of Pediatrics
ASQ	Ages and Stages Questionnaire
ASQ:SE	Ages and Stages Questionnaire: social-emotional
ASQ-TR	Ages and Stages Questionnaire for Turkish children
CBCL	Child Behavior Checklist
CF	Cystic fibrosis
PSQ	Pediatric Sleep Questionnaire
PCD	Primary ciliary dyskinesia
SES	Socio-economic status
ASQ:SE-TR	Turkish version of the Ages and Stages Questionnaire: social-emotional

Introduction

Cilia are hair-like structures that present on the surface of many cells. Abnormality in cilia function and structure causes groups of heterogenic genetic diseases called ciliopathies. Primary ciliary dyskinesia (PCD), the first defined ciliopathy, is caused by genetic defects in motile cilia [19]. There are two types of cilia:motile (motor) and immotile (primary/sensory). Defects of motile cilia, which is located mainly in the respiratory system, ependymal cells on the surface of brain ventricles, and reproductive system, effect fluid mobilization and results in disease [16, 21]. Sensory cilia, which is present in almost every cell type of the human body sense extracellular signals and play role in nerve growth, proliferation, and differentiation [16, 19, 27]. In the embryonic stage, a transient type of motile cilia (nodal cilia) with "9 + 0" microtubule arrangement is present. Problems of nodal cilia, which play role in the left and right body organization, result in laterality defects that can be seen in patients with PCD [16].

PCD is a genetically heterogeneous recessive disorder characterized by congenital impairment of mucociliary clearance that results in a broad spectrum of disease including chronic oto-sino-pulmonary disease, male infertility, and organ laterality defects in approximately 50% of cases [3, 4, 23]. Otorhinolaryngologic symptoms including otitis media with effusion, chronic rhinosinusitis, and hearing impairment are common in patients with PCD [28, 32]. Furthermore, hearing problems have been reported to cause speech delay in PCD patients [29].

PCD was reported to have a negative impact on physical, emotional, and social functioning of patients [7, 8]. Although developmental, behavioral, and social-emotional perspectives of preschool children with PCD have not been studied yet, there are a few studies focusing on school-aged PCD patients [10, 30]. Carotenuto et al. [10] presented that school-aged children with PCD experience anxiety and depression and have more internalizing problems. However, they did not find any difference in the intelligence scores between healthy subjects and PCD patients [10]. Another study, on the other hand, reported increased hyperactivity and inattention findings in school-aged children with PCD [30]. Moreover, patients with PCD may suffer from obstructive sleep apnea syndrome, which is known to cause neurocognitive dysfunction in childhood [17].

Based on clinical observation, we hypothesized that PCD may have potential effects on the developmental and behavioral status of young children. The objective of this study is to explore and describe the developmental, behavioral characteristics, and social-emotional status of preschool-aged children with PCD and compare their results with same age group cystic fibrosis (CF) children and healthy controls. Since the first few years of life is a critical period of development of the brain [37], it is vital to find out developmental and behavioral problems and intervene adverse circumstances at early childhood. Therefore, investigation of the potential negative effects of PCD on developing child is crucial. The current study, to the best of authors' knowledge, is the first reporting the developmental and behavioral aspects of preschool children with PCD.

Material and methods

Population

All of the preschool PCD patients (*n*, 15) followed at Hacettepe University Pediatric Pulmonology Department were invited to enroll the study. Excluding the one with known neurologic disease, 14 patients were included in the current study. A control group of 17 CF patients without any known neurodevelopmental problems was randomly selected among the children treated for CF in the period of study. Moreover, 15 healthy children were randomly selected from general pediatrics clinic. Patients with CF were included in the study to enable a comparison with another chronic pulmonary disease. Children were examined in a period of better health conditions (without upper respiratory tract infections and pulmonary exacerbations). PCD was diagnosed in patients with specific symptoms (respiratory distress at neonatal period, daily non-seasonal nasal congestion, daily wet cough begins in infancy, persistent middle ear effusions, laterality defects) by analyzing high-speed video microscopy and/or abnormal ciliary ultrastructure via electron microscopy and nasal nitric oxide [6]. Measurement of nasal nitric oxide (NO) by NIOX MINO® was performed for only three patients, whose levels of nasal NO were lower than 15 nl/min. Vidoemicroscopy examinations demonstrated the presence of immotile cilia in 12 patients, and slow and dyskinetic ciliary beating in other 2 patients. Transmission electron microscopy of respiratory cilia was analyzed for one patient and the absence of outer dynein arm was detected. Genetic analysis, which was performed in two patients, revealed mutations associated with PCD. Most of the patients were diagnosed at an early age due to the presence of neonatal respiratory distress and situs inversus or history of sibling with PCD. All PCD patients were assessed by an otorhinolaryngologist during their routine clinical follow-up and information was obtained from their medical records. Otoscopic examinations of all patients were reported to be normal. Hearing tests of all patients were normal except two patients with mild hearing loss determined on audiometry test. Cardiac pathologies and laterality defects were also evaluated in all patients. PCD patients were not able to perform pulmonary function test due to their age. Daily chest physiotherapy is recommended to all PCD patients and antibiotics are given for acute respiratory exacerbations.

