Original Article

Positron emission tomography in the prediction of inflammation in children with human immunodeficiency virus related bronchiectasis

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Abstract

There is a lack of objective tools to reliably diagnose exacerbations in bronchiectasis. *The primary aim of this study* was to assess the ability of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to detect sites of active inflammation in children with human immunodeficiency virus (HIV)-related bronchiectasis with or without exacerbations. The secondary aim was to assess whether ^{18}F-FDG-PET/CT results are in agreement with local and systemic inflammatory markers and markers of HIV disease activity. *Forty-one children* with HIV-related bronchiectasis underwent ^{18}F-FDG PET/CT. Data on the presence of a clinical exacerbation were recorded. Serum was collected for CD4 count, HIV viral load, C-reactive protein (CRP) and cytokines IL-8, INF-γ and TNF-α. Induced sputum samples were processed for microbiological culture and for IL-8, INF-γ and TNF-α. Mean age of all children was 8.2±2.2 years. *Twelve subjects showed* ^{18}F-FDG lung uptake while six of them had an exacerbation. There was no difference in the ^{18}F-FDG uptake in participants with or without an exacerbation (P=0.613). Fluorine-18-FDG-PET had a good correlation with the presence of consolidation (P=0.01, OR=6.67). The mean CRP was higher in the subjects with ^{18}F-FDG uptake when compared to those without uptake (51.96±95.12 vs. 13.26±19.87), although this difference was not significant (P=0.09). *In conclusion*, the ^{18}F-FDG-PET technique could not reliably predict the presence of an exacerbation in children with HIV, and its diagnostic value was limited to identifying disease activity on the scan in acute pneumonia cases. Fluorine-18-FDG-PET had no significant correlation with CRP (**or**) with other inflammatory biomarkers and markers of HIV disease activity.

Introduction

Non-cystic fibrosis (NCF) related bronchiectasis is regarded as an “orphan” lung disease [1, 2]. This is largely due to lower research and development activity for this condition. Rates of bronchiectasis have decreased dramatically in developed countries and reports in Finnish children under 15 years indicate a prevalence rate of 0.49 per 100,000 [1, 3-5]. These improvements have been largely attributed to immunization programs, better access to healthcare services and reduction in over-crowded living conditions [3, 6-8]. In developing countries the majority of reported cases of bronchiectasis are also post-infectious [9, 10]. In these communities the burden of respiratory diseases including tuberculosis (TB), coupled with poor access to healthcare services, places children at risk for severe respiratory tract infections. South Africa has borne the brunt of the human immunodeficiency virus (HIV) pandemic, with reported ante-natal infection reaching 30% of the population in 2009 [11]. A large number of children with acquired HIV are therefore at high risk for respiratory tract infections [12].

The manifestation of multiple pulmonary infections, lymphocytic interstitial pneumonitis and tuberculosis are chronic lung damage and bronchiectasis.

The management of bronchiectasis involves aggressive antibiotic treatment of exacerbations, physiotherapy, together with optimal vaccinations to prevent further lung damage and improve quality of life [13, 14]. Current tools to assess disease severity and progression are clinical follow-up with treatment of exacerbations, lung function testing, sputum cultures, imaging and measurement of lung inflammatory biomarkers. All of these tools have their limitations and drawbacks. The definition of an exacerbation is based on the presence of new symptoms which in paediatric patients is limited by the quality of health information provided by the care-giver [14]. Spirometry cannot be performed in children below the age of six years. The current gold standard method to assess lung inflammation includes analysis of airway neutrophils obtained from bronchoalveolar lavage [15, 16]. This has the drawback of being invasive and providing information only on specific lung segments. Sputum cultures are useful to guide antibiotic treatment but do not differentiate between chronic colonization and acute infection. Chest radiography is insensitive and provides gross anatomical localization of pathology, whilst high resolution computed tomography (HRCT) is the gold standard for diagnosing bronchiectasis and can be used for monitoring of structural lung changes. It does not however, provide any information on disease activity. There is also a concern of the patients' radiation burden from HRCT, especially if serial scanning is performed, making this an unattractive option with increased risk during regular follow-up.

There is a need for more reliable and objective tools that can be used to assess the degree of inflammation in order to guide management decisions and aid in the diagnosis of exacerbations in the context of HIV-related bronchiectasis.

