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David Holzmann · Heidi Felix

Neonatal respiratory distress syndrome – a sign of primary ciliary dyskinesia?

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Abstract Primary ciliary dyskinesia (PCD) is a clinically heterogeneous disease. In most cases, its clinical manifestation in children is rather unspecific: chronic infectious rhinosinusitis, recurrent acute infections of the upper and lower airways and chronic otitis media with effusion. Between 1990 and 1998 ten patients were diagnosed as PCD. Nine presented a neonatal respiratory distress syndrome (NRDS) of unknown cause. Six of these patients were newborns treated in the intensive care unit, one of them needed mechanical ventilation. The few cases already described in the literature and the experience with our patients support the possible association of NRDS with PCD.

Conclusion Neonatal respiratory distress syndrome of unknown cause should be added to the list of clinical presentation of primary ciliary dyskinesia, and if further signs and symptoms are indicative of primary ciliary dyskinesia, investigations to explore this disorder are warranted.

Key words Ciliary dyskinesia · Infant · Respiratory distress syndrome · Respiratory tract infections

Abbreviations *NRDS* neonatal respiratory distress syndrome · *OME* otitis media with effusion · *PCD* primary ciliary dyskinesia

Introduction

Primary ciliary dyskinesia (PCD) is a rare and heterogeneous disease with impaired mucociliary transport leading to respiratory disorders, hearing impairment and male infertility [1, 9]. Mucociliary transport is an important primary host defence mechanism which can be disturbed by a change in any of its components, including ciliary activity, periciliary fluid and mucus rheology [8]. PCD can be diagnosed by the combination of thorough clinical examination with functional and structural analysis of the cilia. Major symptoms like chronic productive cough, impaired nasal breathing and rhinorrhoea as well as recurrent upper and lower airway infections in PCD patients are rather unspecific clinical signs that also occur in other diseases like allergy, cystic fibrosis, immune deficiencies and alpha-1-antitrypsin deficiency. Situs inversus occurs only in 50% of PCD patients, whereas only 28% of all patients with situs inversus have PCD [6]. It seems to be highly recommendable, to exclude all other pathologies prior to taking biopsies for ciliary analysis.

In a recent review article by Bush et al. [3], an association of neonatal tachypnoea and PCD was mentioned. The aim of this retrospective study was to elaborate possible clinical features characteristic for PCD, particularly in the neonatal period.

D. Holzmann (✉) · H. Felix
Department of Otorhinolaryngology Head and Neck Surgery,
University Hospital,
Frauenklinikstrasse 24,
8091 Zurich,
Switzerland
e-mail: holzmann@orl.usz.ch
Tel.: +41-1-2555860; Fax: +41-1-2554556

Patients and methods

Between 1990 and 1998, 28 patients were selected on the basis of clinical features (i.e. exclusion of other underlying pathologies) to undergo mucosal biopsies for functional and structural investigations of the cilia. The method has been described elsewhere [5]. In 11 patients, 8 children and 3 adults, a diagnosis of PCD could be made according to the ciliary investigations. One adult patient was excluded from this study because some data of the neonatal period were no longer available. The clinical history of these remaining ten patients was evaluated from birth to the age at diagnosis of PCD according to the charts and clinical investigations.

Results

The clinical signs and symptoms of these ten PCD patients are listed in Table 1. The most constant findings in these patients were chronic rhinosinusitis (100%), chronic bronchitis with chronic productive cough (80%) and otitis media with effusion (OME; 80%); situs inversus was found in five patients (50%).