Evaluation procedures

Children with PCD and CF were evaluated by a multiprofessional team consisting of a child development specialist, developmental pediatricians, and pediatric pulmonologists. All children were assessed in terms of developmental, behavioral, and social-emotional status by a child development specialist and a developmental pediatrician, who were blinded to the condition of the participants. In this study, researchers asked parents "How often do you read books to your child" and "How often do you play or do home learning activities with your child" and questioned the screen time of their child to assess the quality of stimulation in home environment. Children, whose parents replied both questions as "not at all and occasionally," and with screen time above 1 h per day, which is the maximum screen time recommended by American Academy of Pediatrics (AAP) for children under age of six [25], were accepted to have poor quality of stimulation in home environment.

Caregivers of children were questioned for child age, gender, ordinal number, primary caregiver age, marital status, education, and employment status. Socio-economic status (SES) was measured by utilizing the Hollingshead four-factor index of social status, based on education and occupation levels of parents [20].

Evaluation tools

All participants were subjected to a play-based observational evaluation, which was performed by a child development specialist and a developmental pediatrician, to assess developmental problems, language problems, and autism spectrum disorders. Although originally the Ages and Stages Questionnaire (ASQ) is a parent-completed questionnaire, in this study, ASQ was administered via parent interviews in conjunction with the literature [31]. ASQ has 19 age-specific sub-questionnaires assessing the development of children in terms of communication, gross motor skills, fine motor skills, problem solving, and personal-social skills. While children who score lower than cutoffs in at least one domain are accepted as screened positive for developmental delay, ones who score above cutoffs are accepted typically developing [33]. ASQ is increasingly being recommended for the evaluation of development in clinical practice. Ages and Stages Questionnaire for Turkish children (ASQ-TR) [22] was used to assess the development of children in the present study. The sensitivity and specificity of ASQ-TR are 0.94 and 0.85, respectively [22].

The Ages and Stages Questionnaire:Social-Emotional (ASQ:SE) is a screening tool designed to be completed by parents to assess their children's social-emotional behaviors in terms of self-regulation, compliance, communication, adaptive behaviors, autonomy, affect, and interactions with people [34]. The sensitivity and specificity of the Turkish version of ASO:SE (ASQ:SE-TR) are 0.84 and 0.90, respectively [24]. In this study, questions of ASQ:SE-TR were answered by the mothers of the participants.

The Child Behavior Checklist for ages 1.5 to 5 years (CBCL/1.5–5), which is the extended form of the checklist for the children between the ages 2 and 3, is designed to be completed by parents to score their own child's behaviors [1, 2, 15]. CBCL/1.5–5 has seven syndrome scores: (i) emotionally reactive, (ii) anxious/depressed, (iii) somatic complaints, (iv) withdrawn, (v) sleep problems, (vi) attention problems, and (vii) aggressive. Moreover, the combination of emotionally reactive,

anxious/depressed, somatic complaints, and withdrawn scores constitute the "internalizing problems score" and the combination of attention problems and aggressive scores constitute the "externalizing problems score." These scores, together with the seven syndrome scores, and the one item added by the parents, constitute the "total problems score." In this study, CBCL/1.5–5 was completed by mothers to evaluate the behavioral problems of the participants.