Positron emission tomography with 2-[F-18]-fluoro-2-deoxy-D-glucose (^{18}F-FDG-PET) is widely used in the diagnosis of oncological diseases based on high metabolic turnover of saccharides by tumour tissue. In the inflammatory response, neutrophils have an increased expression of glucose transport proteins and there is an up-regulation of the hexokinase activity [17]. Elevated ^{18}F-FDG accumulation in inflamed tissues is not only related to increased glucose metabolism in inflammatory cells, but also by macrophage proliferation and recruitment. This makes ^{18}F-FDG PET an attractive tool for the diagnosis and management of inflammatory pulmonary disease. The co-registration of PET and HCRT therefore has the benefit of both anatomical localisation of pathology with the assessment for disease activity.

There is currently a lack of data on the role of PET-CT in children with non-CF related bronchiectasis, and especially in the context of HIV related bronchiectasis. The primary aim of this study was to evaluate the ability of ^{18}F-FDG- PET to detect sites of active inflammation in children with HIV related bronchiectasis with or without exacerbations. The secondary end-point was to assess

whether ^{18}F-FDG- PET results agreed with local and systemic inflammatory biomarkers or HIV disease activity markers.

Patients, materials and methods

Patients

All HIV-infected children aged 6 to 18 years with HRCT confirmed bronchiectasis, during January 2009-March 2010, attended the Paediatric Chest and Allergy Clinic (Steve Biko Academic Hospital, Pretoria, South Africa) consented to participate in the study. Included participants exhibited symptoms that were suggestive of bronchiectasis, namely a chronic productive cough, clubbing or halitosis and had radiological confirmation of bronchiectasis. HIV testing with a fourth generation HIV Elisa was performed as part of the work-up. Fifty-three participants were screened, forty-three were eligible and enrolled, but two were lost during follow-up. Of the 41 participants, 24 (58%) were male. The median age was 8.2±2.2 years, age range was 6-14 years (Table 1).

Table 1. *Baseline characteristics of children with HIV-related bronchiectasis undergoing ^{18}F-FDG-PET (N=41).*

Characteristics	Mean ± SD
Age	8.2 ±2.2
Male sex	24 (58)
Presence of exacerbation	12 (29.2)
HAART (months)	17.61 ± 17.86
CD 4%	19.34 ± 9.89
HIV_VL (copies/mL)	61.65 ± 254243.50
Bhalla score	13.94 ± 4.32
CRP (mg/mL)	8.76 ± 63.23
Serum	
IL-8¶ (pg/mL)	218.25 ± 178560.20
TNF- α (pg/mL)	2.25 ± 0.94
INF-γ (pg/mL)	204.88 ± 349.80
Sputum	
IL-8 ¶ (pg/mL)	785 ± 9352.06
TNF- α (pg/mL)	1.05 ± 0.70
INF-γ (pg/mL)	15.98 ± 21.50

¶: Geometric means reported; ( ): percentages in parenthesis;

CRP- C reactive protein; IL-8- interleukin 8; HIV_VL- HIV viral load; CD4%- percentage of cluster differentiation 4;

TNF- α- tumour necrosis factor alpha; INF-γ- interferon gamma

SD: Standard deviation

Clinical evaluations

A respiratory exacerbation was characterised, if present at the time of the PET scan. The clinical definition of exacerbation was the presence of at least two of the following criteria: increased tachypnoea or dyspnoea, change in frequency of cough, increase in sputum productivity, fever, chest pain and new infiltrates on the chest X-ray. Pneumonia was diagnosed by the presence of symptoms suggestive of an exacerbation together with consolidation and air bronchograms on chest CT.

Two induced sputum samples were collected by a dedicated physiotherapist from each patient on the same day. One of the samples was sent for microbiological testing, which included microscopy where appropriate, culture, and antibiotic sensitivity, for bacterial pathogens, including *Mycobacterium tuberculosis* as well as viral respiratory pathogens *Respiratory syncytial virus*, *Influenza* A and B, *Parainfluenza* 1-3, *Adenovirus* and *Cytomegalovirus*. The presence of acid-fast bacilli in sputum with a culture of the mycobacteria confirmed the diagnosis of tuberculosis.

A second sputum sample was used for determination of sputum cytokines interleukin-8 (IL-8), interferon gamma (INF-γ) and tumour necrosis factor alpha (TNF-α). Serum and sputum cytokines were measured using the Bio-Plex® suspension bead array system (Bio-Rad Laboratories Inc, Hercules, CA, USA) which utilizes luminex® Xmap™ multiplex technology to enable simultaneous detection and quantitation of multiple different analytes in a single sample.

