

Meeting report

Primary ciliary dyskinesia: a report from ATS 2001, May 18–23, San Francisco

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Abstract

Primary ciliary dyskinesia (PCD) is a genetic disorder of abnormal ciliary structure and function that leads to defective mucociliary clearance, resulting in oto-sino-pulmonary disease, and infertility. The disease is currently under intense investigation by a number of research groups worldwide. At the recent American Thoracic Society meeting in San Francisco in May 2001, two sessions focused on PCD; a symposium session on May 21 with several featured expert speakers was followed by a mini-symposium on Tuesday May 22, with one featured speaker and presentation of nine abstracts covering a range of research topics. Mattias Salathe (University of Miami, USA) and Stephen Brody (Washington University, St Louis, USA) chaired the symposium session. Presentations focused on the clinical spectrum of PCD, the genetics of PCD, a proteomics approach to detail the structure of cilia, the role of cilia in the embryology of situs laterality, and airway epithelial cell biology. The mini-symposium was chaired by Peadar Noone (University of North Carolina, USA) and Malcolm King (University of Alberta, USA) and included presentations on the use of PCD as a human disease model, accurate definition of the phenotype using clinical and cell biologic markers, and molecular studies. The latter reports ranged from isolation of a protein involved in ciliary structure and function to genetic studies using linkage analysis and the candidate gene approach. Clinicians and scientists alike displayed considerable interest at both sessions, and there were several lively question–answer sessions.

Keywords: cilia, dynein, mutations, nitric oxide, primary ciliary dyskinesia

Introduction

The American Thoracic Society Meeting was held this year in San Francisco, California. This meeting is the largest scientific meeting in the world targeted to diseases of the lung, with several thousand delegates in attendance in 2001. Clinicians, scientists, and clinician-scientists attended the meeting, together with a range of personnel from allied fields. Though the main emphasis of the meeting is on the common lung diseases, generally, each year relatively rare diseases get some special attention.

This year, on consecutive days there were two sessions on primary ciliary dyskinesia (PCD), a genetic disease of ciliary structure and function. The sessions were well attended by delegates from a range of disciplines, and the speakers were selected from across the research spectrum. The aims of the presentations were to provide updates on the nature of the disease and its use as a human disease model, and also to report exciting new findings in relation to clinical aspects, cell biology and genetics.

Review

Clinical phenotype

The aspects of the clinical features of PCD were reviewed by two featured speakers, Peter Cole (Host Defence Unit, Brompton Hospital London, UK) and Peadar Noone (University of North Carolina at Chapel Hill, USA). Aruna Sannuti (University of North Carolina at Chapel Hill, USA) also presented clinical and phenotypic data from a prospective study of a large cohort of patients with PCD. The high proportion of patients with a history of neonatal respiratory distress, recurrent otitis media, and a requirement for ear drainage tubes was again emphasized. The importance of a careful diagnostic work-up and accurate phenotyping for subsequent genetic studies was stressed. Of particular note was the report of isolation of mucoid *Pseudomonas aeruginosa* in older patients (9 out of 54) with PCD. This is usually regarded as a strong marker of cystic fibrosis (CF), a similar but distinct airway host defence disease. Normal ion transport in nasal epithelia in a subset of patients, the presence of situs inversus in 50% of patients, and very low levels of nasal nitric oxide (NO) in all PCD patients (see below) appeared to rule out coexistent CF. This observation may yield insights into the pathogenesis of *Pseudomonas* infection in patients with chronic failure of the mucociliary apparatus other than CF.

Cell biologic aspects of PCD

In the symposium session, Dr Stripp (University of Rochester, USA), Dr Sisson (University of Nebraska, USA) and Dr Forteza (University of Miami, USA) all presented overviews of the complexity of airway epithelia, ciliary development, signaling systems, and cilia in host defence.