Pediatric Sleep Questionnaire (PSQ) is a tool to evaluate sleep-related breathing disorders in children [11]. PSQ is composed of 22 items evaluating frequency and severity of snoring, apnea at night sleep, breathing difficulty during sleep, daytime sleepiness, attention deficit, hyperactivity, and other pediatric obstructive sleep apnea symptoms. The mean of the scores of all items is the total score of PSQ and the score above 0.33 is usually accepted positive for sleep-related breathing disorders. In this study, parents of children with PCD completed the validated Turkish version of Pediatric Sleep Questionnaire [40] for the assessment of sleep related breathing disorders.

Statistical analyses

Statistical analyses were performed with the IBM SPSS for Windows Version 22.0. Numerical variables were summarized as mean ± standard deviation or median [minimum-maximum]. Categorical variables were given as frequencies and percentages. Categorical variables were compared by chi square test. Normality of the continuous variables was evaluated by Kolmogorov Smirnov test. Differences between the groups according to continuous variables were determined by one way ANOVA or Kruskal Wallis test as appropriate. Posthoc comparisons were done by Tukey or Connover-Dunn test. Differences between two independent groups according to continuous variables were determined by Mann Whitney *U* test. A *p* value less than 0.05 was considered as significant.

Results

In the current study, 14 children with PCD (7 boys and 7 girls) aged 46.5 ± 17.5 months, 17 children with CF (5 boys and 12 girls) aged 51.0 ± 14.7 months, and 15 healthy children aged 48.8 ± 14.0 months (6 boys and 9 girls) were included. Three of the children in each PCD and CF groups were born between 35 and 36 weeks. None of the children was small for gestational age. Head circumferences of all children were in the normal range. Neurological examinations of all patients were normal and none of the patients had a symptom of hydrocephalus in the PCD group. All participants had normal biometry except one patient in CF group with lower weight for age. In the CF group, the numbers of patients suffered from vitamin A and vitamin E deficiency were 2 and 1, respectively. Oxygen saturation of all patients with PCD and CF were within the normal range. While the median age at the diagnosis in PCD group was 16 (1–48) months, it was 2 years (6 months-8 years) in the CF group. The median of the number of hospitalizations in PCD and CF patients were 2 (0–8) and 1 (0–8), respectively. It is worth noting that the CF patient with delay in more than one domain had only one single hospitalization at the age of 5 months. While the median of number of hospitalizations in patients with no developmental delay or delay in only one domain was 2.5 (1–8), it was 1.5 (0–3) in patients with developmental delay in more than one domain.

Maternal education was higher in the control group than in the PCD and CF groups (*p*, 0.01). SES was also higher (lower Hollingshead-Redlich index) in the control group (*p*, 0.03). However, both maternal education and SES did not statistically differ between the PCD and CF groups. PSQ scores of all the PCD patients were normal. Only one PCD patient had a slightly higher PSQ score compared to the rest of the group. However, this patient had normal apnea hypopnea index according to the polysomnography test. Other sociodemographic characters (listed in Table 1) and the quality of stimulation in home environment, and the status of attending preschool/kindergarten were not statistically different between the three groups.

None of the children in the three groups had developmental evaluation prior to this study. Parents were questioned for concerns about their child's development. While five parents in the PCD group stated concerns about their child's language development, parents of children in the CF and the healthy control groups did not express any concern.

The numbers of children screened positive for developmental delay by ASQ and ASO:SE are presented in Table 2. All patients with developmental delay were accepted to a developmental follow-up program and referred to early intervention services based on their special needs. None of the healthy subjects were delayed on any domain of ASQ. The number of children with a developmental delay at least in one of the domains of ASQ was higher in the PCD group compared to both CF group (*p*, 0.01) and healthy subjects ($p < 0.001$). It was also higher in the CF group compared to healthy subjects (*p*, 0.04).

Higher number of patients with PCD was screened positive for developmental delay in more than one domain of ASQ compared to the other groups (*p*, 0.002). In the PCD group, positive screening for developmental delay was statistically higher than the other groups in terms of communication (*p*, 0.0003) and problem-solving (*p*, 0.001). In terms of fine motor delay, there was no difference between patients with PCD and CF. However, delayed fine motor skills was more common in children with PCD and CF compared to healthy subjects (*p*, 0.002). There was no difference among the three groups in gross motor and personal-social domains. None of the children in all the three groups had a score above the cut-off, which indicates a social-emotional problem in ASQ:SE-TR.

