Primary ciliary dyskinesia (PCD) is a rare inherited disease with a prevalence of about 1:20,000. The underlying pathogenesis is disrupted ciliary function, which results in delayed mucus transportation leading to chronic inflammation, mainly in the upper and lower respiratory tract. Although the pathogenesis of the disease and its clinical presentation is somewhat understood, data regarding the prevalence of accompanying symptoms is limited, especially in the field of otorhinolaryngology. A total of 44 patients diagnosed with PCD answered a questionnaire regarding the diagnosis and clinical presentation of the disease, their medical history and clinical manifestations, and medical treatment in the field of otorhinolaryngology. The majority of participants (70%) had seen a physician more than 50 times before the diagnosis was made at an average age of 10.9 ± 14.4 years. As much as 59% of all patients had recurring problems at the paranasal sinuses and 69% of these patients needed corresponding surgical intervention. Even more patients (81%) suffered from recurring otitis media and, as a result, 78% of these patients underwent paracentesis with temporary tympanostomy tubes at least once at an average age of 9.5 ± 13.0 years. Otorhinolaryngologic symptoms, especially chronic otitis media and chronic rhinosinusitis, are frequently associated with PCD. Surgical intervention to treat these symptoms is common. The awareness of this disease should be raised, especially among ENT physicians, and surgical intervention should be indicated carefully.

Keywords Cilia · Primary ciliary dyskinesia · Rhinosinusitis · Otitis media

Introduction

Most cell types carry either immotile or motile monocilia (single cilia) or multiple cilia, which are involved in various processes important for development and/or organ integrity [1]. Motile cilia are responsible for the clearance of the mucous membranes of the upper and lower respiratory tract. With a regular, fast and synchronous beating pattern, dust and other inhaled particles are eliminated from the respiratory tract. The debris is transported in a layer of mucus, much like a conveyor belt [2, 3]. Additionally, beating cilia are essential in the male and female genital tracts, the paranasal sinuses, the middle ear and the Eustachian tube [4]. The mechanism of beating cilia and the way debris is transported is mostly understood [5].

Primary ciliary dyskinesia (PCD) is an autosomal recessive disorder leading to an impairment of ciliary function and mucosal clearance leading to recurrent upper and lower respiratory tract infections. In addition, PCD patients
regularly suffer from otitis media, chronic sinusitis and infertility.

About 50% of PCD patients are also diagnosed with a mirror-image organ arrangement, which, in combination with chronic sinusitis and bronchiectasis, is called Kartagener syndrome. In rare cases, there are also other forms of heterotaxy [6].

Due to the low incidence, the prevalence of PCD is difficult to assess. Most studies report a prevalence of between 1:15,000 and 1:50,000. Assuming that many mild cases remain undiagnosed, an estimate of 1:4,100 might be closer to reality [7, 8]. In Germany, the total number of patients is estimated to be 4,000, including 900 (23%) children and adolescents [9].

Confirmation of a tentative PCD diagnosis is made using brush biopsy and adjacent high-speed video microscopy where the ciliary beat frequency and beating pattern are analyzed [10]. Other diagnostic instruments include transmission electron microscopy [11], high-resolution immunofluorescence microscopy [12] and nasal nitric oxide assessment [13]. In addition, various genetic defects, which can be screened for, have been described [14].

Although there is convincing evidence that an early diagnosis and treatment improve long-term outcome, diagnosis is often made late [6]. The reason may be that PCD is a clinical syndrome, often difficult to distinguish from other disorders. Furthermore, patients may consult different medical subspecialties, depending on the predominant clinical manifestation [15].

As the upper and lower airway is primarily affected by PCD, symptoms can be divided into pulmonary symptoms and ENT manifestations. ENT symptoms include chronic rhinitis, recurrent and chronic rhinosinusitis and recurrent otitis media [7]. Although these otorhinolaryngologic manifestations have been well described [16], data regarding their prevalence, the associated symptoms and the role of the ENT specialist in the diagnostic process are currently lacking [17].

Materials and methods

The study was performed at the Department of Otorhinolaryngology, Head and Neck Surgery at the University Hospital Mannheim. The study protocol was reviewed and approved by the local ethics board of the Medical Faculty Mannheim, University of Heidelberg. Written informed consent was obtained from all the participants.

A questionnaire was published in “Zielenfocus”, the journal of the German PCD support group “Kartagener Syndrom und Primäre Ciliäre Dyskinesie e. V.”. Furthermore the questionnaire was sent to 63 PCD patients under the care of the Department of Pediatrics, University Medical Center Freiburg. In those cases where the patients were children or adolescents, the questionnaire was sent to the caregivers.

The questionnaire included three sets of questions. The first set addressed personal data such as age, sex, age at diagnosis, whether the patient has a situs inversus, the speciality of the doctor who had diagnosed PCD, the total number of consultations until the diagnosis of PCD was made and the area of initial manifestation (to which the answer was limited to “ear”, “nose”, “lung” and “other”). In addition, patients were asked to rate the relevance of the ENT physician in the diagnostic process of PCD on a scale from 1 (“no relevance”) to 10 (“high relevant”).