In the context of accurate diagnosis and phenotyping Dr Sannuti (University of North Carolina at Chapel Hill, USA) and Dr Estelle Escudier (Inserm 492, Creteil, France) presented data on a novel method using computer technology imaging to accurately categorize ciliary dynein arm defects in subgroups of patients with PCD. Dr Sannuti showed that defects of the outer dynein arm are more specific for PCD than defects in the inner dynein arm (IDA), such that the IDA may be vulnerable to the effects of non-specific (non-PCD) chronic inflammation. Dr Escudier showed that although the IDA may be difficult to characterize, a method using computer rotation of ciliary electron microscopic images may be useful to diagnose a proportion of patients as having genetically determined defects in the IDA. Both computer-aided analyses presented by Drs Sannuti and Escudier of EM images appeared to be reproducible and useful for phenotyping patients with PCD, particularly in cohorting PCD patients for genetic studies.

Low nasal NO levels have been observed to be a strong feature of PCD, and Teresa Wodehouse (Brompton

Hospital, London, UK) and Michael Larj (University of North Carolina at Chapel Hill, USA) presented data to confirm this observation. Both speakers showed large ($n > 50$) datasets of patients with PCD exhibiting very low exhaled levels of NO in nasal air, quite different to normals and disease controls. The cause of the low levels of NO is presently unknown, but speculation ranged from defective expression of the nitric oxide synthase enzyme, iNOS, to a primary defect related to the genetic mutation causing PCD. Dr Larj showed that parents of patients with PCD (presumably obligate carriers) without any clinical disease can have intermediate levels of nasal NO. Finally, Karin Storm Vans Gravesende (Boston University, USA) showed a relationship between sequence variants in the genes encoding for two of the three NO synthase isoforms (NOSII and NOSIII) and the diagnosis of PCD in a group of well-characterized patients with the disease. The observation of low levels of NO in PCD thus remains unknown, but continued study of this phenomenon may shed light on the source and role of NO in the upper airway, particularly as related to host defence.

Proteomic and genetic approaches in PCD

Ciliary structure is very complex, but one approach to isolating the abnormalities in PCD is proteomics. Larry Ostrowski and Yan Zhang (both from University of North Carolina, USA) presented data on the isolation and identification of proteins from the culture of cells from a patient with PCD and missing IDA who had undergone transplantation. Using protein gel electrophoresis, a protein band was identified as missing from an axonemal isolate of the patient's airway epithelial cells. The protein was identified as DNAH7, an axonemal dynein heavy chain. Although a specific mutation in DNAH7 was not identified in the patient, this protein is thought to be important for anchoring or assembly of the axonemal heavy chain dynein in the IDA in normal human cilia.

Several genetic studies were presented showing that the use of candidate genes is a useful approach to identify the mutations that cause PCD. Hannah Mitchison (University of London, UK) presented an overview of genetic approaches, while Gaelle Pennarun (Institut National de la Sante, Paris, France), Maimoona Zariawala (University of North Carolina at Chapel Hill, USA) and Michal Witt (The Institute of Genetics, Poland) showed data from ongoing genetic studies in PCD. Pennarun and co-workers reported the first mutations in the DNAI1 gene in 1999 using the candidate gene approach, and at the meeting she reported the further efforts of the group in testing candidate genes from two nonhuman models, *Chlamydomonas* (HP28) and a mouse model (*hfh4*). Dr Zariawala showed mutations in DNAI1 in a well characterized group of patients with PCD and outer dynein arm defects in two unrelated families. These mutations included the previously reported splice mutation on one allele, and novel

mutations (a missense mutation, W568S and a nonsense mutation, W568X) on the opposite allele. Finally, Dr Witt showed that the linkage analysis in a large group of patients with PCD may be useful, especially if the phenotype is strong. Patients with situs inversus and PCD yielded especially high lod scores (>4) in a region of chromosome 15q, while the total PCD patient group (with and without situs inversus) yielded a lower mean lod score

Conclusion

The sessions illustrated the general interest in PCD, with an international attendance from many countries. Although PCD is relatively rare, it is likely to be under-recognized, and further definition of the phenotype at a clinical and cell biologic level, as described at the meeting, is likely to increase our ability to recognize true genetic-linked abnormalities in ciliary structure and function causing PCD in humans. Studies of the role of NO in PCD are likely to increase our understanding of the role of NO in the airway, and its relationship to ciliary structure and function. Genetic studies will allow more precise definition of the molecular abnormalities leading to PCD, increase our understanding of ciliary structure and function, and allow further development of methods to modulate cilia *in vivo* using novel treatments.