Table 1 Sociodemographic characteristics of the three groups

	Primary ciliary dyskinesia (*n*, 14)	Cystic fibrosis (*n*,17)	Healthy children (*n*,15)	*p* value
Maternal age[b]	31.7 ± 5.8	33.5 ± 6.3	34.0 ± 4.7	0.531
Paternal age[b]	35.1 ± 6.9	37.5 ± 7.9	36.5 ± 4.6	0.616
Maternal education (years)[a]	8.0 (0–16)	8.0 (1–16)	14.0 (5–16)	0.019
Paternal education (years)[a]	8.0 (5–16)	11.0 (2–16)	16.0 (3–16)	0.770
Number of household[a]	4.5 (3–7)	4.0 (2–10)	4.0 (3–6)	0.642
Number of children[a]	2.0 (1–5)	2.0 (1–3)	2.0 (1–4)	0.418
Birth order[a]	2.0 (1–5)	2.0 (1–3)	1.0 (1–4)	0.438
Consanguinous marriage[c]	7 (50%)	8 (47%)	2 (13%)	0.069
Hollingshead-Redlich index[a]	4.0 (2–5)	4.0 (2–5)	3.0*(2–5)	0.037

[a] Median values and minimum-maximum values are presented

[b] Mean values and standard deviations are presented

[c] Percentages are presented

*Group, which makes the statistical difference

The PCD patients were divided into two groups: (i) patients with no delay or screened positive for developmental delay in only one domain (*n*, 8) and (ii) patients screened positive for developmental delay on more than one domain (*n*, 6). Patients who have developmental delays on more than one domain had lower SES (higher Hollingshead-Redlich index) than the other PCD patients (*p*, 0.04). Respiratory and ear-nose-throat problems of these two groups are presented in Table 3. Statistical analysis could not be performed between these two groups due to the small sample size. None of the patients with developmental delay on more than one domain had hearing impairment. Clinical severity of disease was similar among PCD patients in either group. Pediatric Sleep Questionnaire scores of all PCD patients were below 0.33.

In terms of behavior problems, patients with CF had statistically higher internalizing problem scores on CBCL compared to healthy subjects (*p*, 0.03), but not higher compared to PCD patients (*p*, 0.33). CF and PCD patients had higher internalizing, externalizing, and total problem scores than healthy controls. On the other hand, problem scores of the three groups were not statistically different (see Table 4). Among PCD patients, children with developmental delays on more than one domain had statistically higher (*p*, 0.043) externalizing and total problem scores (*p*, 0.02) compared to PCD patients with no delay or delay in only one domain.

Discussion

Defining the developmental risks in early childhood is vital for the referral of child to early intervention services timely. Early detection of developmental and behavioral problems is also crucial for better academic and psychosocial outcomes of children with PCD. However, the literature lacks in terms of the data regarding developmental status of preschool-aged children with PCD. The present study, which questioned the possible effects of PCD on development and behavior of children, revealed that positive screening for developmental

Table 2 Distribution of the number of children with delay in the domains of the Ages and Stages Questionnaire

	Primary ciliary dyskinesia (*n*, 14)	Cystic fibrosis (*n*, 17)	Healthy subjects (*n*, 15)	*p* values
Communication	6*	0	0	0.0003
Gross motor	1	0	0	0.297
Fine motor	7*	5*	0	0.002
Problem solving	5*	0	0	0.001
Personal-social	3	1	0	0.810
Social emotional	0	0	0	
Delay in any domain	11*	5	0	< 0.001
Delay in more than one domain	6*	1	0	0.002

*Group, which makes the statistical difference

Table 3 Distribution of the number of the clinical characteristics of PCD patients according to developmental delay in Ages and Stages Questionnaire

	Number of patients with no developmental delay or delay in only one domain (*n*, 8)	Number of patients with developmental delay in more than one domain (*n*, 6)
Persistent rhinitis	4	4
Recurrent sinusitis	1	0
Recurrent pneumonia	5	2
Bronchial hyperreactivity	6	3
Recurrent upper airway infections	7	1
Nasal polyposis	1	0
Recurrent middle ear problems	4	1
History of hearing loss	5	0
Current mild hearing loss	2	0
Situs inversus totalis	6	5
Major cardiac defect	0	1[a]
Prematurity	2	1
Hospitalization in the newborn period	7	5
Hospitalization in the first year of life	6	3
Exacerbations requiring hospitalization in the last year	0	1
High score of Pediatric Sleep Questionnaire	0	0

[a] Left-transposition of great arteries, ventricular septal defect

*Hypothesis test could not be done due to the insufficient number of patients in each groups

delay is more common in patients with PCD compared to both patients with CF and healthy subjects.

