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Full title: Chronic lung disease in patients with perinatally acquired HIV in England: a retrospective case-note review.

Short title: Chronic lung disease in PA-HIV

Authors:

1. Penelope K. ELLIS; BMedSci, University of Sheffield

2. Fiona SHACKLEY; MBChB, Paediatric Immunology & Infectious disease, Sheffield Children's NHS Foundation Trust

3 Kelechi UGONNA; PhD, University of Sheffield

4. Clare E. RYAN; MBChB, Doncaster and Bassetlaw Teaching Hospitals NHS Trust

5. David HUGHES, FRCR, Department of Radiology, Sheffield Children's Hospital.

6. Stephen OWENS; PhD, Department of Paediatric Immunology and Haematopoietic Stem Cell Transplantation, Great North Children's Hospital, Newcastle upon Tyne Hospital National Health Service (NHS) Foundation Trust

7. Philip BROWN; MBChB, University of Newcastle

8. Andrew RIORDAN; FRCPCH, Department of Paediatric Infectious Diseases and Immunology, Alder Hey Children's NHS Foundation Trust

9. Chinenye I. ILOZUE; MBChB, Liverpool University Hospitals NHS Foundation Trust

10. Sarah L. ROWLAND-JONES; PhD, University of Sheffield

11. Paul J. COLLINI; PhD, University of Sheffield

Corresponding author: Paul J Collini

Department of Infection, Immunity & Cardiovascular Disease, L Floor, University of Sheffield, Medical School, Beech Hill Road, Sheffield, S10 2RX

p.collini@sheffield.ac.uk

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Abstract

Chronic lung disease (CLD) is common in individuals living with perinatally-acquired HIV (PA-HIV) in southern/eastern Africa. Most of the UK PA-HIV population are African. We conducted a case-note review of CLD in three UK PA-HIV cohorts (n=98). 8.1% had bronchiectasis or obliterative bronchiolitis, 19.2% had ring/tramline opacities on chest x-ray. There may be unrecognised and underdiagnosed CLD among PA-HIV in the UK.

Key point of this research

Adolescents in SE-Africa with perinatally-acquired HIV have a high prevalence of chronic lung disease (CLD).

This case-note review addressed whether the phenomenon exists in the UK where many with perinatally-acquired HIV are Africa-born.

The CLD prevalence was higher than expected and warrants further study to mitigate any long-term consequences.

Introduction

Reports from southern and eastern (SE)-Africa describe high rates of chronic lung disease (CLD) in children and adolescents living with perinatally acquired HIV (PA-HIV). These identify phenotypes of chronic cough, breathlessness and hypoxia, underpinned by radiographic abnormalities consistent with obliterative bronchiolitis (1,2,3). Although CLD has been associated with delayed HIV diagnosis and later antiretroviral therapy (ART) initiation, it is also prevalent in those established early on ART and "slow-progressors" presenting in early adolescence (1,4,5).

It is not clear to what extent this CLD is driven directly by HIV-associated inflammation or by the particular health-care availability, environmental exposures and socio-economic conditions of sub-Saharan Africa (1). PA-HIV adolescents in the US have more obstructive airways disease, but data from other high-income settings are limited (6). Those living with PA-HIV in the UK may benefit from earlier diagnosis and ART initiation, better childhood vaccination coverage, and reduced household air pollution and circulating respiratory pathogen exposure than in SE-Africa (1). However, 56% of the UK PA-HIV population was born abroad, three-quarters are Black African and many present late (7). The epidemiology of CLD in the UK PA-HIV population is unknown. We set out to determine the prevalence and phenotype of recorded CLD in patients living with PA-HIV attending 3 north of England regional HIV centres.