Venous blood (1.5 mL) was collected and quantitatively analysed for: i) circulating concentration of CRP-acute phase reactant; ii) circulating $CD4^+$ T lymphocytes; iii) HIV-1 viral loads; and iv) cytokines IL-8, INF-α and TNF-γ. Physicians who carried out the scan diagnosis were blinded to clinical data, morphological testing and special investigations.

^{18}F-FDG PET/CT scanning

Whole body ^{18}F-FDG PET scans were acquired on a PET-CT scanner (Biograph, Siemens) from the skull top to the pelvis after fasting for a minimum of 4h. Patients received a dose of ^{18}F-FDG based on their body weight using the following formula: ((body weight/10) +1))*37MBq with a minimum activity of 74MBq and a maximum of 370MBq. Images from PET/CT were acquired at 60min after intravenous injection of ^{18}F-FDG. This study measured the maximum standardised uptake value (SUVmax) in four zones of the lungs using whole body ^{18}F-FDG-PET

Fluorine-18-FDG PET images were analyzed for the presence or absence of active 'lesion' sites by two experienced and blinded as above nuclear medicine physicians by consensus. Two blinded as above radiologists used the Bhalla scoring system to score the CT scans [18]. The Bhalla score is a qualitative CT scoring system to assess the severity of bronchiectasis, based on nine morphologic changes such as; peri-bronchial thickening, mucous plugging, abscesses or bronchiectatic sacculations,

emphysema, bullae and consolidation or collapse. The Bhalla score is based on subtracting the value of the CT score from 25, with 25 indicating normal lungs and zero being severe bronchiectasis.

Ethics

The study protocol and informed consent had ethical approval from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria. All parents signed an informed consent and assent was obtained from each participant where applicable.

Statistical analysis

Statistical analysis was performed using Stata Release 10 (Statacorp LP, College Station, TX, USA). The Fisher exact test was used for analysis of categorical variables and the Mann-Whitney U test for non-parametric variables. Statistical significance was defined as $P<0.05$.

Results

The baseline characteristics of all participants are reflected in table 1. There was positive tracer lung uptake on PET scans in 18 (46.9%) participants. Twelve participants (29.2%) had a clinical exacerbation at the time ^{18}F-FDG-PET was performed and 6 of them had positive uptake on ^{18}F-FDG-PET. There was no significant difference in the ^{18}F-FDG SUV of participants with exacerbation versus no exacerbation at PET scan (P=0.61). The sensitivity and specificity of PET to detect exacerbations were 50% and 59% respectively.

Of the 18 participants with tracer uptake, 9 had bilateral uptake, in segments in both the right and left lung. There was uptake in the left lower lobe in 7 of the 18 participants, rendering it the most common lobe having ^{18}F-FDG uptake in all participants.

Of the total study population there was consolidation on the CT scan in 12 participants. Of these participants, 3 had clinical exacerbation at the time of PET and 9 had positive ^{18}F-FDG uptake at the time of ^{18}F-FDG-PET, this was statistically significant (P=0.01) (Fig. 1). There was no difference in mean SUVs between subjects with or without presence of a bacterial organism in culture (P=0.73). There was microbiological confirmation of mycobacterial infection in three patients with two having *mycobacterium tuberculosis* complex and another *mycobacterium avium intracellulare* infection at the time of the PET scan. All participants with active TB had positive uptake on ^{18}F-FDG-PET. The mean SUV were higher for the participants with consolidation as compared to those with TB (4.4 vs. 2.5), although two of the TB positive participants had received two and three months of treatment respectively.

