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Quantitative 99mTc-albumin colloid Nasal Mucociliary Clearance as outcome in primary ciliary dyskinesia

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ABSTRACT

Background:
Primary ciliary dyskinesia (PCD) is an inherited disorder where dyskinetic cilia cause impaired mucociliary clearance (MC) of upper and lower airways. Airway ciliary movement can be indirectly tested in vivo after administration of a radiolabeled tracer to the lower airways for assessment of pulmonary MC or to the nose for assessing Nasal MC (NMC). With this study we aimed to investigate NMC as a quantifiable study outcome parameter in PCD.

Material and Methods:
This single centre proof-of-concept study on NMC velocity investigated patients with PCD across different genotypes and nasal Nitric Oxide (nNO) levels. Healthy controls (HC) were used for comparison.

NMC was determined as velocity in mm*min$^{-1}$ of a nasally applied $^{99m}$Tc-albumin colloid tracer. By use of a gamma camera, repeated dynamic series of images each lasting 30 seconds were acquired during a 10-minute period and digitally stored.

Results:
NMC velocity was investigated in seven patients with PCD (aged 9 to 31 years) and five adult HC’s. Mean NMC velocity in HC’s (8.5 mm*min$^{-1}$) was significantly higher compared to PCD (0.00 mm*min$^{-1}$), $P<0.0001$). NMC was completely absent in all included patients with PCD across different PCD genotypes and regardless of nNO values. Success rate was 100% in both groups.

Conclusion:
NMC velocity discriminated highly significant between PCD and HC’s. We suggest here a fast and feasible set up for NMC measurements that is easily applicable for any clinical trial involving PCD medication aimed for the nasal compartment, a step before or parallel to moving into the lungs.
INTRODUCTION

Primary ciliary dyskinesia (PCD; MIM244400) is a multi-system disorder predominantly considered as a respiratory motile ciliopathy in which the dyskinetic cilia cause impairment of mucociliary clearance resulting in chronic destructive infectious and inflammatory disease of the upper and lower airways.

Currently, approximately 50 genes have been identified to harbor variants to cause PCD [1] [2]. However, the number of characterized disease-causing PCD mutations is steadily increasing. Most mutations associated with PCD are autosomal recessive. Less frequently, X-chromosomal recessive or de novo autosomal dominant inheritance has been described [3].

Completed randomized clinical trials directed towards patients with PCD are yet sparse [4], [5], [6]. Pharmaceutical companies have become increasingly interested in developing precision medicine as potential future treatment for PCD. This includes development of mRNA transcript therapy and designing correctors for ciliary proteins in patients with PCD related to their specific genotypes. Consequently, an even higher need for relevant outcomes for future clinical trials in PCD have emerged.

So far, there are no published studies on precision medicine in PCD.

A ⁹⁹ᵐTc tracer mucociliary clearance test can be used as an indirect in vivo functional test of ciliary movement in upper and lower airways and can be measured specifically in the nasal compartment as nasal mucociliary clearance (NMC) as well as separately in the pulmonary compartment as total pulmonary radioaerosol mucociliary clearance (PRMC).

In previous studies on isolated NMC only semi-quantitative measures have been applied [7], [8], whereas whole-lung PRMC has been investigated for quantitative diagnostic measures [9], [10], [11] as well as for whole lung MC studies in healthy controls [12] and for outcome parameters in randomized clinical trials in cystic fibrosis [13], [14].

NMC holds potential as an in vivo functional test that can deliver outcomes in future clinical trials for nasal PCD drugs, but so far quantitative references have been lacking.

AIM

In this proof-of-concept study we aimed to show quantitative measures of NMC velocity and the discrimination between NMC velocity in PCD and health.
The scope of the study was to investigate NMC as a potential outcome parameter, and not as a supplemental diagnostic test in PCD work up.

MATERIAL AND METHODS
Study design
Our study was a small prospective, single centre proof-of-concept pilot study investigating NMC velocity in a subset of patients with PCD from the cohort of the Danish PCD Centre and with healthy controls for comparison.

Patients
Children and adult patients from the cohort of the Danish PCD Centre and healthy adult controls were included for assessment of NMC velocity according to the following inclusion criteria:

PCD: Patients with PCD were all diagnosed according to the ERS and ATS guidelines criteria \[15\] with a known biallelic pathogenic PCD gene defect and additional abnormal TEM, abnormal ciliary function test and a nasal NO test. Informed consent was collected from all the patients prior to inclusion.