Methods

A retrospective case-note review of respiratory diagnoses in 6-30 year-old PA-HIV patients attending paediatric and transition HIV clinics in Sheffield, Liverpool and Newcastle. Local clinical teams used a standardised protocol to extract demographic and HIV disease data, respiratory diagnoses and verbatim chest radiology reports. We chose data items based on those used in studies from SE-Africa (2,5). We considered CLD was present based on documentation of a clinical diagnosis and/or chest radiographic changes. A standardised defintion of CLD in this population does not exist. The SE-Africa PA-HIV studies report bronchieactasis and obliterative bronchioloitis as the principal CLDs (2,3). The majority did not describe reversible airways disease. Adult HIV studies mainly report COPD, bronchogenic carcinoma and pulmonary hypertension. We therefore defined a clinical diagnosis of CLD as bronchiectasis, obliterative bronchioloitis and any other chronic lung condition except asthma, tuberculosis, lymphocytic interstitial pneumonia (LIP) or any with a clear a genetic aetiology. Informed by the African reports and Norton et al., we defined radiographic changes of CLD as any report showing ring/tramline opacities, bronchial wall thickening, a nodular/reticulonodular/reticular pattern, or moderate/severe atelectasis on chest x-ray (CXR) and decreased attenuation consistent with small airway disease on high resolution computed tomography (HRCT) (2, 3, 8, 9). Anonymised summary data from each site were collated and analysed in Sheffield. Radiology reports were classified according to the Fleischner Society Glossary of Terms by an independent consultant paediatric respiratory radiologist. Where an individual had the same abnormality reported more than once, we only counted a single instance. If a report recorded more than one type of abnormality, we counted each separately. Informed by the non-parametric distribution of the data, the Mann Whitney

97 U-test and Fisher's exact test were used to compare continuous and categorical data
98 respectively in SPSS. Sub-studies were registered and approved as service evaluations at
99 Sheffield Teaching Hospital NHS Foundation Trust (NFT), Sheffield Children's Hospital
100 NFT, Doncaster and Bassetlaw Teaching Hospitals NFT, Newcastle-Upon-Tyne Hospital
101 NFT, Liverpool and University Hospitals NFT and Alder Hey Children's NFT.
102

Results

98 individuals were included; 51 (52%) were female, median age was 17.9 (interquartile range 14.1-21.4) years. 67 (68.4%) were Black African, 12 (12.2%) mixed African, 9 (9.2%) White British and 9 (9.2%) other. 64 (65.4%) were non-UK born. Median age at HIV diagnosis was 4.5 (1.9-9.0) years and 49/83 with available data initiated ART within a year of diagnosis. Median nadir CD4 was 280.0 (149.5-462.5) cells/mm^3; 73.5% had undetectable viral loads and 82.7% had a CD4 > 350 cells/mm^3 at last clinic visit.

27 (28%) had a significant lung disease documented in their clinical record, with "bronchiectasis" and "community acquired pneumonia" most prevalent (Table 1). 8 (8.1%) had bronchiectasis or obliterative bronchiolitis recorded and we considered these as significant CLDs. They did not differ significantly by age, gender, UK birth, age at HIV diagnosis, time to ART initiation or nadir CD4 from those without CLD. They were, however, admitted to hospital with respiratory tract infection (RTI) significantly more often than individuals without CLD; median 1.5 (0.8-2.3) vs 0.0 (0.0-0.3) events, p=0.012 respectively. There were trends for those with CLD to be more likely to have had any RTI (88% vs 66%, OR 3.678, 95% CI 0.60 to 42.63, p=0.27) and a higher frequency of outpatient RTI diagnosed (median 3.0 (0.5-12.75) vs 1.0 (0.0-3.0), p=0.096) (supplementary data table S1).

73 individuals had CXR performed at least once, median 2 (1-4), 23 had no evidence of imaging available and records were not accessible for 2. In total 57 of the 120 CXR reports described abnormalities. 41 out of the 73 individuals had ≥1 abnormal CXR. The most prevalent abnormality was ring/tramline opacities (19.2%) (Table 1). 8 individuals had a total

128 of 13 HRCT scans; 12 (92.3%) reported abnormalities, most often bronchiectasis. 7/8 had ≥1
129 abnormal HRCT.
130
131 Clinical diagnoses and radiological identification of CLD differed by place of birth. Among
132 sub-Saharan Africa-born compared to UK-born individuals, the prevalence of a clinical
133 diagnosis of bronchiectasis/obliterative bronchiolitis was 10.5% versus 3.6% ; CXR
134 ring/tramline opacities 36.4% versus 15.8% and HRCT bronchiectasis 83.3% versus 0.0%,
135 respectively (Table 1).

Discussion

We have found a high prevalence of radiological abnormalities suggestive of CLD in this ART-era, UK-based cohort of individuals living with PA-HIV. 7 had a diagnosis of bronchiectasis (6 supported by HRCT) and another obliterative bronchiolitis. These diagnoses were also associated with increased RTI frequency.