In terms of behavioral problems, children with CF were reported to have more internalizing problem scores on Child Behavior Checklist [36, 38]. While higher internalizing problems scores of CBCL in school-aged PCD patients were reported in the literature [10], evaluation of the behavioral profile of preschool-aged PCD patients remain absent. In accordance with the literature, the current study presented statistically higher internalizing problem scores of patients with CF compared to healthy controls. Although internalizing, externalizing and total problem scores of PCD patients were higher than healthy controls, scores were not statistically different. However, within the PCD group, patients with developmental delay in more than one domain had higher externalizing and total problem scores compared to the remaining patients with PCD. In conjunction with the literature, where behavioral problems were reported to be more common in children with developmental delay [5, 14], this study revealed that PCD patients with more developmental problems tend to have higher behavioral problem scores.

The children of parents with higher SES are known to have higher quality of home environment and better developmental outcomes. Therefore, the current study considered SES as a potential factor influencing developmental status of children, and, within the PCD group, we found that patients with the delay in more than one developmental domain tended to have lower SES. However, PCD and CF groups did not differ in terms of SES and quality of home environment. Therefore, it would be misleading to associate the high frequency of potential developmental delay of the PCD group solely with SES. Preschool-aged children with chronic illness were reported to have higher risk of vulnerability on all developmental domains [9]. This study investigated two different chronic illnesses, PCD and CF, in terms of all developmental domains. Developmental delay in fine motor skills was higher in both PCD and CF groups compared to healthy subjects. There are conflicted results in previous studies on motor development of children with CF. While motor performance was found to be normal in preschool children with CF in a study [18], another study reported gross and fine motor delays in CF children [12]. Developmental delay on gross motor domain was observed in neither PCD nor CF groups in the current study. Fine motor abilities can vary based on whether a child has had exposure to tools that require fine motor skills such as scissors, pencils etc. The authors speculate that the higher number of children with delay in fine motor skill domain in the CF and PCD groups

Table 4 Internalizing, externalizing, and total problem scores on the Child Behavior Checklist

	Primary ciliary dyskinesia (*n*, 14)	Cystic fibrosis (*n*, 17)	Healthy subjects (*n*, 15)	*p* value
Internalizing problem score[a]	12.9 ± 6.0	16.6 ± 7.5*	9.9 ± 7.5	0.035
Externalizing problem score[a]	12.1 ± 8.3	12.1 ± 7.1	10.7 ± 4.8	0.811
Total score[a]	39.6 ± 15.7	43.9 ± 17.6	32.6 ± 17.5	0.181

*Group, which makes the statistical difference

[a:] Mean values and standard deviations

may be associated with the presence of a chronic illness and/or lower SES of children and/or decreased exposure to activities developing fine motor skills.

In the literature, there are few reports on the cognitive profile of PCD patients. Carotenuto et al. [10] found no differences in terms of intelligence scores between 10 school-aged PCD patients and 34 healthy subjects. On the other hand, another study showed higher hyperactivity and inattention findings in school-aged PCD patients without intelligence assessment [30]. In this study, children screened positive for delays in communication and problem-solving domains were only in the PCD group. Furthermore, it should be noted that five parents who had concerns about their child's development were in the PCD group and there were no parents with a developmental concern in the other two groups.

Although motile and sensory cilia are structurally similar to each other, their defects have distinct clinical manifestations [19, 26]. It has been shown that overlap can be present between sensory and motor ciliopathies [16]. Motile cilia was found to express sensory bitter taste receptors similar to tongue, which means it has sensory functions [21]. In the literature, concomitance of retinitis pigmentosa, which is one of the sensory ciliopathies, and PCD was reported in a few cases [13]. Moreover, it was reported that the risk of bronchiectasis increases in adults with autosomal dominant polycystic kidney disease, which indicates accompanying motile cilia dysfunction [16]. Furthermore, there are a few case reports of patients with Usher syndrome having PCD findings [21]. Nearly half of the PCD patients have situs inversus, although PCD is a result of a genetic defect in motile cilia [16, 19]. Embryonic node, which is responsible for laterality defects, was reported to include both motile and non-motile cilia. Non-motile cilia play role in the sensation of the flow, while motile cilia are responsible for the extra-embryonic fluid movement [16]. Therefore, PCD patients with laterality defects may have a higher risk of developing concomitant sensory cilia defects. In our cohort, which included only preschool-aged PCD patients, laterality defects were found to be more frequent than previous studies probably due to the fact that children with laterality defects diagnosed with PCD earlier. On the other hand, ependymal cells on the surface of cerebral ventricles are lined by motile cilia, which have role in cerebral spinal fluid movement. Although cerebral ventriculomegaly and hydrocephalus were shown in animal models with PCD and enlargement of ventricles or hydrocephalus was rarely reported in PCD patients [39], none of PCD patients had a symptom of hydrocephalus in the current study.

