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Imaging lung function abnormalities in primary ciliary dyskinesia using hyperpolarised gas ventilation MRI

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INTRODUCTION

Primary ciliary dyskinesia (PCD) is a genetic condition causing progressive lung disease, which starts during early childhood. Identifying early lung disease is therefore important for the initiation and assessment of early intervention to maintain lung health (1, 2). Assessment of lung function in PCD may have a significant clinical overlap with cystic fibrosis (CF) (3), the aim being to identify small, but clinically significant airways obstruction within the lung. Spirometry is insensitive to early lung abnormality in CF and PCD, however the lung clearance index (LCI) derived from multiple breath washout (MBW) can detect early ventilation heterogeneity in patients with CF (4). Recent studies utilising LCI in PCD have however highlighted that the relationship between pathophysiology and functional changes in PCD may not be entirely consistent with CF (3, 5, 6). Hyperpolarised gas ventilation MRI has been proven to be highly sensitive to early lung disease (7, 8), response to treatment (9) and to the deterioration of lung function (10) in CF and is well tolerated by children as young as 5 years (11). In this study we present our findings of preliminary studies with hyperpolarised gas ventilation MRI in children with PCD.

METHODS

This is a retrospective analysis of children diagnosed with PCD, referred to our centre for clinical assessment to further investigate their lung function. These patients had either normal FEV_1 or mild to moderate airflow obstruction (12, 13) but with on-going symptoms. On the day of testing all subjects were free from pulmonary exacerbation, were not undergoing any new acute treatments and felt well. Each child performed hyperpolarised gas ventilation MRI, MBW and spirometry. This study was performed under clinical research governance for retrospective research using clinical data.

3D volumetric hyperpolarised helium-3 (^{3}He) ventilation MR images and ^{1}H anatomical images were acquired during the same breath-hold on a 1.5T GE scanner (14). From these images two indices were calculated; (i) ventilation defect percentage (VDP), which quantifies the percentage of the lung volume that is not ventilated, and (ii) the mean coefficient of variance of ventilated image signal intensity (CV), a metric of regional ventilation heterogeneity. ^{1}H steady state free precession MR images were separately acquired for assessment of lung morphology and mucus (15). Previous CT imaging was also reviewed for comparison when available.

MBW was performed as previously described (16) and the parameters LCI, S_{cond} and S_{acin} were calculated. The upper limit of normal for LCI was defined as >7.4 (16).

Due to the small sample size, Spearman correlations were performed between lung function and MRI metrics. A p-value <0.007 was deemed to be statistically significant after Bonferonni correction.

RESULTS

11 children with PCD (8 female) were assessed and their individual demographics, lung function and MRI metrics are summarised in Table 1. Seven children had situs inversus totalis.

All 11 children had ventilation defects on ventilation MRI (Figure 1). Defects were mostly small and heterogeneously distributed, with multiple defects present on most image slices throughout the lungs. One subject (B) had significant mucus plugging evident in the left

lower lobe on ^{1}H MRI and on previous CT, which was associated with a large ventilation defect evident in all image slices.

Five children (A, B and I-K) had abnormal LCI (>7.4 (16)) and six (A, B, G and I-K) had mild-moderate airflow obstruction on spirometry (FEV_1/FVC z-score <LLN and FEV_1 z-score >-3.02). All children with abnormal LCI also had abnormal FEV_1 and one child had abnormal spirometry with LCI just below the upper limit of normal. The six children with airflow obstruction also had the highest VDP values.

There were only significant correlations between VDP and; LCI (Figure 2), and FEV_1/FVC (r=-0.83,p=0.003). CV did not significantly correlate with FEV_1 or FEV_1/FVC but demonstrated the closest correlation with LCI (r=0.71, p=0.02).

Seven children (B-D, F, H-J) had comparable CT imaging performed within 3.5 years prior to MRI (B-1year, C–8months, D-3.4years, F-3.4years, H-3.4years, I-1year, J-3.5years prior). Patient H and I had normal CT images. Patients C, D and F had bronchial wall thickening. Patient B, C and J had CT findings of mucus plugging (B, J) or bronchiectasis (C, J) that correlated with ^{3}He and ^{1}H MRI.

DISCUSSION

In children with PCD, lung ventilation abnormalities are evident on hyperpolarised gas ventilation MRI despite the presence of normal LCI and FEV_1. When compared to our healthy control cohort of 10 children (aged 7.1-15.6 years) previously reported (7), none of the healthy controls had visible defects and all had VDP values <1.88% and LCI values <7.4. Computed tomography imaging in PCD suggests a predominance of middle and lower

lobe disease (17). In the group we present, ventilation defects were observed in these lung regions, but there were often additional ventilation defects present in the upper lobes, possibly caused by mucus plugging that precedes structural change.

