PAEDIATRIC BRONCHIECTASIS IN AUCKLAND, NEW ZEALAND; NON-INVASIVE SCREENING FOR CILIARY DYSFUNCTION AND AIRWAY INFLAMMATION.

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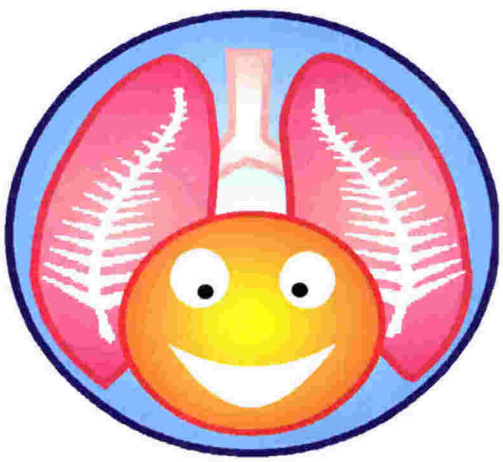
RESEARCH LOGO



“Happy Healthy Kiwi Lungs”

ABSTRACT

Background: 'Bronchiectasis' is usually a progressive disease defined as bronchial dilatation, with or without associated bronchial wall and lung parenchymal damage, and classically with pus in the bronchial lumen. There is no knowledge on the prevalence, aetiology, and severity of paediatric bronchiectasis in New Zealand. Primary ciliary dyskinesia (PCD) is an inherited disorder that can cause bronchiectasis and is characterised by specific structural ciliary abnormalities leading to impaired ciliary motility. It has been suggested that ciliary abnormalities may predispose Maori and Pacific Island people to bronchiectasis, but appropriate expertise and non-invasive technology to accurately investigate the condition has not been available in New Zealand. Additionally the exhaled gas nitric oxide (NO), a non-invasive marker of some types of airway inflammation, has been suggested as a useful screening test for PCD. The aims of this thesis were to:

1. Define the demographics, causes, and severity of the known paediatric bronchiectasis population of Auckland.
2. Establish a method for detecting primary and secondary ciliary dysfunction.
3. Explore non-invasive methods for differentiating primary and secondary ciliary disease.
4. Determine the prevalence of PCD in paediatric bronchiectasis in Auckland.

Methods: Observations were made on children with bronchiectasis who attended the Starship Children's Hospital, and a cohort of healthy children recruited from local Auckland schools. A retrospective review of the demographics and radiology scores (CXR and HRCT scan) as a measure of disease severity was made. The results were compiled into a bronchiectasis database and a measure of socio-economic factors (NZDep96 index) was incorporated. Equipment was created for the photometric method of assessment of ciliary beat frequency (CBF). After piloting, 3 prospective studies were undertaken to evaluate skin prick allergy tests, exhaled and nasal NO, lung function and a nasal brushing for assessment of CBF and ultrastructural analysis in the normal and diseased children.

Results: The estimated prevalence of paediatric bronchiectasis in Auckland was ~2/10,000 and was disproportionately more common in the Pacific Island (6.3/10,000) and Maori children (2.8/10,000). Eighty eight percent of cases had bilateral disease, and 64% had 4 or more lobes involved. There was a wide range of presumed aetiologies but over half remained undiagnosed despite extensive investigation. The median duration of symptoms before diagnosis was 3.2 years, and a median of 4 respiratory admissions pre-diagnosis. The NZDep96 index suggested significant associated socio-economic deprivation. A non-invasive protocol to brush nasal epithelium and the technology to assess CBF was created and piloted. Ethnic normal values were established for NO and CBF for healthy European and Pacific Island children. Insufficient Maori children could be recruited. CBF and NO values were not low and comparable with frequencies reported internationally using similar methodologies. Exhaled NO levels did not differ significantly between the children with bronchiectasis and controls, or between the bronchiectatic children who were and were not prescribed inhaled steroids. However CBF and nasal NO were lower in the children with bronchiectasis than controls. The percentage of abnormal ciliary structural defects in the control children was 3 times higher than reported controls, with no difference across ethnic

groups. Similar abnormalities were seen in the children with bronchiectasis. These abnormalities were central microtubule defects, tubular additions or deletions, and partial dynein arm defects. In the individual children with bronchiectasis who had low CBF and nasal NO, no single primary ciliary defect was identified to conclusively diagnose PCD.

Conclusions: Paediatric bronchiectasis is common and severe in Auckland, New Zealand but the condition has been neglected in terms of recognition. It is hoped that the establishment of a bronchiectasis database for children will not only facilitate collaborative research but also act as a template for a national bronchiectasis database for New Zealand, which can be used to support applications for health resources and funding. Importantly the thesis has resulted in a non-invasive method for assessing ciliary structure and function that could be used to investigate New Zealand children and adults. A wide variety of ciliary abnormalities were found in the New Zealand children that were most likely secondary phenomena, and the incidence of PCD in the population examined, if present, is small. More work is needed to increase the ciliary structural and functional 'library' for New Zealand children, and particularly for Maori children who were under assessed in this work. The possibility of another vulnerability factor, as yet not identified, either of innate immunity or airway defences may still underlie the high prevalence of bronchiectasis in New Zealand.

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LIST OF ABBREVIATIONS

ABPA	Allergic broncho-pulmonary aspergillosis
ALL	Acute lymphocytic leukaemia
AML	Acute myeloid leukaemia
ASD	Atrial septal defect
ASH	Action on Smoking and Health
ATP	Adenosine triphosphate
ATS	American Thoracic Society
CBF	Ciliary beat frequency
CF	Cystic fibrosis
CM	Clinical modification
cNOS	Constitutive nitric oxide synthase
C of V	Coefficient of variation
CSOM	Chronic suppurative otitis media
CT	Computed tomography
CXR	Chest radiograph
DHST	Delayed hypersensitivity skin tests
DOB	Date of birth
ENT	Ear, nose and throat
eNO	Exhaled nitric oxide
ERS	European Respiratory Society
FEF_{25-75}	Forced expiratory flow between 25-75% of the FVC
FEV_1	Forced expiratory volume in one second
FH	Family history
FRC	Functional residual capacity
FTT	Failure to thrive
FVC	Forced vital capacity
GORD	Gastroesophageal reflux disease
GP	General practitioner
HFA	Health Funding Authority

HRCT	High resolution computerised tomography
ICD	International classification of disease
IL	Interleukin
iNOS	Inducible nitric oxide synthase
ISAAC	International study of asthma and allergies in childhood
KS	Kolmogorov-Smirnov test
LIP	Lymphocytic interstitial pneumonia
LLL	Left lower lobe
LRTI	Lower respiratory tract infection
LUL	Left upper lobe
MMR	Measles, mumps, rubella
MRSA	Methicillin resistant Staphylococcus aureus
MTT	Mucociliary transit time
NBT	Nitroblue tetrazolium
NF-κB	Nuclear factor kappa B
NHI	National Health Index
nNO	Nasal nitric oxide
NO	Nitric oxide
nNOS	Neuronal nitric oxide synthase
NZDep96	New Zealand deprivation index 1996
PCD	Primary ciliary dyskinesia
PCR	Polymerase chain reaction
PDA	Patent ductus arteriosus
RLL	Right lower lobe
RML	Right middle lobe
ROC	Receiver operator curve
RSV	Respiratory syncytial virus
RUL	Right upper lobe
SaO_2	Arterial oxygen saturation
SD	Standard deviation
TLC	Total lung capacity
TNF	Tumour necrosis factor
URTI	Upper respiratory tract infection
VC	Vital capacity
VSD	Ventricular septal defect
WHO	World Health Organisation