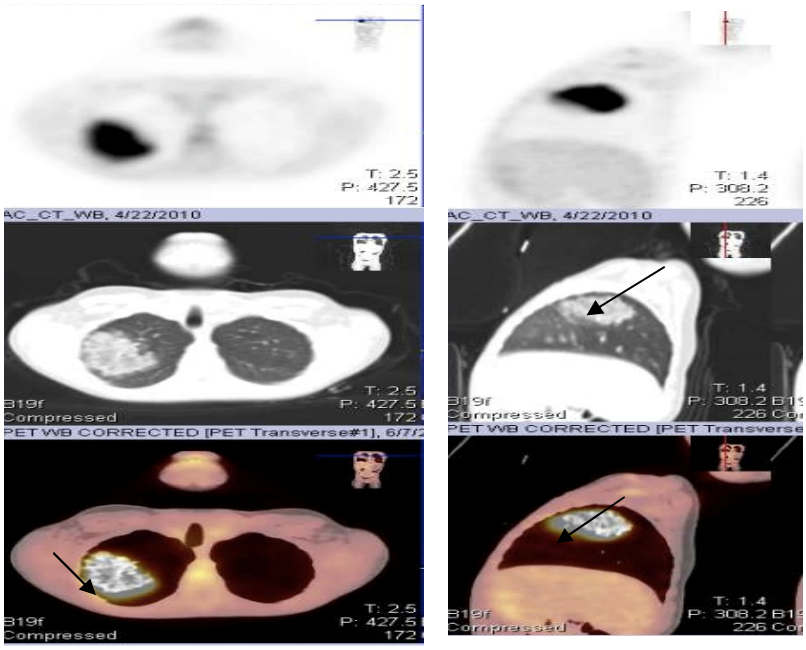

Figure 1. Transverse and axial views ^{18}F-FDG PET/CT of patient with consolidation and positive ^{18}F-FDG uptake in the right upper lobe (arrows).

All participants were on highly active antiretroviral treatment (HAART), 22 having HIV virological suppression with viral loads of <25 copies/mL. There was no significant difference between participants with: (i) positive ^{18}F-FDG uptake versus those with no uptake and number of months on HAART (P=0.37); (ii) positive ^{18}F-FDG uptake versus no uptake and CD4% (P=0.99); or (iii) positive ^{18}F-FDG uptake and no uptake and HIV viral load (P=0.23).

There was no significant difference in the Bhalla score when comparing participants with ^{18}F-FDG uptake 13.2±1.1 versus no ^{18}F-FDG uptake14.9±0.8 (P=0.20). There was presence of bronchiectasis in 116 lobes of the participants. The most affected lobes were the left lower lobe and right lower lobe in 42 and 26 of all involved lobes respectively.

In both serum and sputum, IL-8 was the prominently elevated cytokine Table 2. There was no correlation between serum and sputum IL-8 and the Bhalla score (P=0.32 and P=0.37) respectively. As reflected in Table 2 there was not a significant difference in all other parameters except for INF-γ which was more elevated in the serum than in the sputum.

Table 2. *Inflammatory markers for children with HIV-related bronchiectasis with and without ^{18}FDG uptake on PET/CT*

Inflammatory marker	No ^{18}F-FDG uptake (-) N= 23	^{18}F-FDG uptake (+) N=18	P values for (+) vs (-)
CRP (mg/ml)	4.2±19.9	15.0± 95.1	0.11
Neutrophil (x10^9/l)*	4.2± 6.3	3.9 ±2.9	0.87
Sputum cytokines			
IL-8 (pg/mL)	l222.5±9203.0	1799.0±10341.0	0.62
TNF- α (pg/mL)	1.9±3.4	1.0±2.3	0.67
INF-γ (pg/mL)	2.1±23.1	18.4±19.3	0.39
Serum cytokines			
IL-8 (pg/mL)	113.3± 4194.0	1205.3±549.0	0.32
TNF- α (pg/mL)	5.9± 18.0	12.8±10.6	0.68
INF-γ (pg/mL)	118.7± 431.6	150.0±181.7	0.50

*: neutrophils measured in serum; FDG: fluorodeoxyglucose; CRP: C reactive protein; IL-8: interleukin 8; TNF-α: tumour necrosis alpha; INF- γ: interferon gamma; Wilcoxon ranksum test done for comparing subjects with and without ^{18}F-FDG uptake.