Ventilation MRI has been shown to be more sensitive than LCI and FEV_1 for detection of ventilation abnormalities in CF (7). The ventilation images we report suggest this finding is consistent in children with PCD. LCI and FEV_1 inherently reflect global lung function averaged across the whole lung, this potentially masks mild ventilation heterogeneity. Ventilation MRI however provides high spatial resolution assessment of ventilation abnormalities at a given static lung volume, providing assessment of both the size and nature of un-ventilated lung regions and also the heterogeneity of ventilation. The imaging metric VDP appears to be sensitive to lung disease in PCD and, despite the small patient numbers, correlates with LCI, a pattern consistent in CF (7, 18), suggesting that the two techniques may be reflecting similar pathophysiology.

A possible limitation of this analysis is the fact that CT imaging was not performed in all patients at the same time for comparison. However, we have previously shown that ^{3}He MRI has greater sensitivity to mild lung disease than CT (7) and the radiation burden of CT is a concern in this group of young patients. Indeed, avoiding exposure to ionising radiation was a key factor in the referral for ventilation MRI. With recent advances in ^{1}H MRI the sensitivity of structural MRI to detect lung disease has also increased (19, 20). When employed alongside hyperpolarised gas MRI, this would allow detailed sensitive assessment of both functional and structural lung disease without the need for sedation or ionising radiation. We recognise however that at present this technology is limited to specialist centres, however with the advent of xenon-129 ventilation MRI the technology is

now clinically accessible to any large hospital with MRI capability. The small sample size is a limitation of this work, which may restrict the generalizability of these findings to all people with PCD.

In conclusion, ventilation defects are present in children with PCD even in the presence of normal LCI and FEV_1. This pattern is consistent with findings in patients with CF, and suggests that hyperpolarised gas ventilation MRI is a sensitive method for detecting lung disease in children with PCD.

135 Table 1: Patient demographics, lung function and ventilation MRI metrics for all 11 patients. Diagnostic information on; Cilia beat frequency

136 and pattern, nasal nitric oxide, genetics and electron-microscopy findings, are supplied where available.

Patient	A	B	C	D	E	F	G	H	I	J	K	Mean
Sex	F	F	F	F	F	F	F	F	M	M	M	
Age (years)	14.7	9.4	14.4	12.1	12.2	17.0	17.3	10.1	7.3	16.5	15.7	13.3
Height (cm)	160.6	140.2	165.0	155.5	154.5	151.9	146.6	125.9	120.3	162.5	179.2	151.1
Weight (kg)	39.0	26.0	66.0	66.0	44.5	45.0	45.0	24.0	21.0	56.0	86.5	47.2
FEV_1 z-score	-2.11	-3.24	-0.67	0.57	0.69	0.56	-2.36	0.17	-3.02	-1.47	-2.06	-1.09
FEV_1/FVC z-score	-1.73	-3.24	-0.5	-1.00	-1.44	-1.49	-2.32	0.52	-3.05	-3.03	-1.67	-1.72
LCI	8.76	7.78	6.94	6.03	6.79	7.35	7.34	6.41	11.09	10.7	8.55	7.98
S_{cond}	0.03	0.10	0.06	0.03	0.02	0.05	0.06	0.05	0.07	0.06	0.09	0.06
S_{acin}	0.29	0.08	0.12	0.07	0.06	0.03	0.18	0.07	0.28	0.17	0.14	0.12
VDP (%)	13.20	11.75	4.67	2.60	2.05	6.60	7.54	3.20	20.07	20.68	4.99	8.85
CV (%)	19.10	12.99	12.45	15.60	10.79	13.36	12.25	11.72	19.84	22.67	15.21	15.06
Cilia beat frequency (Hz) and pattern	6.5 Static or very reduced amplitude	2.9 Stiff, barely flickered	6.7 Normal	11.7 Dyskinetic motion	10.9 Jerking-like motion	5.8 Dyskinetic motion	- Static Cilia	5.8 Stationary or dyskinetic motion	5.8 Static or very stiff motion	2.6 Static	18.4 Dyskinetic, stiff motion	
Nasal nitric oxide (nL/min)	30	<1.5	31.5	8.4	161.1	6.3	17.7	5.4	3.6	6.3	7.8	
Genetics	-	DNAH5	DNAAF5 heterozygous	-	CCDC103	-	-	-	-	DNAL1	-	
EM Findings	Absence of inner & outer dynein arms	Absence of inner & outer dynein arms	No defect found	Slight increase in microtubular defects. Slight increase in ciliary disorientation.	No defect found	Absence of inner dynein arms	Absence of inner & outer dynein arms	Absence of inner & outer dynein arms	Lack of inner dynein arms & displacement of the central microtubular pairs	Absence of outer dynein arms	Absence of inner dynein arms	

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Figure Legends:

