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SHORT COMMUNICATION

Primary ciliary dyskinesia and humoral immunodeficiency — Is there a missing link?

Mieke Boon [a,*], Kris De Boeck [a], Mark Jorissen [b], Isabelle Meyts [c]

[a] *Department of Pediatrics, Pediatric Pulmonology, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium*
[b] *Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Gasthuisberg Leuven, Herestraat 49, 3000 Leuven, Belgium*
[c] *Department of Pediatrics, Pediatric Immunology, University Hospital Gasthuisberg, Herestraat 49, Leuven, Belgium*

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Abstract
Background: Primary ciliary dyskinesia (PCD) and humoral mmunodeficiency (HID) are both rare disorders which cause recurrent upper and lower respiratory tract infections.
Objective: To examine the concurrence of PCD and HID in a patient cohort with known PCD.
Methods: Retrospective review of the patient files.
Results: We describe 11 patients of a cohort of 168 patients with PCD (6.5%) with a combination of PCD and some form of HID. The patients all presented with typical clinical symptoms for PCD, however the role of the concomitant immunological abnormalities is not clear.
Conclusion: PCD and HID coincided in 6.5% of the patients. We suggest that a common pathophysiological pathway results in both disorders.

Introduction

Primary ciliary dyskinesia (PCD) is a rare disorder (prevalence 1/20.000), caused by congenital dysmotility of the motile cilia. It is mainly inherited in an autosomal recessive manner, but up till now more than 20 different genes have been reported [1]. Patients with PCD present with recurrent upper and lower respiratory tract infections, leading to bronchiectasis and chronic lung disease and rarely respiratory insufficiency [1]. Humoral immunodeficiency (HID) is another common cause of recurrent infections of the upper and lower respiratory tract. Common variable immunodeficiency disorder (CVID) is a rare (prevalence around 1/75.000) entity, characterized by hypogammaglobulinemia, defective specific antibody production and an increased susceptibility to recurrent infections [2]. Selective IgA deficiency and isolated IgG subclass deficiency (IgG_2 or IgG_3

* Corresponding author. Department of Pediatrics, Pediatric Pulmonology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16343820; fax: +32 16343842.
E-mail addresses: mieke.boon@uzleuven.be, miekeboon@yahoo.com (M. Boon).

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Abbreviations

HID	humoral immunodeficiency
iNOS	inducible nitric oxide synthase
PCD	primary ciliary dyskinesia
SPAD	specific polysaccharide antibody deficiency

deficiency) on the other hand are found more frequently, and in some patients they are the only identifiable cause of recurrent respiratory tract infections. However, the relevance of these findings has been discussed [3]. Isolated subclass deficiencies have been reported in up to 2% of a healthy population, without any clinical symptom [4]. Finally, specific polysaccharide antibody deficiency (SPAD) points to patients with a specific defect in the generation of antibodies to polysaccharides [5].

However unexpected, there is one report of a concomitant presentation of both disorders [6].

Methods

We retrospectively reviewed the files of our patients with PCD and examined the concurrence of PCD and HID. PCD was defined as abnormal ciliary motility after ciliogenesis in vitro with or without ultrastructural abnormalities. This technique excludes secondary ciliary dyskinesia due to infections or toxic substances and is able to reliably detect PCD with normal ultrastructure [7,8]. For patients with PCD and normal ultrastructure, genetic analysis of *DNAH11* was performed if DNA of the patient was available. In selected patients with PCD due to dynein deficiency, genetic analysis of *DNAH5* was performed. HID was defined as a value more than 2 SDs below the normal mean for age. SPAD was defined as poor response to unconjugated pneumococcal vaccine: a less than twofold increase in antibody titers in 50% of the tested serotypes indicates a poor response [9]. The indication for checking immunoglobulin status was extensive respiratory symptoms in all of the patients. Patients were clinically stable at the moment of sampling. Hence, there was no acute infection, but a state of chronic infection as is often the case in patients with PCD. Clinical data were derived from the patient files. Lung function results (if available) are expressed as % predicted of FEV_1.

Results

For 168 patients with proven PCD, immunoglobulin levels were available in 96, IgG subclasses in only 68. Abnormal results for one or more antibody or antibody subclass were found in 11/68 (16.1% or 6.5% of the total cohort).

Table 1 presents the clinical, ultrastructural and genetic presentation of PCD and the type of HID. When compared to an age-matched control group of patients with PCD without HID, FEV_1 was not significantly lower (median 75.6% versus 83.9%, p 0.508, related-samples Wilcoxon signed rank test). However 6/11 (54%) patients have intermittent or chronic infection with *Pseudomonas aeruginosa*, as opposed to only 22/157 (14%) in those without HID (χ^2 p 0.003).

Discussion

The fact that PCD concurs with HID in 16.1% (6.5% of the total cohort) is striking, but might be coincidental. Several causal hypotheses can be postulated. 1) Although hematopoietic cells are one of the few cell types that lack primary cilia, they express intraflagellar transport proteins needed for the formation of the immune synapse [10] and dysfunction might cause PCD as well as HID. 2) Ciliary epithelial cells are shown to have an antigen-presenting function [11] and therefore antigen presentation might be disturbed in PCD. On the other hand nasal epithelial cells might have an immunomodulatory effect on specific IgA and IgG antibody response [12] and therefore antibody responses might be disturbed in PCD. 3) Dysfunction of inducible nitric oxide synthase (iNOS) has been postulated as a possible mechanism of low nasal NO values in PCD [13], and iNOS is involved in IgA class-switch recombination in mice [14]. Therefore dysfunction of iNOS could play a role in both disorders. 4) Increased immunoglobulin consumption due to chronic infection. 5) PCD could cause cytokine dysfunction disturbing the immunoglobulin maturation. 6) PCD genes could act as modifier genes for HID genes or vice versa. The fact that two sibling pairs present with PCD and HID supports the constitutional origin of the findings.

Not all PCD cases in our cohort have been tested for antibody deficiency, although it is suggested to rule out immune dysfunction prior to start a workup for PCD [15]. However, in selected patients the history is more suggestive of PCD, i.e. when situs inversus, infertility or neonatal respiratory problems are present and thus immunological screening is not performed systematically.

It is unclear whether antibody deficiency influences outcome, but since 5/11 patients are treated with replacement therapy this may impact outcome.

Although we lack clear proof of a link, we recommend to check antibody titers in patients with PCD. The diagnosis of HID can be important since immunoglobulin substitution is an effective treatment in selected patients.

Author's contribution

MB conceived of the study, collected the data and drafted the manuscript. KDB and IM conceived of the study, aided in the drafting of the manuscript and have read and approved the final manuscript. MB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

The authors declare that they have no competing interests.

Part of these data have been presented as poster presentation at the Symposium on Experimental Rhinology and Immunology of the Nose (SERIN) congress 2013, Leuven, Belgium and at the 12th International Congress on Pediatric Pulmonology (CIPP) 2013, Valencia Spain.

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