A similar prevalence of CLD and chest radiographic abnormalities might be expected nationally as our cohort appears representative of the UK PA-HIV population; in 2017 the Collaborative HIV Paediatric Study (CHIPS) had a median age 14.9 years, 54% were female, 77% Black African and the 56% non UK-born had a median age at HIV diagnosis of 9-12 years (7).

The rate of bronchiectasis in our cohort is greater than expected given the UK incidence for 18-30 year-olds is 43.4 per 100,000 person-years (10), albeit data aren't available for the general UK paediatric population. Indeed, it is similar to the 5.7% reported in a pre-2000 USA cohort of predominantly ART-naive individuals living with PA-HIV (11). However, while in the pre-ART-era bronchiectasis was driven by *pneumocystis jirovecii* pneumonia (PCP), TB and LIP, only a single individual with bronchiectasis in our study had such a history. The ART-era, USA Paediatric HIV/AIDS Cohort Study (12) reported a higher rate of PA-HIV cases 'using asthma medication' but a similar rate of 'diagnosed asthma' than controls. Another US cohort found more fixed airflow obstruction in those with PA-HIV (6). Both potentially indicate the existence of unrecognised CLD.

The combined prevalence of bronchiectasis, obliterative bronchiolitis and CXR ring/tramline opacities in our population is 27.3%, considerably lower than the prevalence of CLD in SE-African studies (1,2,3,4). Among those born in sub-Saharan Africa in our study, 10.5% had bronchiectasis/obliterative bronchiolitis compared with only 3.6% of UK-born. Higher age at HIV diagnosis, longer periods of uncontrolled HIV viremia, untreated lower RTIs and environmental factors may drive the higher prevalence of CLD in that setting (2,3,5). The association between inpatient RTI and CLD diagnoses suggest the severity of RTI may be an important contributor to the development of CLD; a previously undocumented finding. Albeit at lower rates than those living with PA-HIV, age-matched HIV-seronegative individuals from SE-Africa also have some limitation in lung function further indicating a role for local environment (5).

Importantly, irrespective of setting, those who acquire HIV in adulthood have increased risk of CLD (13). Early life exposures will affect peak lung development and set an adult lung function trajectory for obstructive airways disease (14). Thus, taken together with our findings, it may be that early life exposures in sub-Saharan Africa and chronic HIV infection will drive CLD in a proportion of the UK PA-HIV population who will be vulnerable to further deterioration of respiratory function through adulthood.

This study is limited by the retrospective design and the incompleteness of case notes. Pre-UK health care information for the 65.4% of individuals born outside the UK were also unavailable. We did not search primary care records so could not evaluate RTIs managed in the community. Diagnoses, radiology reports and other record data were not always standardised and original radiology images were often unavailable. Not all imaging was followed-up so we could not determine resolution or progression of changes. Thus, our definition of CLD from radiographic findings was pragmatic and based on single reports (9).

We were unable to determine the duration of observation and timing of diagnoses precisely enough to calculate CLD incidence or trends over time. As the median age at HIV diagnosis was 4.5 years and a high proportion were born in sub-Saharan Africa, we cannot exclude a role for undocumented, pre-UK arrival early life lung insults such as LIP in CLD pathogenesis. While PA-HIV populations in other low- and middle-income regions will share similar risks for CLD to those from SE-Africa, published data on CLD in these populations are sparse. However, migrants from these areas are rare among the UK PA-HIV population.

Our study detected a signal for a higher than expected prevalence of CLD in the UK PA-HIV population. This may reflect the high proportion who spent their early years with undiagnosed HIV in sub-Saharan Africa. Further investigation of 'hidden' and potentially progressive CLD in UK PA-HIV cohorts is now required to understand its true prevalence, change over time and optimal prevention and treatment to mitigate significant respiratory disability.

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Contributions:

P.K.E., P.J.C., F.S., and K.U. contributed to conception and design. P.K.E., C.E. R., S.O., P. B., A.R. and C.I.I. performed data collection. D.H. provided clinical advice on data interpretation. P.K.E., and P.J.C. performed data analysis. All authors contributed to writing the manuscript and approved final version.