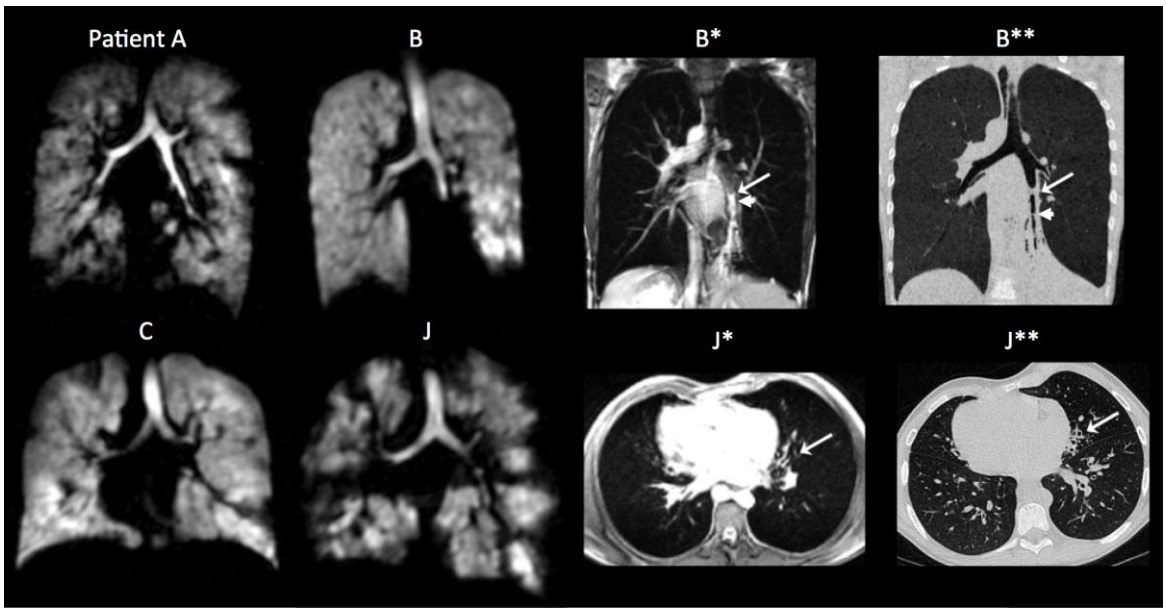

Figure 1: Representative single ^{3}He MR ventilation image slices from four patients with PCD, with representative ^{1}H MRI and CT slices for patients B and J. The patient letter corresponds to Table 1 and throughout the text. The four examples demonstrate the types of ventilation defects seen. Patient C had spirometry and LCI values within the normal range, where as patients A, B and J had abnormal spirometry and LCI. Patient B has a collapsed left lower lobe with dilated bronchi (see arrows) and mucus plugs (arrowhead) evident on ^{1}H MRI (B*) (the arrow on ^{1}H MRI points to a dilated bronchus containing high signal mucous) and CT (coronal 4mm minimal intensity projection CT - B**). These findings correspond with the clear-cut ventilation defects on ^{3}He MRI (the CT image was performed approximately 8 months prior to MRI). Patient J has bronchiectasis evident on both ^{1}H MRI (J*) and CT (J**) (see arrows) in the left middle lobe and right lingular segment where ventilation defects are apparent on ^{3}He MRI. It is worth noting however that the CT image in this patient predates the MRI by 3.5 years and it may be the case that structural abnormalities may be more prevalent if CT were to be performed at the time of the MRI.

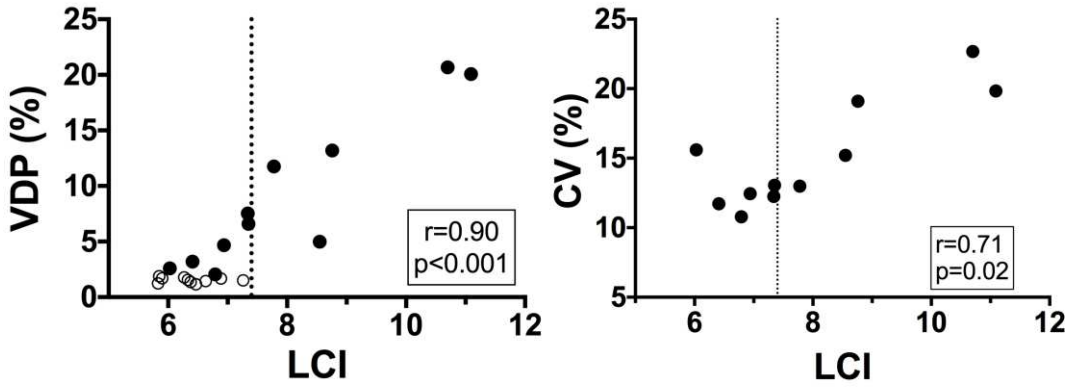

Figure 2: Spearman correlations between lung clearance index (LCI) and both ventilation defect percentage (VDP) and coefficient of variance of ventilated image signal intensity (CV) for the patients with PCD (closed circles). The dashed vertical line at an LCI value of 7.4 represents the upper limit of normal (16). When comparing VDP and LCI we have added healthy control data (open circles) for reference, these data points were not included in the Spearman correlation analysis.

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