The second set of questions assessed otologic manifestations of the disease such as the age of the first episode of otitis media and how often the patient had to be treated with antibiotics because of otitis media. More focused questions were asked of ventilation tube (VT) insertions if these had been used: the age of first insertion, the number of subsequent insertions and the cause of insertions. Furthermore, the presence of persisting hearing impairment was assessed and the patients were asked whether they had received speech therapy in the past.

The third set of questions covered the paranasal sinuses. The patients were asked how often there had been an inflammation of the paranasal sinuses and at what age this inflammation first occurred, how often they had to take antibiotics because of these infections and whether they had X-ray examinations due to acute or chronic sinusitis. Finally, patients were asked whether they had undergone sinus surgery and, if so, at what age.

Statistical analysis and plotting was done using “R” version 2.11.0, an open source environment for statistical computing and graphics [18]. For statistical analysis like situs inversus compared to the age of diagnosis and situs inversus compared to the number of consultations, the exact Mann–Whitney–Wilcoxon rank-sum test as a non-parametric test was used. A p value less than 0.05 was considered statistically significant.

Results

Forty-four patients or caregivers of children with PCD returned the questionnaire. The response rate from those sent the questionnaire personally was 46% (29 out of 63). Diagnostic details of the patients who had previously been diagnosed with PCD in the Department of Pediatrics, University Medical Center Freiburg, were available and had been collected independently from our study.

In 27 of these 29 patients diagnosis of PCD was made on the basis of at least one abnormal confirmatory test, including ciliary beat analysis, electron microscopy, high-resolution
immunofluorescence microscopy or genetic analysis [14]. In 24 of the 27 PCD patients, the ciliary beat was assessed by high-speed video microscopy. All individuals had either immotile or dyskinetic cilia. In 15 patients, an outer dynein arm defect was identified by electron microscopy and/or immunofluorescence microscopy. In three patients, electron microscopy identified inner dynein arm abnormalities. In seven individuals, analysis identified mutations in the reported PCD genes. Four patients carried DNAH5 mutations, two had DNAI1 mutations and one had KTU mutations. In the two remaining patients, results of confirmatory tests were not available, but the clinical picture was consistent with either Kartagener syndrome or primary ciliary dyskinesia.

In the other 15 patients, PCD was diagnosed at various other specialized clinical centers throughout Germany including one or more confirmatory tests.

Epidemiology

Of the participants, 45% were male and the average age of all participants was 28.8 ± 22.8 years. The patients were first diagnosed with PCD at a mean age of 10.9 ± 14.4 years; 70% had an accompanying situs inversus and 32% (the largest group) had seen a doctor between 50 and 100 times until the diagnosis of PCD was made (Fig. 1). The first symptoms of PCD were seen in the lungs of 51% of the patients, the nose and sinuses of 35% of patients and the ears of 14% of patients.

An accompanying situs inversus led to a significant earlier diagnosis of PCD (p = 0.026, Fig. 2). Situs inversus also highly negatively correlated with the number of consultations before the diagnosis of PCD was made (p = 0.0006, Fig. 3).

The average score of the ENT physicians’ relevance rating was 5.2 ± 3.7 on a scale of 1 (“no relevance”) to 10 (“high relevant”). Figure 4 shows a histogram of the data. Patients diagnosed by their ENT doctor (38%) were
significantly ($p = 0.005$) older compared to patients diagnosed by other specialists.

**Chronic otitis media and related diseases**

Only 19% of patients surveyed did not suffer from recurring otitis media. The remaining 81% were, on average, $2.3 \pm 3.4$ years old when they were first affected with otitis media. As much as 38% of patients with recurrent otitis media needed more than 30 antibiotic treatments in their life due to the disease, 28% needed between 10 and 30 treatments and 46% needed less than 10. Of the patients with recurring otitis media, 78% received a tympanostomy tube (VT) in the past. The average age at which the first VT was inserted was $9.5 \pm 13.0$ years. After this first paracentesis, 32% of all PCD patients needed a second one, 15% needed a third and 32% needed more than three. As much as 17% needed ear surgery other than paracentesis with a VT and 72% reported persistent auditory impairment; 26% had received speech therapy in the past.

**Chronic rhinosinusitis and related diseases**

Of the returned questionnaires, 59% documented that patients had previous recurrent problems concerning the paranasal sinuses in terms of rhinosinusitis. The affected PCD patients had their first sinusitis diagnosed at an average age of $6.8 \pm 5.4$ years; 25% of patients with recurrent rhinosinusitis did not receive antibiotic treatment; 19% needed antibiotics up to 10 times, 24% up to 30 times and 32% more than 30 times. On average, affected children received antibiotic treatment for recurrent sinusitis 25 times until they reached the age of 10 years.

Of the patients suffering from recurring nasal problems, 86% underwent further diagnostic measures regarding their sinusitis leading to ionized radiation such as X-ray or computed tomography at least once. Finally, 69% of these patients with recurrent rhinosinusitis had to undergo sinus surgery at least once.