Discussion

No difference in SUV-max values of sites of lung-involvement were found between those with clinical exarcebation and those without. Hypothetically, this may relate, to the plethora of variables and their inter-individual contribution to ^{18}F-FDG uptake in such patients, to the lack of a gold standard as well as to an anamnestic effect by the care-giver or participants. Under inflammatory conditions, neutrophils and activated macrophages display a high ^{18}F-FDG uptake which is in part due to the up-regulated glucose transporter system and to an increase of affinity for deoxyglucose increased by various cytokines and growth factors [19, 20]. This mechanism might explain the positive correlation between the rate of ^{18}F-FDG uptake in the lung field and the number of neutrophils present in the bronchoalveolar lavage fluid [21]. Others have demonstrated with cell autoradiography that neutrophils are the predominant cells that take up ^{18}F-FDG in bronchoalveolar lavage fluid of CF participants [17]. A recent study with 20 CF participants found that the use of SUV above 3, could distinguish between foci of low or high tracer uptake intensity, and scans showing high tracer uptake supported the clinical definition of exacerbation [22]. Contrary to this, there was no difference in the level of serum neutrophils between participants with or without ^{18}F-FDG uptake. This was also shown by others who showed a lack of uptake in subjects with CF bronchiectasis despite elevated sputum neutrophils [23]. Although cells are continually migrating to the inflammatory site**,** mucociliary clearance and cough are responsible for their removal from the lungs. We could not demonstrate elevation of serum neutrophils in subjects with ^{18}F-FDG uptake. This may be due to the fact that we measured serum neutrophils distant from the "inflammatory site" and therefore could not indicate local lung inflammatory milieu. The implication of this finding is that in HIV-related bronchiectasis, systemic neutrophils may not as highly activated despite seemingly adequate immune restoration by

antiretroviral therapy and HIV virological suppression, as demonstrated by elevated level of neutrophils in our population. We also postulate that in the context of HIV, there is not only a quantitative defect in immune cells, but also a qualitative defect resulting in functionally ineffective neutrophils which may lack metabolic activity.

In line with previous studies, there was a correlation between ^{18}F-FDG uptake and the presence of consolidation on the CT scan [24]. This further emboldens the aspect that a PET study is more reliable in acute lobar pneumonia where there are sufficient numbers of neutrophils at the inflammatory site.

In our series, the majority of participants with positive ^{18}F-FDG uptake and consolidation did not fulfil the clinical criteria of an exarcebation. This may suggest that ^{18}F-FDG PET is more sensitive in assessing inflammation and thus superior than the clinical assessment for the detection of bronchiectasis inflammation and the presence of exacerbations.

In the current study systemic and pulmonary cytokines IL-8, TNF- γ and INF-α were elevated. IL-8 which is produced by neutrophils was the cytokine that was most significantly elevated in our study [25, 26]. Despite the presence of these cytokines in serum and sputum, we could not demonstrate significant uptake on the ^{18}F-FDG-PET scan. This may be explained by the fact that the majority of subjects in our study population had a positive culture of pathogens in their airways. The presence of colonizing organisms has been postulated to produce factors that suppress the respiratory burst of the neutrophils by affecting surface receptors or through the presence of substances capable of affecting neutrophil activity in mucus [27]. Others demonstrated a correlation between IL-8 and a modified Bhalla score [22], unlike our findings. This may relate to the fact that they had a much smaller study population (27 subjects) than the current study, and that their study population involved children with heterogeneous causes of bronchiectasis.

Importantly, in the series presented, the elevated CRP and the intensity of ^{18}F-FDG uptake were marginally statistically significant. This finding concurs with the ^{18}F-FDG studies which have been found to quantitatively delineate lung infection and inflammation in a diverse group of lung diseases including CF, pneumonia, pulmonary fibrosis and interstitial pneumonitis [17, 24, 28, 29].

The limitations of our study were the small sample size which may explain the lack of correlation of ^{18}F-FDG uptake to the inflammatory markers or could be because of a different explanation, such as another functioning mechanism at play. We also did not perform bronchoalveolar lavages to obtain sputum neutrophils.

There is a lack of a significant correlation of ^{18}F-FDG uptake and clinical analysis of exacerbations, although the presence of ^{18}F-FDG uptake in subjects without exacerbation suggests that ^{18}F-FDG may be more sensitive in assessing inflammation than currently available tools like systemic

and sputum cytokines and acute phase reactants [22]. This study provides pilot data for a larger trial sufficiently powered to investigate the association of ^{18}F-FDG PET and inflammatory biomarkers.

In conclusion, ^{18}F-FDG-PET technique could not reliably predict the presence of an exacerbation in children with HIV, and its diagnostic value was limited to identifying disease activity on scan in acute pneumonia cases. Fluorine-18-FDG-PET had no significant correlation with CRP or with other inflammatory biomarkers and markers of HIV disease activity.

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The authors declare that they have no conflicts of interest.

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