In our cohort, the number of the patients who were screened positive for developmental delay was higher in the PCD group. Contrary to expectations, this finding was not related to hearing impairment or the severity of the disease. On the other hand, mutations of DYX1C1, which is associated with dyslexia and neuronal migration in the developing neocortex, were reported in PCD patients [35]. In our study population, only two patients had genetic evaluation and DYX1C1 mutations were not detected in these two patients. Considering all of the aforementioned studies and findings of this study, the developmental delay of PCD patients may be attributed to the overlap of sensory and motor ciliopathies, effects of mutations on neurodevelopment or the unknown neurodevelopmental effects of motile cilia located in cerebral ventricles.

ASQ is a screening tool, which limited us to make a definite conclusion about developmental status of children. However, in preschool period, to screen children for developmental delays and identify the children with potential risk of developmental delay is highly crucial. In the current study, the sample size of PCD patients was limited due to the inherent challenge of the early diagnosis of PCD, and we believe that larger sample size studies and gold standard developmental assessment tools appropriate for this age group are needed to confirm our findings.

Conclusion

To the best of our knowledge, this is the first study exploring the developmental problems and behavioral characteristics of preschool children with PCD. The current work revealed that children who screened positive for developmental delay is more common in PCD patients compared to patients with CF and healthy children under 6 years of age. Since it is crucial to find out potential developmental delays and refer the child to early intervention services in time, clinicians should closely monitor preschool-aged patients with PCD in terms of developmental and behavioral problems. Future studies utilizing exact diagnostic tools with larger sample size are needed to confirm the results presented in the current study.

Authors' contributions Zengin Akkus P and Gharibzadeh Hizal M conceptualized and designed the study. They were responsible for all the assessments of patients. They drafted the initial manuscript, revised the manuscript, and approved the final manuscript.

Ilter Bahadur E, Esref S, and Ozdemir G were responsible for collecting data, they revised the manuscript and approved the final manuscript.

Karahan S carried out the statistical analyses, interpreted the statistical data, reviewed the manuscript, and approved the final manuscript.

Yalcin E, Dogru Ersoz D, and Kiper N interpreted the data, reviewed the manuscript, and approved the final manuscript.

Ozmert EN and Ozcelik U conceptualized and designed the study, supervised all the assessments of patients. They interpreted the statistical data, reviewed the manuscript, and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from parents of all participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee of the Hacettepe University Faculty of Medicine approved the study design. This article does not contain any studies with animals performed by any of the authors.