Healthy controls (HC): Healthy non-smoking non-pregnant and non-breastfeeding adults who gave their informed consent to the NMC velocity study were included. Fertile female volunteers, HC as well as patients with PCD, were all obliged to perform a negative pregnancy test before inclusion.

Exclusion criteria: Subjects with acute upper respiratory infection were excluded to avoid false low NMC velocity values as a consequence of secondary impaired nasal ciliary transport. Patients with PCD who reported stable chronic rhinitis symptoms were not excluded.
Determination of NMC Velocity

A $^{99m}$Tc-albumin colloid tracer was used for the NMC velocity test where one small droplet of 1.85 MBq $^{99m}$Tc-albumin colloid dissolved in isotonic saline was administered to the concha media by a Hamilton syringe. With this small droplet size (2.5 $\mu$l) it was easy to administer the tracer precisely to the nasal concha media.

The radiation dose for a full NMC measurement was 25 $\mu$Sv.

The subject had radioactive reference sources ($^{57}$Co) attached to the nasal tip and anterior to the tragus, respectively, while the gamma camera was facing the profile of the subject (Figure 1).

The reference sources served as point of direction and as reference for movement of the head in case of which this was corrected for to precisely calculate the velocity. The tracer movement was defined as the most forward front of the tracer.

A dynamic series of 20 images each lasting 30 seconds was acquired during a 10-minute period and digitally stored. The nasal mucociliary transport could be read directly from the screen image by image and the NMC velocity was calculated according to the following equation, since one image = 0.5 minutes:

$$NMC \text{ velocity \ mm \cdot \ min}^{-1} = X \ mm \ (\text{of tracer movement from nasal tip marker towards tragus marker}) \ Y \text{ images} \ast \ 0.5 \text{ minutes}$$

The resolution of the gamma camera was 4.66 mm/pixel (Matrix: 128*128 pixels).

Nasal NO measurement

Nasal NO was measured using the stationary CLD88sp FeNO chemiluminescence analyser (ECO MEDICS® AG, Duernten, Switzerland) and measurements were performed according to the recommended technical standards [16].

Nasal NO gas was aspirated via a nasal olive probe inserted into one nostril. Mean nNO concentration in ppb was calculated from triple measurements in each subject.

All subjects had nNO sampled during velum closure, preferentially by exhalation against resistance, and if this was not possible for a subject, sampling was performed during breath hold.
The sampling flow rate was 0.33 L·min−1 and conversion from nNO concentration in ppb to nNO production rate (nL·min−1) was calculated as follows:

\[
\text{Nasal NO (ppb) \times flowrate (L\cdot min^{-1}) = nasal NO (nL\cdot min^{-1}).}
\]

Ambient NO was recorded before each measurement.
Nasal NO was measured on the same day as NMC assessment.

**PCD Genetics**
A Next Generation Sequencing (NGS) panel including the following 34 PCD genes was used:

C21orf59, CCDC103, CCDC114, CCDC151, CCDC65, CCDC39, CCDC40, CCNO, CENPF, DNAH11, DNAH5, DNAH8, DNAH9, DNAI1, DNAI2, DNAL1, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DRC1, GAS8, HYDIN, INVS, LRRC6, MCIDAS, OFD1, RSPH1, RSPH2, RSPH3, RSPH4A, RSPH9, SPAG1, ZMYND10.

**HSVM and TEM**
Nasal ciliary beat pattern and beat frequency was determined from High-Speed Video Microscopy (HSVM) ciliary function analysis of nasal brush biopsy material. Nasal ciliary ultrastructure was determined by Transmission Electron Microscopy (TEM) from a nasal curette scraping biopsy. HSVM and TEM were performed as standard diagnostic testing in all patients with PCD included in the study and according to guidelines [17] [18] [19].

**STATISTICS**
Wilcoxon rank sum test was used to compare means of NMC velocity values between PCD and HC. P-value < 0.05 was considered statistically significant.

