Pulmonary radioaerosol mucociliary clearance in primary ciliary dyskinesia

To the Editor:

Primary ciliary dyskinesia (PCD) is a genetic condition affecting one in 10,000–40,000 people from birth [1]; cilia fail to beat, and the airway clearance of mucus and debris is severely impaired. If untreated, this results in progressive lung infection leading to bronchiectasis and ultimately respiratory failure. Additionally, delayed diagnosis has implications for genetic counselling, appropriate management of glue ear and fertility advice. Early diagnosis and appropriate treatment are believed to improve outcome. The diagnosis of PCD is highly specialised and results can remain inconclusive, despite state of the art equipment and diagnostic techniques. A European consensus statement [2, 3] highlighted that there is no “gold-standard” diagnostic test; diagnosis requires expert review of clinical history and screening tests (nasal nitric oxide measurement) alongside analysis of ciliary function and ultrastructure [2]. It is recommended that ciliary activity of respiratory epithelial cells obtained by nasal or bronchial brushing is recorded using a high-speed video camera mounted on a microscope. The images are played back in slow motion to analyse ciliary beat pattern (CBP) and frequency (CBF). Transmission electron microscopy (TEM) is used to assess ciliary ultrastructure [4]. Diagnostic uncertainty can be caused by secondary damage of the epithelium during sampling or due to infection or inflammation of epithelia; this damage can lead to abnormalities of ultrastructure, CBF and CBP. Furthermore, diagnosis is hindered by normal ciliary ultrastructure in 3–30% of cases of PCD [5, 6]. To improve diagnostic certainty, a variety of further investigations can be employed [2], including reanalysis of CBF, CBF and TEM following culture of the cells at an air–liquid interface [7, 8], or using immunofluorescence microscopy [9] to identify ciliary proteins. A single-centre study has previously reported the use of pulmonary radioaerosol mucociliary clearance (MCC) in the diagnosis of PCD [10]. The method is based on clearance patterns after the inhalation of a radioaerosol tracer. It provides a whole-lung functional test for pulmonary radioaerosol MCC. The investigation is noninvasive and has been used in thousands of patients with other lung diseases, as young as ~5 years. The authors reported that MCC was an effective noninvasive functional test for PCD [10] but the study was preliminary, and the feasibility of this complex technique and interpretation of data have not been assessed in other centres. We therefore conducted a study to replicate the results using a standardised protocol. This study was approved by the National Research Ethics Service (South Central committee 11/SC/0192) and all subjects gave written informed consent.

We assessed pulmonary radioaerosol MCC in six adult patients previously diagnosed with “classical” PCD (table 1) according to European Respiratory Society consensus guidelines [2] compared with four healthy controls. PCD and control groups were similar in age and sex distribution but PCD patients had impaired lung function (mean FEV₁ 74% (range 36–105%) predicted in PCD patients and 97% (range 93–100%) predicted in controls) (table 1). Participants inhaled nebulised technetium-99m labelled nanocoll (GE Healthcare, Little Chalfont, UK) via a DeVilbiss 646 nebuliser (DeVilbiss Healthcare, Somerset, PA, USA) while breathing to ensure the best deposition in the central airways, as described previously [11]. Planar

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age years</th>
<th>HSV findings</th>
<th>TEM findings</th>
<th>nNO ppb</th>
<th>FEV₁ L</th>
<th>FEV₁ % predicted</th>
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<td>84</td>
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<td>ODA defect</td>
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<td>3.26</td>
<td>105</td>
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<tr>
<td>4</td>
<td>61.1</td>
<td>Static and twitching</td>
<td>ODA and IDA defect</td>
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<td>0.6</td>
<td>36</td>
</tr>
<tr>
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<td>71</td>
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<tr>
<td>6</td>
<td>18.9</td>
<td>Dyskinetic and uncoordinated</td>
<td>Axonemal disorganisation and absent IDAs</td>
<td>40</td>
<td>3.12</td>
<td>80</td>
</tr>
</tbody>
</table>

HSV: high-speed video microscopy; TEM: transmission electron microscopy; nNO: nasal nitric oxide; FEV₁: forced expiratory volume in 1 s; ODA: outer dynein arm; IDA: inner dynein arm.
Gamma camera images were taken at time 0, 1, 2, 4 and 24 h on a dual-head GE Infinia gamma camera (GE Systems, Milwaukee, WI, USA). A single-photon emission computed tomography/computed tomography scan and krypton-81 ventilation images were also obtained to characterise the initial distribution, allow attenuation correction and define the lung outline to assist interpretation of clearance data [12]. Geometric mean image data were interpreted after applying attenuation correction. Image analysis was carried out blind to patient group.

The mean percentage radioaerosol cleared was significantly greater in the control than in the PCD group at both 1 h (mean 24.0% (95% CI 3.4%) versus 2.3% (95% CI 6.1%)) and 4 h (46.3% (95% CI 8.7%) versus 24.2% (95% CI 11.1%)) (fig. 1). By 24 h, clearance was similar in the two groups (66.2% (95% CI 7.1%) versus 57.9% (95% CI 12.8%)). The technique was well tolerated by the subjects and there were no adverse events. Cooperation is needed from participants and it is unlikely that the test would be possible in pre-school children.

Our study adds to the limited data that pulmonary radioaerosol MCC might be a useful diagnostic adjunct for diagnosing PCD. The expertise required to conduct the studies and interpret the data are likely to limit it to specialist nuclear medicine centres. The normal clearance of the aerosol by 24 h demonstrates alternative methods of airway clearance in PCD than MCC, including chest clearance physiotherapy (the subjects were advised to undertake their normal physiotherapy regimen between the 4- and 24-h images), cough and macrophage activity. It provides reassurance of the safety of this radioaerosol technique. Further data are required to confirm whether the technique will be useful for differentiating patients with considerable secondary ciliary damage or for diagnosing patients with "atypical PCD" (e.g. normal ciliary ultrastructure).

Pulmonary radioaerosol mucociliary clearance is reduced in PCD patients and might prove useful in diagnosis [http://ow.ly/uP5Vg]

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References


