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Article

Impact of Primary Ciliary Dyskinesia Clinical Features on Time Lag to Diagnosis in Egypt: A Retrospective Cohort Study

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Abstract. *Background***:** Primary ciliary dyskinesia (PCD) is a chronic respiratory disease that causes chronic morbidity and affects overall health. It presents with wide range of respiratory and sinopulmonary complaints that are not specific to PCD and are commonly misdiagnosed with other more common conditions such as repeated respiratory infections, allergic rhinitis, asthma, and aspiration syndromes. This frequently delays the diagnosis and complicates the course. The study aims at determining the time lag to the diagnosis of PCD in Egypt and identifying whether any of the main PCD features could have an impact on that time. *Methods:* Retrospective cohort study was conducted at Alexandria University Children's Hospital by reviewing the medical records of 43 Egyptian PCD patients. These patients were referred for evaluation from January 2015 to December 2022. Their main clinical features, age at onset of symptoms, and age at established diagnosis were all retrieved from records. *Results:* Mean age at diagnosis and mean diagnostic lag for the study cohort were 5.92±3.93 and 5.87±3.94 years, respectively. The mean diagnostic lag for patients with a history of neonatal respiratory distress (NRD) and those with situs anomalies was 4.65±3.98 and 5.05±3.93 years, respectively. Patients without a history of NRD and those with normal situs had a longer diagnostic lag. *Conclusions:* Although PCD symptoms usually appear early in life, diagnosis often gets delayed. The presence of a history of NRD or situs abnormalities promotes early suspicion of PCD and helps establish the diagnosis at younger ages. However, neither of them achieves a statistically significant effect.

Keywords: Primary ciliary dyskinesia, Diagnosis, Egypt.

Background

Primary ciliary dyskinesia (PCD) is an illness that predominately affects the respiratory tract by impairing the motility of the cilia[1-4]. Despite the wide phenotypic spectrum, four criteria have been defined by Leigh et al. as being strongly linked to PCD. These features include early-onset year-round moist cough, nasal congestion, neonatal respiratory distress (NRD), and situs abnormalities. A history of NRD and situs anomalies showed the greatest specificities, with 89% and 85% values, respectively[5].

Numerous modalities have been used to aid in diagnosis. Some techniques include transmission electron microscopy (TEM), exhaled nasal Nitric Oxide, molecular testing for PCD-causing mutations, and video microscopy for ciliary beat pattern and frequency. Despite these numerous diagnostic tools, many cases fail to be diagnosed or are diagnosed too late[6]. Several factors contribute to this delay, including the lack of a standardized diagnostic test, the complexity, the high cost, and the unavailability of several diagnostic tools, especially in developing countries. Many illnesses that overlap clinical symptoms with PCD, like cystic fibrosis, asthma, and aspiration syndromes, add to this delay[7,8].

Early diagnosis can lead to better outcomes and reduce respiratory morbidity through the timely application of different therapeutic techniques that help in the clearance of secretions and the prevention of bacterial colonization. Early diagnosis also eliminates unnecessary imaging, endoscopy, and laboratory tests[9,10].

This study aims at determining the time lag to the diagnosis of PCD in Egypt and identifying whether any of the main PCD features could have an impact on that time.

Patients

A cohort of 43 Egyptian PCD patients was recruited. They were diagnosed with PCD in the period starting from January 2015, when PCD diagnosis was started, to December 2022. The diagnosis was established based on the European Respiratory Society diagnostic guidelines[11].

Methods

Study design: Retrospective cohort study.

Study setting: Tertiary health care facility.

Recruitment center: Alexandria University Children's Hospital, Alexandria, Egypt. The study has been conducted after getting approval from Alexandria University Ethics Committee (IRB number: 00012098).

Outcome measures: Age at onset of symptoms, sex, residence, and modalities of confirming the diagnosis were recorded. The primary outcomes were age at established diagnosis and the diagnostic lag, calculated by measuring the interval between the onset of the initial symptoms and the establishment of the diagnosis. Additionally, the four criteria defined by Leigh et al., including early-onset year-round moist coughing, nasal congestion, NRD, and situs anomalies, had been specifically collected and recorded. NRD was defined as unexplained respiratory

difficulties in full-term newborns that needed admission to a neonatal intensive care unit and Oxygen support for at least one day[5].