References

1. Achenbach TM (1992) Manual for the child behavior checklist/2–3 and 1992 profile: profile for boys and girls. Auswertungsbögen. Department of Psychiatry, University of Vermont
2. Achenbach TM, Rescorla LA (2000) Manual for the ASEBA preschool forms and profiles, vol 30. University of Vermont, Research center for children, youth, & families, Burlington
3. Afzelius BA (1976) A human syndrome caused by immotile cilia. Science (New York, NY) 193(4250):317–319
4. Afzelius BA, Stenram U (2006) Prevalence and genetics of immotile-cilia syndrome and left-handedness. Int J Dev Biol 50(6):571–573. https://doi.org/10.1387/ijdb.052132ba
5. Baker BL, McIntyre LL, Blacher J, Crnic K, Edelbrock C, Low C (2003) Pre-school children with and without developmental delay: behaviour problems and parenting stress over time. J Intellect Disabil Res 47(Pt 4-5):217–230
6. Barbato A, Frischer T, Kuehni CE, Snijders D, Azevedo I, Baktai G, Bartoloni L, Eber E, Escribano A, Haarman E, Hesselmar B, Hogg C, Jorissen M, Lucas J, Nielsen KG, O'Callaghan C, Omran H, Pohunek P, Strippoli MP, Bush A (2009) Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. Eur Respir J 34(6):1264–1276. https://doi.org/10.1183/09031936.00176608
7. Behan L (2016) Primary ciliary dyskinesia: a biopsychosocial approach. PhD Thesis, University College Cork
8. Behan L, Rubbo B, Lucas JS, Dunn Galvin A (2017) The patient's experience of primary ciliary dyskinesia: a systematic review. Qual Life Res Int J Qual Life Asp Treat Care Rehab 26(9):2265–2285. https://doi.org/10.1007/s11136-017-1564-y
9. Bell MF, Bayliss DM, Glauert R, Harrison A, Ohan JL (2016) Chronic illness and developmental vulnerability at school entry. Pediatrics 137(5):e20152475. https://doi.org/10.1542/peds.2015-2475
10. Carotenuto M, Esposito M, Di Pasquale F, De Stefano S, Santamaria F (2013) Psychological, cognitive and maternal stress assessment in children with primary ciliary dyskinesia. World J Pediatr 9(4):312–317. https://doi.org/10.1007/s12519-013-0441-1
11. Chervin RD, Hedger K, Dillon JE, Pituch KJ (2000) Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med 1(1):21–32
12. de Almeida Thomazinho P, de Miranda Chaves CR, Passaro CP, Meio MD (2011) Motor delay in cystic fibrosis infants: an observational study. Early Hum Dev 87(12):769–773. https://doi.org/10.1016/j.earlhumdev.2011.05.012
13. De Brauwer PJ, Blaise P, Hermans G, Boniver V, Bartsch P, Rakic JM (2010) Retinitis pigmentosa and bronchiectasis: a case report on a rare association suggestive of a common underlying primary ciliary dyskinesia (PCD). Bull Soc Belge Ophtalmol (314):9–14
14. Dekker MC, Koot HM, van der Ende J, Verhulst FC (2002) Emotional and behavioral problems in children and adolescents with and without intellectual disability. J Child Psychol Psychiatry Allied Discip 43(8):1087–1098
15. Erol N, Simsek Z, Oner O, Munir K (2005) Behavioral and emotional problems among Turkish children at ages 2 to 3 years. J Am Acad Child Adolesc Psychiatry 44(1):80–87
16. Ferkol TW, Leigh MW (2012) Ciliopathies: the central role of cilia in a spectrum of pediatric disorders. J Pediatr 160(3):366–371. https://doi.org/10.1016/j.jpeds.2011.11.024
17. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K (2010) Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea. Pediatrics 126(5):e1161–e1167. https://doi.org/10.1542/peds.2010-0688
18. Gruber W, Orenstein DM, Paul K, Huls G, Braumann KM (2010) Motor performance is better than normal in preschool children with cystic fibrosis. Pediatr Pulmonol 45(6):527–535. https://doi.org/10.1002/ppul.21098
19. Hildebrandt F, Benzing T, Katsanis N (2011) Ciliopathies. N Engl J Med 364(16):1533–1543. https://doi.org/10.1056/NEJMra1010172
20. Hollingshead AB (1975) Four factor index for social status. Yale University Press, New Haven
21. Horani A, Ferkol TW (2016) Primary ciliary dyskinesia and associated sensory ciliopathies. Expert Rev Respir Med 10(5):569–576. https://doi.org/10.1586/17476348.2016.1165612
22. Kapci EG, Kucuker S, Uslu RI (2010) How applicable are ages and stages questionnaires for use with Turkish children? Top Early Child Spec Educ 30(3):176–188. https://doi.org/10.1177/0271121410373149
23. Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW (2013) Primary ciliary dyskinesia. Recent advances in diagnostics, genetics, and characterization of clinical disease. Am J Respir Crit Care Med 188(8):913–922. https://doi.org/10.1164/rccm.201301-0059CI
24. Kucuker S, Kapci EG, Uslu RI (2011) Evaluation of the Turkish version of the "ages and stages questionnaires: social-emotional" in identifying children with social-emotional problems. Infants Young Child 24(2):207–220
25. Media and Young Minds (2016) Pediatrics 138(5):e20162591. https://doi.org/10.1542/peds.2016-2591
26. Nonaka S, Tanaka Y, Okada Y, Takeda S, Harada A, Kanai Y, Kido M, Hirokawa N (1998) Randomization of left-right asymmetry due to loss of nodal cilia generating leftward flow of extraembryonic fluid in mice lacking KIF3B motor protein. Cell 95(6):829–837
27. Pazour GJ, Dickert BL, Vucica Y, Seeley ES, Rosenbaum JL, Witman GB, Cole DG (2000) Chlamydomonas IFT88 and its mouse homologue, polycystic kidney disease gene tg737, are required for assembly of cilia and flagella. J Cell Biol 151(3):709–718
28. Prulière-Escabasse V, Coste A, Chauvin P, Fauroux B, Tamalet A, Garabedian E-N, Escudier E, Roger G (2010) Otologic features in children with primary ciliary dyskinesia. Arch Otolaryngol Head Neck Surg 136(11):1121–1126
29. Sagel SD, Davis SD, Campisi P, Dell SD (2011) Update of respiratory tract disease in children with primary ciliary dyskinesia. Proc Am Thorac Soc 8(5):438–443
30. Sismanlar Eyuboglu T, Aslan AT, Ceylan A, Soysal AS, Budakoglu II, Ulukavak Ciftci T, Kokturk O (2018) Neurocognitive disorders and sleep in children with primary ciliary dyskinesia. Pediatr Pulmonol 53(10):1436–1441. https://doi.org/10.1002/ppul.24133
31. Small JW, Hix-Small H, Vargas-Baron E, Marks KP (2018) Comparative use of the ages and stages questionnaires in low- and middle-income countries. Dev Med Child Neurol 61:431–443. https://doi.org/10.1111/dmcn.13938
32. Sommer JU, Schäfer K, Omran H, Olbrich H, Wallmeier J, Blum A, Hörmann K, Stuck BA (2011) ENT manifestations in patients with primary ciliary dyskinesia: prevalence and significance of otorhinolaryngologic co-morbidities. Eur Arch Otorhinolaryngol 268(3):383–388