**ETHICS**
The study was approved by the local ethics committee of Copenhagen, DK (journal no. H-C-2007-0061). Informed consent was obtained from all participating subjects.
RESULTS

We included seven patients with PCD (median age 14 years, range 9 to 31 years) and five healthy subjects (HC) (median age 39 years, range 20 to 50 years). In patients with PCD, NMC showed to be completely absent, as NMC velocity was 0.0 mm*min\(^{-1}\) in all seven patients (100%), regardless of PCD genotype and nasal NO values. In HC’s mean NMC velocity was 8.5 mm*min\(^{-1}\) and significantly higher compared to the PCD group (P<0.0001) as shown in Table 1 and as illustrated in the digital films Figure 2a (HC) and 2b (PCD).

Patients with PCD genotypes associated with hallmark TEM outer dynein arm defects (N=3, 43%) had biallelic defects in DNAH5, DNAI1 and CCDC114, respectively. Four patients (57%) had PCD genotypes associated with no detectable TEM defects (DNAH11 and HYDIN) or minor and sometimes not visible TEM defects (RSPH9) (Table 1).

Success rate for a first conclusive test was 100% for both the PCD and HC group. The NMC film read outs showed the droplet area in the nose to be small and well defined without spreading over a significant area which made the tracer movement easy to read.

Post measurement digital correction of the NMC velocity was necessary in one case only, a 31-year-old patient with PCD, where movement of the tragus reference indicated head movement during the 10 minutes of acquisitions. From determining the distance (mm) of the tragus reference movement, the nasal tracer movement could be re-calculated by subtracting the distance of the tragus reference movement. The correction resulted in a change from a false detectable NMC velocity of 3.6 mm*min\(^{-1}\) to a corrected NMC velocity of 0.0 mm*min\(^{-1}\).

DISCUSSION

To our knowledge, this is the first study to show quantitative data on NMC velocity (mm*min\(^{-1}\)) by use of a \(^{99}\text{Tc}\)-albumin colloid tracer as an in vivo nasal test of a radiolabeled tracer travelling from a fixed point in the nose towards a reference source. Up to now, studies on NMC have been sparsely reported and with different outcome measures. In a previous study from De Boeck and colleagues, an abnormal NMC was defined semi-quantitatively as either no motion of a radioaerosol droplet towards a reference source or as the droplet travelling less than half of the expected distance, when applying a nasal \(^{99}\text{Tc}\)-albumin colloid tracer to patients with PCD and healthy individuals.
In a study by Naclerio and colleagues, NMC by use of a $^{99m}$Tc labelled tracer was defined as time for the amount of the tracer sprayed into the nose to be reduced by half [8]. Discrimination between healthy subjects and patients with PCD was highly significant for the applied NMC velocity test in this study. By use of a precise quantitative measure of NMC velocity given in mm*min$^{-1}$ we expect the method to be able to detect even smaller intermediate changes in NMC velocity in the spectrum from 0.0 to normal (healthy) NMC values, when going from absent clearance in PCD to hopefully some measurable nasal clearance if ciliary function in PCD could be medically partially restored.

In PCD lungs, long term lung function evolution has shown to vary considerably between groups of patients with PCD [20] and growing evidence indicates that patients with specific genetic defects may have more severe lung disease [21] [22] [23]. Whether the geno-phenotypically more severe PCD subjects are also associated with more severely reduced pulmonary MC has yet to be investigated.

Geno-phenotypical variation in PCD nasal compartment is well established, as nasal ciliary beat pattern and nasal ciliary frequency obtained by HSVM has been described to vary considerably across different PCD genotypes [3]. Nasal NO values which are usually very low in PCD may correlate to ciliary function [24], [25], [26] also varies in PCD. Normal nasal NO levels have been described in some but not all patients with PCD who harbor gene-defects related to normal TEM, and higher nasal NO has been described in some but not all patients with PCD where ciliary function is less compromised [25], [27]. Correlating to this, NMC velocity could also vary across different PCD genotypes and possibly also increase if ciliary motility improved due to therapeutic PCD protein correction.

However, in this pilot study we found NMC to be completely absent in all tested patients with PCD regardless of nasal NO values and PCD genotype. Genotypes associated with classic TEM outer dynein arm defects (DNAH5, DNAI1 and CCDC114) and genotypes associated with no detectable TEM defects (DNAH11 and HYDIN) or minor and sometimes not visible TEM defects (RSPH9) [28] were all represented in this study (Table 1).
All patients with PCD in our study had abnormal ciliary beat pattern and sub-normal range nasal NO production rates below the recommended cut off value of 77 nl/min to discriminate patients with PCD from healthy subjects [19], [29].