Statistical analysis

Data were collected and analyzed using Statistical Package for Social Science (SPSS) program (ver 25)[12]. Kolmogorov-Smirnov test of normality revealed no significance in the distribution of the variables, so the parametric statistics was adopted.[13] Data were described using minimum, maximum, mean, standard deviation, standard error of the mean, and 95% CI of the mean[14]. Categorical variables were described using frequency and percentage. Comparisons were carried out between two studied independent normally distributed variables using independent sample t test[15]. An alpha level was set to 5% with a significance level of 95%. Statistical significance was tested at p value <.05[16]

Results

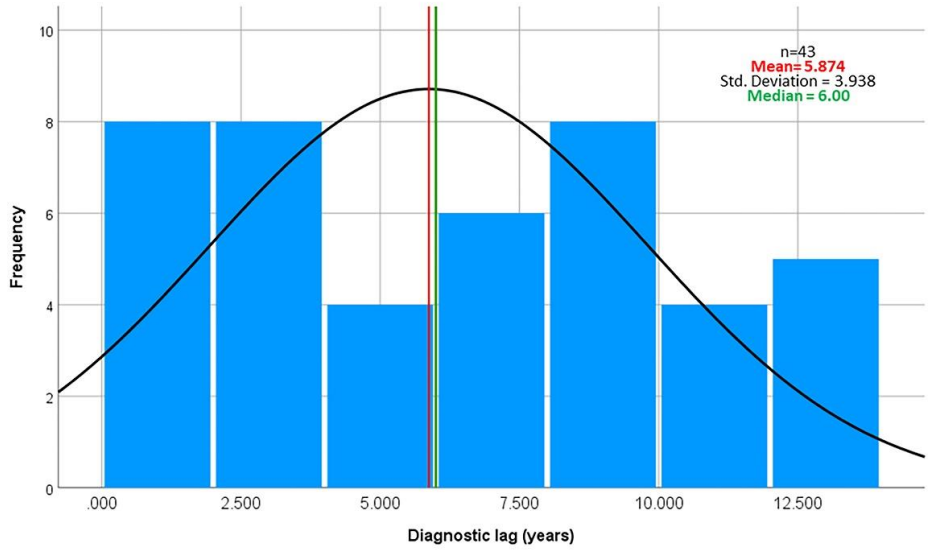
Of the 43 studied patients, 18 (41.86%) were males, and 25 (58.14%) were females. 19 of the 43 patients (44.19%) inhabited urban areas, while the remaining 24 (55.81%) lived in rural areas. Regarding age at first symptoms, 36 (83.72%) patients experienced their first symptoms during the neonatal period (not necessarily NRD), whereas the remaining 7 (16.28%) experienced their first symptoms beyond the neonatal period but before the end of the sixth month of life. 25 of the 43 included patients were diagnosed based on confirmatory genetic tests, while 2 had been diagnosed through a pathognomonic TEM ciliary defect, and the remaining 16 had been diagnosed based on both positive genetics and TEM findings. Table 1 summarizes some of the demographic and clinical data of the research participants.

Table 1: Demographic and clinical data of the study cohort (n=43)

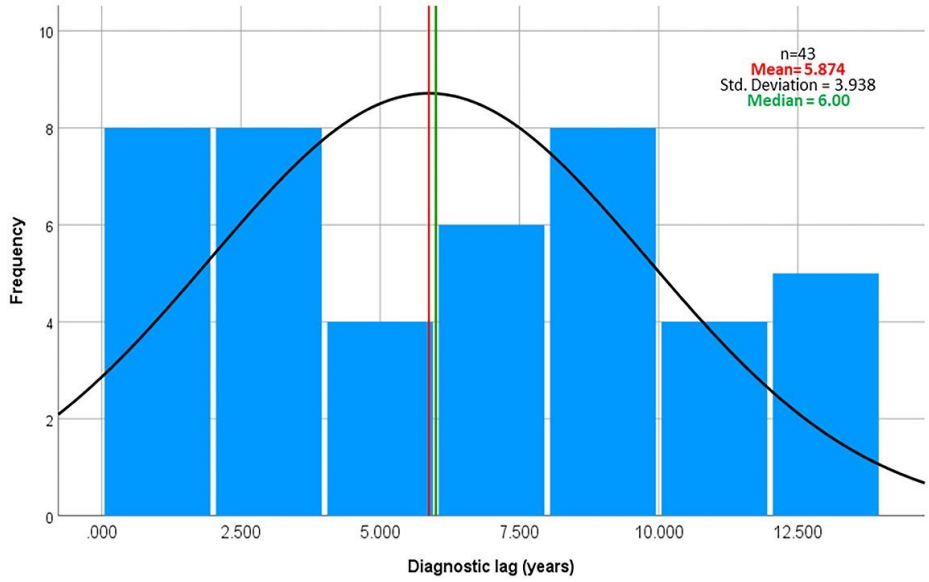
	n (%)
Sex	
- Male	18 (41.86%)
- Female	25 (58.14%)
Residence	
- Urban	19 (44.19%)
- Rural	24 (55.81%)
Age at first symptom	
- During neonatal period	36 (83.72%)
- After neonatal period and before 6 months of age	7 (16.28%)
Modality of confirming the diagnosis	
- Genetics alone	25 (58.14%)
- TEM findings alone	2 (4.65%)
- TEM and Genetics	16 (37.21%)