Nineout of ten patients had a documented neonatal respiratory distress syndrome (NRDS) with tachypnoea and oxygen desaturation requiring oxygen supply. The patient without NRDS was a preterm infant (35 weeks gestation) whereas the other eight were term infants. They were born at 38–41 6/7 weeks of gestation and all had spontaneous delivery except one who was delivered with forceps. Their birth weight was 2900–4100 g. In eight out of nine patients, respiratory distress occurred 1–5 h after birth and after normal primary adaptation with normal APGAR score. All patients were treated either in the intensive care or intermediate care unit with 30–100% oxygen supply from 24 h to 3 days. In one out of nine patients, intubation for mechanical ventilation for 3 days was necessary. This case was already described in an earlier case report [7]. In all nine patients causes such as hyaline membrane disease, aspiration syndromes, neonatal pneumonia, pneumothorax as well as cardiovascular and metabolic diseases [11] could be excluded. In none of the patients was an abnormal amount or colour of the amniotic fluid documented. Thus the cause of the NRDS remained unclear in all nine patients. They all survived without NRDS sequelae.

Table 1 Clinical manifestations of patients with PCD

Clinical manifestation	No PCD (n = 18) (%)	PCD (n = 10) (%)[a]
Neonatal respiratory distress of "unknown cause"	0 (0)	9 (90)
Recurrent/chronic bronchitis	10 (56)	98 (98)
Recurrent pneumonia	7 (39)	7 (70)
Bronchiectasis	4 (22)	4 (40)
Situs inversus	2 (11)	65 (65)
Chronic infectious rhinosinusitis	10 (56)	10 (100)
Nasal polyps	1 (0.6)	23 (23)
Atrophic rhinitis	1 (0.6)	0 (0)
Chronic OME	1 (0.6)	78 (78)
Congenital heart failure	2 (11)	0 (0)
Congenital immunological disorder	2 (11)	0 (0)
Gastro-oesophageal reflux	2 (11)	0 (0)

[a] Ten patients, one excluded because of poor documentation

Discussion

Comparing the clinical pattern of the ten PCD patients and the 18 patients without, there are obvious differences in the prevalence of diseases like infections of the respiratory tract. However, chronic airway infections (e.g. chronic/recurrent bronchitis, recurrent pneumonia and chronic rhinosinusitis) are also rather unspecific [13], as documented in our patients. Thus, it seems to be important to exclude other diseases (e.g. cystic fibrosis, allergy, immune deficiency) prior to testing for ciliary dysfunction [5]. The combination of nasal polyps and bronchiectasis seem to be very specific clinical signs. However, they usually occur within the second decade of life, which diminishes its diagnostic value in children. PCD patients suffer more frequently from OME than other patients suggesting that OME is a more specific symptom of PCD.

However, the difference in incidence of neonatal respiratory distress of "unknown cause" is most striking. One of the patients without PCD developed NRDS, however, the origin could be clearly associated with the severe congenital heart failure, for which the infant underwent heart surgery later. In the PCD group, there were no other underlying diseases such as heart failure, bronchopulmonary dysplasia, sepsis etc. In the literature, there are few articles on the relation of PCD and NRDS. Certain situations of mucociliary dysfunction relevant to the neonate are seen in ventilator-associated lung injury and bronchopulmonary dysplasia [8]. In a review article Bush et al. [3] summarised the literature mentioning a relation between PCD and NRD. This review included the report of a retrospective analysis of six PCD patients manifesting a NRDS of unknown origin by Whitelaw et al. [14] and a study by Greenstone et al. [4] of 30 PCD patients. The observations of Whitelaw et al. [14] are in accordance with our results (Table 2), whereas Greenstone et al. [4] noted an association of NRD and PCD only on the basis of an interview with the patients, in which they "gave a history of neonatal chest infection". Although a major subject was not NRDS in PCD patients, it would have been interesting to have had detailed clinical documentation (e.g. gestational age, mode of delivery, birth weight, APGAR score, year of birth, amount and duration of oxygen supply, age at PCD diagnosis).