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Table 1. Record of lung disease and prevalence of abnormalities on chest radiograph and high-resolution computed tomography, n (%)

Diagnosis of lung disease as recorded in clinical notes:	UK Born n=28	SSA born n=57	Born elsewhere / unknown* n=13	Total n =98
Asthma	1 (3.6)	1 (1.8)	0 (0.0)	2 (2.0)
Bronchiectasis	0 (0.0)	6 (10.5)	1 (7.7)	7 (7.1)
Obliterative Bronchiolitis	1 (3.6)	0 (0.0)	0 (0.0)	1 (1.0)
LIP	1 (3.6)	1 (1.8)	2 (15.4)	4 (4.1)
PCP	4 (14.3)	0 (0.0)	1 (7.7)	5 (5.1)
Pneumonia	2 (7.2)	4 (7.0)	1 (7.7)	7 (7.1)
Pulmonary/Disseminated TB	0 (0.0)	6(10.5)	0 (0.0)	6 (6.1)
CXR	n =19	n =44	n = 10	n = 73
Atelectasis	1 (5.3)	0 (0.0)	1 (10.0)	2 (1.7)
Consolidation	8 (42.1)	4 (9.1)	3 (30.0)	15 (12.5)
Lymphadenopathy	0 (0.0)	2 (4.5)	0 (0.0)	2 (1.7)
Non-cavitating nodules	1 (5.3)	3 (6.8)	4 (40.0)	8 (6.7)
Reticular pattern	4 (21.1)	2 (4.5)	1 (10.0)	7 (5.8)
Ring/tramline opacities	3 (15.8)	16 (36.4)	4 (40.0)	23 (19.2)
Normal	9 (47.4)	37 (84.1)	7 (70.0)	53 (44.2)
No report available	3 (15.8)	7 (16.0)	0 (0.0)	10 (8.3)

HRCT	n = 0	n = 6	n = 2	n =8
Atelectasis	0 (0.0)	1(16.7)	1(50.0)	2 (15.4)
Bronchiectasis	0 (0.0)	5 (83.3)	1(50.0)	6 (46.2)
Consolidation	0 (0.0)	1(16.7)	1(50.0)	2 (15.4)
Non-cavitating nodules	0 (0.0)	2 (33.3)	0(0.0)	2 (15.4)
Normal	0 (0.0)	1(16.7)	0(0.0)	1 (7.1)

CXR, chest x-ray; HRCT, high resolution computed tomography; IQR; interquartile range; LIP, Lymphocytic interstitial pneumonia; n, number of individuals with finding; PCP, pneumocystis jirovecii pneumonia; RTI, respiratory tract infection; TB, Tuberculosis. * 6 of these had unknown places of birth

Supplementary Table S1 Distribution of characteristics by diagnosis of bronchiectasis or obliterative bronchiolitis

	Sample, median (IQR) or n (%)			
Characteristic	Bronchiectasis or obliterative bronchiolitis (n=8)	No bronchiectasis or obliterative bronchiolitis (n=90)	Difference (Confidence Interval)	P value
Gender, female	2 (25.0.)	49 (54.4)		0.469
Age	19.8 (17.0-24.0)	17.45 (14.0-21.0)	0.99 (-3.1 to 4.8)	0.550
Born outside the UK [#]	7 (87.5)	57 (67.9)		0.428
Age at HIV Diagnosis [§]	4.3 (1.8-6.7)	4.5 (1.9-9.1)	- 0.6 (-4.9 to 2.8)	0.622
Years HIV Diagnosis to ART initiation[$]	0.1 (0.0-1.0)	0.1 (0.0-3.0)	0.0 (-3.0 to 0.2)	0.659
Nadir CD4 Cell count, cells/	265.0 (256.5-456.5)	280.0 (143.0-534.5)	105.0 (-60.0 to 246.0)	0.327
Number of outpatient RTI per patient	3.0 (0.5-12.75)	1.0 (0.0-3.0)	2.0 (0.0 to 3.0)	0.096

Number of times admitted to hospital for RTI	1.5 (0.8-2.3)	0.0 (0.0-0.3)	1.0 (0.0 to 2.0)	0.012

ART, antiretroviral therapy; IQR, interquartile range; RTI, respiratory tract infection; UK, United Kingdom

Data available for 92 individuals. §Data available for 90 individuals. $Data available for 83 individuals