**Discussion**

The diagnosis of PCD is often made late [19] and patients suffering from this disease must endure a long and unnecessary ordeal. As 70% of the participants of the study needed to see a doctor more than 50 times before the diagnosis of PCD was made, awareness regarding this disease needs heightening.

To assess the prevalence and significance of otorhinolaryngologic co-morbidities of PCD, a questionnaire regarding the diagnosis, symptoms and the way they were treated was published in the association journal of the German PCD support group. Furthermore, 63 PCD patients cared for at the Department of Pediatrics, University Medical Center Freiburg received copies of the questionnaire.

**Epidemiology**

The participating patients were first diagnosed with PCD at the age of $13.4 \pm 14.8$ years, which is relatively old compared to the mean age of 4.4 years as described in other studies [17, 20]. The large group of patients with situs inversus was significantly younger at the time of diagnosis and saw a physician less frequently, which was consistent with previous work [20]. This may be explained by the fact that without this prominent phenomenon, the diagnosis of PCD is much more difficult to make [21]. This theory is supported by the fact that patients who were diagnosed by their ENT doctor were significantly older compared to those diagnosed by other specialists. The demographics of our population is dissimilar to that of other studies, possibly due to the high number of patients with ENT-related symptoms. This selection bias is the major limitation of the present study as patients with ENT-related problems might have had a stronger motivation to participate in studies regarding ENT symptomatology.

**Chronic otitis media and related diseases**

As disturbed ciliary motion causes mucus to be retained in the middle ear [22], 81% of the patients had a recurring otitis of the middle ear already at an age of $2.3 \pm 3.4$ years. This is consistent with previously published data [23, 24].
The extensive use of antibiotics, especially in children with recurring otitis media, is in accordance with the current consensus statement [7]. In addition, 63% of all patients with recurrent otitis media received ventilation tubes. As stated above, the average age of VT insertion was 9.5 ± 13.0 years. Compared to healthy children in other studies [25], 9.5 years may seem old but can be explained, as OME in patients with PCD continues well into adulthood [16, 26–28]. Management of late VT insertion does not come without problems, as it may lead to persistent mucoid discharge and there is still debate about the advantage of VTs in improving the hearing thresholds of PCD patients [19, 29]. A permanent otorrhea (often seen in VT-treated PCD patients) may also complicate the use of hearing aids.

As a possible result of the prolonged otitis media with effusion, 58% of the participants had a permanent auditory impairment. The high prevalence of impaired hearing in our population differs from previously published data [26]. Majithia et al. assessed the hearing level of 71 children with PCD between 3 and 16 years in a retrospective study using pure tone audiograms and found that 100% of the participants reached a 0-dB hearing threshold by the age of 12 years. A possible explanation for the high number of patients with “permanent auditory impairment” in our study may be that in our cross-sectional study a “persistent” hearing impairment can be stated at a very young age.

In contrast to the current consensus statement on diagnosis and treatment of PCD in children [7], other reviews have found at least level IV evidence for the utility of surgical treatment in PCD [19]. Considering the high percentage of patients receiving surgical intervention in our population and the above-mentioned problems, we believe the indication for VT insertion requires more research.

Chronic rhinosinusitis and related diseases

Children with PCD tend to have a massive watery to mucoid nasal secretion, which can be purulent during infections. In the absence of mucociliary activity, airflow and gravity prevent mucus stasis [30]. Differentiation between a prolonged common cold and PCD can sometimes be difficult as chronic rhinitis remains from the neonatal period [31].

Most of our participants reported the first infections of recurring problems regarding paranasal sinuses appearing at an average age of 6.8 ± 5.4 years. This age seems low, since the frontal and sphenoidal sinuses are underdeveloped in PCD patients [7] and the sinuses themselves are generally not fully developed in children [32].

First-line treatment for the recurring problems of paranasal sinuses in our patients was repeated (>10) antibiotic treatments. An adequate and prolonged treatment is recommended in the consensus statement on diagnosis and treatment of PCD in children [7]. However, no comparable data regarding the frequency of antibiotic medication in PCD patients is available. Nearly all patients reporting recurring problems with their sinuses received X-ray diagnostics at least once and underwent paranasal sinus surgery. Although nasal polyposis is uncommon in patients with PCD (none of the 30 PCD patients in one study presented with nasal polyps [33]), functional endoscopic sinus surgery (FESS) seems to improve symptomatology. This improved symptomatology and decreased incidence of hospitalization lowered the need for medical therapy compared to patients not receiving FESS [34, 35]. A comparison to other studies on surgical interventions for sinus problems in PCD patients is difficult as data are lacking.

Conclusion

ENT manifestations are frequent in PCD and heavily contribute to general morbidity. This is often associated with surgical intervention, repeated antibiotic treatment and diagnostics utilizing X-ray.

For the early diagnosis of PCD patients and an adequate disease management, it is important for ENT specialists to familiarize themselves with this disease. Surgical intervention should be carefully indicated in these patients.

Conflict of interest There is no conflict of interest.

References