Limitations to the study
The study was a pilot study and as such with a limited number of patients. Even though not all PCD genotypes were represented in the patient group, the distribution between PCD genotype related to classic TEM defect and non-hallmark TEM defect [18] was approximately 50-50% and NMC velocity absent in all patients regardless of genotype. Despite small numbers we found highly significant discrimination between PCD and health.
Future larger NMC studies to further investigate age effect and genotype effect are warranted.

Subjects were exposed to a radioactive tracer ($^{99m}$Tc-albumin colloid) but the diminutive tracer droplet size of 2.5 μl resulted in a very low radiation dose of 25 μSv for a full NMC measurement, only a ¼ of the radiation exposure from a chest x-ray (0.1 mSv) and equivalent to three days of background radiation in Denmark.

Head movements during the 10 minutes of acquisitions, causing movement of the nasal tracer may lead to false negative readings of NMC velocity. Assessment of tragus reference movement as an indicator of head movement is therefore essential at each post measurement reading. In this study head movement requiring post measurement correction only occurred in one subject. Post measurement digital correction was easily performed by subtracting the distance of the tragus reference movement from the total distance of the nasal tracer movement.

Nasal infections can cause secondary ciliary dysmotility (SCD) and result in abnormal nasal mucociliary transport as previously shown by De Boeck and colleagues [7]. This should be taken into consideration when timing for NMC velocity measurement, and NMC measurement should be postponed if the patient suffers from an acute upper respiratory infection.
In summary, we found NMC velocity to be a feasible, painless, and very rapid *in vivo* measurement of the MC in the nasal compartment of the upper airways in both children and adults. NMC velocity measurement only required 10 minutes testing, and the amount of radiation exposure was minimal which favors NMC velocity for repeated measurements, e.g., at fixed time points before and during a clinical trial.

This quantitative test for NMC velocity could be an important tool in future clinical trials for nasal medication specifically directed towards patients with PCD, either by using NMC as a forerunner for further studies on whole-lung MC by PRMC, or for combined studies testing both nasal and lung medication in PCD by NMC and PRMC, respectively.

**CONCLUSION**

With this proof-of-concept study we found $^{99m}$Tc-albumin colloid NMC velocity measurement to be a quantitative test that is highly feasible, highly discriminative between PCD and health and with a very low radiation exposure.

We found an excellent success rate to perform the NMC test of 100% in both the PCD group and the HC group.

NMC velocity measurement could be a potential important outcome parameter to test nasally administered drugs in future clinical trials designed specifically for patients with PCD.
ABBREVIATIONS

CP defect: Central Pair Defect,
HC: Healthy controls
HSVM: High Speed Video Microscopy
MC: Mucociliary Clearance
NGS: Next Generation Sequencing
NMC: Nasal Mucociliary Clearance
nNO: Nasal nitric oxide
ODA defect: Outer Dynein Arm defect
PCD: Primary ciliary dyskinesia
PRMC: Pulmonary Radioaerosol Mucociliary Clearance
TEM: Transmission Electron Microscopy
SCD: Secondary Ciliary Dysmotility
Table 1:

<table>
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<tr>
<th>Subject no.</th>
<th>Group</th>
<th>NMC velocity (mm·min⁻¹)</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Nasal NO (ppb)</th>
<th>Nasal NO (nL·min⁻¹)</th>
<th>Ciliary beat frequency by HSVM</th>
<th>Ciliary beat pattern by TEM</th>
<th>Ciliary ultrastructure by TEM</th>
<th>PCD gene</th>
<th>Conclusive first test</th>
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<td>ODA defect</td>
<td>DNAH5</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>PCD</td>
<td>0.0 *)</td>
<td>31</td>
<td>F</td>
<td>24</td>
<td>7.9</td>
<td>Almost immotile (1-2 Hz)</td>
<td>Residual flickering</td>
<td>ODA defect</td>
<td>CCDC114</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 1:
Figure 1. Photo of a ten year old showing the gamma camera facing the profile of the subject during the 20 minute dynamic acquisitions after the administration of the radiolabelled tracer to the nasal concha media. A $^{57}$Co marker is attached to the tip of the nose and to the anterior tragus of the ear leaning against the camera. The tragus marker is not visible on the photo. The photo is shown with consent from both parents and the child.