To prove the hypothesis that the incidence of NRDS in PCD patients is higher than in a normal population, it is important to exclude all patients with a NRDS of known origin. Nevertheless, this was not the case in all studies: in one study on a series of 12 neonates with PCD and NRDS [3] in which 1 out of 12 had a congenital cyanotic heart failure, four additional neonates were recorded with anaemia requiring blood transfusion, and four patients had evidence of sepsis with positive blood

Table 2 Comparison of clinical patterns in PCD patients: own cases and review of the literature

Patient	Male/ female	Birth year	Weeks of gestation	Mode of delivery	Birth weight (g)	Duration of O_2 supply	Percentage O_2 required	Hospitalisation time	NRDS	Chronic bronchitis	Recurrent pneumonia	Situs inversus	Bronchiectasis	Chronic infectious rhinosinusitis	Nasel polyps	OME	Age at diagnosis of PCD
Own cases																	
1[a]	F	1993	41 3/7	Forceps	3340	36 h	30–100	10days	Yes	Yes	Yes	Yes	No	Yes	No	Yes	2 weeks
2[a]	F	1991	41 1/7	Spontaneous	3370	24 h	50–80	3 weeks	Yes	Yes	Yes	No	No	Yes	No	Yes	11 months
3	M	1992	40 1/7	Spontaneous		36 h		4 weeks	Yes	No	Yes	No	No	Yes	No	Yes	2 years
4	F	1997	39	Spontaneous	3450	36–48 h	30–100	10 days	Yes	No	No	Yes	No	Yes	No	Yes	4 weeks
5	F	1986	41 6/7	Spontaneous	3220	17 days		23 days	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	2 months
6	M	1958	41	Spontaneous	4100	3 days	30–80	2 weeks	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	39 years
7	M	1980	40	Spontaneous	3390	2 days	30–100	13 days	Yes	Yes	No	Yes	Yes	Yes	No	No	9 years
8 [7]	M	1992	404/7	Spontaneous	3530	3 days (intubated)		11 days	Yes	Yes	No	Yes	No	Yes	No	No	2 weeks
9	F	1973	FG 35	Spontaneous	2560	No	No	13 days	No	Yes	Yes	No	Yes	Yes	Yes	Yes	17 years
10	F	1986	38	Spontaneous	2900	36 h	50–100	2 weeks	Yes	Yes	Yes	No	No	Yes	No	Yes	8 years
11[b]	M	1942	"Term"	Spontaneous	"No"	"Some days"	?	"5 weeks"	No	Yes	Yes	No	Yes	Yes	Yes	Yes	55 years
Other studies																	
1 [14]	M	?	38	Spontaneous	2600	?	30% + chest physio	4 weeks	Yes	?	?	No	No	Yes	?	?	?
2 [14]	M	?	38	Sec. caes. (disprop)	2610	Intubated for unknown time	?+ chest physio	?	Yes	Yes	Yes	Yes	No	Yes	?	Yes	?
3 [14]	M	?	41	Spontaneous	3560	?	?	?	Yes	Yes	?	No	No	?	?	?	7 weeks
4 [14]	F	?	?	Forceps for fetal distress	3045	5 days	?+ chest physio	4 weeks	Yes	Yes	Yes	Yes	Yes	Yes	?	Yes	?
5 [14]	M	?	Term infant	Spontaneous	3160	?	?+ chest physio	?	Yes	Yes	?	Yes	No	No	?	Yes	?
6 [14]	F	?	"Delay in second stage"	"forceps for delay in second stage"	3530	6 days	?	?	Yes	Yes	Yes	Yes	?	Yes	?	Yes	?
[10]	F	1994	39	Spontaneous	2550	?	?	?	Yes	?	?	Yes	?	?	?	?	2 months

[a] Siblings
[b] Patient excluded because of imprecise data on the neonatal period

cultures (*Enterobacter cloacae* or *Pseudomonas aeruginosa*). Furthermore, there are two case reports. Losa et al. [7] described the child who was integrated in our study (patient 8) and Oggiano and colleagues [10] presented a term infant with Turner syndrome who had a NRDS, the origin of which was also unclear. In the latter case, no further details on the therapy (i.e. duration and amount of oxygen supply) were given (Table 2).

Although neonatal respiratory distress occurs in 5% of term infants, the incidence of NRDS in our patient group was striking and seems to be in accordance with the suspicion already noted in the literature.

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