The mean age at established diagnosis for all included patients was 5.92±3.93 years, with a mean time lag to diagnosis of 5.87±3.94 years. Figure 1 illustrates the pattern of distribution, the mean, and the median for both the age at established diagnosis and the diagnostic time lag. Both were normally distributed. Regarding clinical manifestations, all patients (100%) had early-onset year-round moist coughing and early-onset year-round nasal congestion. 19 (44.18%) patients gave a history of NRD, while 27 (62.79%) had situs anomalies.

Figure 1: Histogram with distribution curve of age at established diagnosis (years) (A) and the diagnostic lag (years) (B) (Kolomogorov-Smirnov (KS) (D) test was not statistically significant (p=.068; p=.090; respectively).



(A)



(B)

As regards the 19 patients with a history of NRD who exhibited their first symptom at birth, diagnosis was established at a mean age of 4.65±3.98 years. Their mean time lag to diagnosis was 4.65±3.98 years. The remaining 24 patients did not have a history of NRD. Although 17 (70.83%) of these 24 patients experienced their first symptoms during the neonatal period, the diagnosis was established at a mean age of 6.93±3.66 years, with a mean lag to diagnosis of 6.84±3.69 years. Table 2 compares the age at established diagnosis and the diagnostic time lag between children with a history of NRD and those without.

Table 2: Age at established diagnosis and the diagnostic lag between patients with and without a history of neonatal respiratory distress

	History of neonatal respiratory distress		Test of significance (*p*-value)
	Yes	**No**	
Age at established diagnosis (years)			
- n (%)	19 (44.18%)	24 (55.82%)	$t_{(df=41)}$ =1.950
- Min-Max	0.17-13.00	1.00-12.00	*p*=.058 (NS)
- Mean (years) ± SD	4.65±3.98	6.93±3.66	
- SE of mean	0.91	0.75	
- 95.0% CI of the mean	2.73-6.57	5.38-8.47	
Diagnostic lag (years)			
- n (%)	19 (44.18 %)	24 (55.82%)	$t_{(df=41)}$=1.868
- Min-Max	0.17-13.00	1.00-12.00	*p*=.069 (NS)
- Mean (years) ± SD	4.65±3.98	6.84±3.69	
- SE of mean	0.91	0.76	
- 95.0% CI of the mean	2.73-6.57	5.28-8.41	

n: Number of patients; Min-Max: Minimum to Maximum; SD: Standard deviation; SE: Standard error; CI: Confidence interval; t: Independent sample t-test; df: Degree of freedom; *p*: Probability of chance (error); NS: Statistically not significant ($p \geq 0.05$)

In this study, situs inversus totalis was the only detected situs abnormality. It affected all of the 27 patients with situs anomalies. Although 22 (81.48%) of these 27 patients experienced their first symptoms during the neonatal period, the diagnosis was established at a mean age of 5.10±3.93 years, with a mean lag to diagnosis of 5.05±3.93 years. The remaining 16 patients had a normal situs. Although 14 (87.50%) of these 16 patients experienced their first symptoms during the neonatal period, the diagnosis was established at a mean age of 7.30±3.64 years, with a mean lag to diagnosis of 7.28±3.66 years. Table 3 compares the age at established diagnosis and the diagnostic time lag between those with situs anomalies and those with normal situs.