33. Squires JPL, Bricker D (1999) The ASQ user's guide for the ages & stages questionnaires: a parent-completed, child-monitoring system, 2nd edn. Paul H. Brookes Publishing Co, Baltimore
34. Squires J, Bricker D, Twombly E (2003) The ASQ: SE user's guide. Paul H. Brooks Publishing Co, Baltimore
35. Tarkar A, Loges NT, Slagle CE, Francis R, Dougherty GW, Tamayo JV, Shook B, Cantino M, Schwartz D, Jahnke C, Olbrich H, Werner C, Raidt J, Pennekamp P, Abouhamed M, Hjeij R, Köhler G, Griese M, Li Y, Lemke K, Klena N, Liu X, Gabriel G, Tobita K, Jaspers M, Morgan LC, Shapiro AJ, Letteboer SJ, Mans DA, Carson JL, Leigh MW, Wolf WE, Chen S, Lucas JS, Onoufriadis A, Plagnol V, Schmidts M, Boldt K, Roepman R, Zariwala MA, Lo CW, Mitchison HM, Knowles MR, Burdine RD, Loturco JJ, Omran H (2013) DYX1C1 is required for axonemal dynein assembly and ciliary motility. Nat Genet 45(9):995–1003. https://doi.org/10.1038/ng.2707
36. Thompson RJ Jr, Gustafson KE, Hamlett KW, Spock A (1992) Psychological adjustment of children with cystic fibrosis: the role of child cognitive processes and maternal adjustment. J Pediatr Psychol 17(6):741–755
37. Tierney AL, Nelson CA 3rd (2009) Brain development and the role of experience in the early years. Zero Three 30(2):9–13
38. Ward C, Massie J, Glazner J, Sheehan J, Canterford L, Armstrong D, Jaffe A, Hiscock H (2009) Problem behaviours and parenting in preschool children with cystic fibrosis. Arch Dis Child 94(5):341–347. https://doi.org/10.1136/adc.2008.150789
39. Wessels MW, den Hollander NS, Willems PJ (2003) Mild fetal cerebral ventriculomegaly as a prenatal sonographic marker for Kartagener syndrome. Prenat Diagn 23(3):239–242. https://doi.org/10.1002/pd.551
40. Yuksel H, Sogut A, Yilmaz O, Kutluay E (2011) Reliability and validity of the Turkish version of the pediatric sleep questionnaire: a tool for prediction of sleep related breathing disorder. Tuberk Toraks 59(3):236–241