Table 3: Age at established diagnosis and the diagnostic lag between patients with and without situs anomalies

	Situs anomalies		Test of significance (p-value)
	Yes	**No**	
Age at established diagnosis (years)			
- n (%)	27 (62.79%)	16 (37.21%)	$t_{(df=41)}$=1.816
- Min-Max	0.17-13.00	1.00-12.00	p=.077 (NS)
- Mean (years) ± SD	5.10±3.93	7.30±3.64	
- SE of mean	0.76	0.91	
- 95.0% CI of the mean	3.55-6.66	5.36-9.25	
Diagnostic lag (years)			
- n (%)	27 (62.79%)	16 (37.21%)	$t_{(df=41)}$=1.833
- Min-Max	0.17-13.00	1.00-12.00	p=.074 (NS)
- Mean (years) ± SD	5.05± 3.93	7.28± 3.66	
- SE of mean	0.76	0.91	
- 95.0% CI of the mean	3.49-6.60	5.32-9.22	

n: Number of patients; Min-Max: Minimum to Maximum; SD: Standard deviation; SE: Standard error; CI: Confidence interval; t: Independent sample t-test; df: Degree of freedom; p: Probability of chance (error); NS: Statistically not significant ($p \geq 0.05$)

Discussion

The mean age at establishing the diagnosis among the study cohort was 5.92±3.93 years, which is older than the mean age reported in a survey conducted in 26 European countries in 2010 by Kuehni et al. (4.03 years for Western Europe, 5.26 years for Eastern Europe, 5.05 years for Southern Europe, and 4.63 years for Northern Europe)[17].

This old age of diagnosis and the long diagnostic lag (mean values of 5.92±3.93 and 5.87±3.94 years, respectively) may be attributed to the complexity, high expense, and limited availability of the diagnostic tools. Furthermore, non-specific symptoms of the disease can be confused with other medical conditions. The rarity (estimated prevalence of 1 in 10,000 live births) and unfamiliarity of PCD have aggravated the delay[18].

In the current study, all participants experienced chronic, year-round wet coughing and nasal congestion. As a result, they did not have any discernible impact either on the age at diagnosis or the diagnostic lag. The history of unexplained NRD at full-term gestation is a highly specific feature that motivates physicians to evaluate patients for PCD promptly, especially when other PCD symptoms are present[5]. In the current study, when comparing the age at established diagnosis between patients with a history of NRD and those without, it was found to be younger in those with a history of NRD. Additionally, this group also had a shorter

diagnostic lag. However, no statistically significant difference was achieved between those with a history of NRD and those without, as regards the age at established diagnosis and the diagnostic time lag (*p* values were .058 and .069, respectively; *p* is significant when <.05). This is in contrast to a previous study conducted by Goutaki et al., which reported statistically significant younger ages at diagnosis among children with a history of NRD[19].

Situs anomalies are among the most prevalent manifestations that drive patients and their families to seek medical care at a young age[1,5,20]. In the current study, when comparing the age at established diagnosis between patients with situs anomalies and those with normal situs, it was found to be younger in those with situs anomalies. Additionally, this group also had a shorter diagnostic lag. However, there was no statistically significant difference between the two groups as regards the age at established diagnosis and the diagnostic time lag (*p* values were .077 and .074, respectively; *p* is significant when <.05). This was in line with a study conducted by Coren et al. at Royal Brompton Hospital, United Kingdom[7].

Although this is the first study from Egypt to evaluate diagnostic time lag in PCD, it has some limitations. It describes one center's experience with a relatively small sample size. Moreover, delayed diagnosis may be confounded by other unstudied factors. In the future, more extended multicenter prospective studies on a larger number of patients are required to determine whether any other factors can help in early diagnosis.

Conclusion

Primary ciliary dyskinesia is challenging to diagnose, and patients are at risk of developing complications. Even though patients may exhibit several PCD-suggestive symptoms early in life, diagnosis is frequently delayed. Although the time lag to diagnosis was shortened when either NRD or situs anomalies were present, neither achieved statistical relevance. More large-scale prospective studies are needed to identify risk factors for diagnostic delay and factors that can facilitate early detection.

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Data availability: The data are available upon request.

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