

# Chronic lung disease in Canadian aboriginal children is not caused by abnormal cilia

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**BACKGROUND:** It has been suggested that abnormalities of the airway cilia are responsible for some of the increased prevalence of bronchiectasis among the Polynesian population of New Zealand.

**OBJECTIVE:** To determine whether abnormalities of the ciliary axoneme were present in Cree children with recurrent pneumonia.

**DESIGN:** Retrospective identification of Cree children under 18 years of age with three or more documented episodes of pneumonia, at least one of which was severe enough to require hospitalization. Physical examination and nasal brushing for ciliary ultrastructure were performed on those who consented to participate in the study.

**SETTING:** Out-patient department of Moose Factory General Hospital, the referral hospital for the James Bay Region of Northern Ontario.

**PATIENTS:** Ten children (seven males; three females) met the diagnostic criteria and lived in Moose Factory or Moosonee. Six patients (five boys, one girl, mean age 7 years 2 months) consented to examination and nasal brushing.

**RESULTS:** Although the percentage of abnormal cilia (21%) was three to seven times greater than that reported for the control population, the abnormalities seen were characteristic of acquired axonemal defects rather than primary ciliary dyskinesia.

**CONCLUSIONS:** In this population, recurrent pneumonia did not appear to be associated with congenital defects of the ciliary axoneme (primary ciliary dyskinesia). This is

consistent with a review of published transmission electron microscopy studies of nasal cilia from the Maori of New Zealand.

**Key Words:** *Aboriginal peoples, Mucociliary clearance, Pneumonia, Primary ciliary dyskinesia*

## La maladie pulmonaire chronique chez les enfants autochtones canadiens n'est pas causée par des cils anormaux

**HISTORIQUE :** On a émis l'hypothèse que des anomalies des cils des voies aériennes sont responsables d'une part de l'augmentation de la prévalence des bronchiectasies dans la population polynésienne de la Nouvelle-Zélande.

**OBJECTIF :** Déterminer si des anomalies de l'axonème ciliaire étaient présentes chez les enfants Cree présentant des pneumonies récidivantes.

**MODÈLE :** Identification rétrospective d'enfants Cree de moins de 18 ans ayant présenté trois épisodes ou plus de pneumonie documentés, dont au moins un suffisamment grave pour nécessiter une hospitalisation. Un examen physique et un brossage nasal pour ultrastructure ciliaire ont été pratiqués chez les individus qui acceptaient de participer à l'étude.

**CONTEXTE :** Service des consultations externes du Moose Factory General Hospital, établissement où sont dirigés les patients pour la région de la baie James du Nord de l'Ontario.

**PATIENTS :** Dix enfants (sept garçons, trois filles) remplissaient les critères du diagnostic et vivaient soit à Moose Factory ou à Moosonee. Six patients (cinq garçons et une fille, d'âge moyen de 7 ans et deux mois) ont consenti à l'examen physique et au brossage nasal.

**RÉSULTATS :** Même si le pourcentage de cils anormaux (21%)

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était de trois à sept fois plus élevés que celui rapporté pour la population témoin, les anomalies observées étaient plutôt caractéristiques de malformations acquises de l'axonème ciliaire que d'une dyskinesie ciliaire primaire.

**CONCLUSIONS :** Dans la population étudiée, les pneumonies ré-

cidivantes n'ont pas semblé être associées à des malformations congénitales de l'axonème ciliaire (dyskinésie ciliaire primaire). Ceci concorde avec une revue des études publiées sur la microscopie électronique en transmission des cils du nez des Maori de la Nouvelle-Zélande.

**T**here is a greater frequency and severity of respiratory infections and otitis media among the First Peoples of Canada than in the general Canadian population, even when living conditions and economic status are considered (1). It has been reported that the frequency of pneumonia in aboriginal children is more than 17 times higher than that of nonaboriginal children, otitis media is diagnosed more than twice as often and the hospital admission rate for lower respiratory tract infection is 5.9 times greater (2). This phenomenon of excess pulmonary morbidity in aboriginal children has sometimes been referred to as 'native lung'.

Polynesians from New Zealand also suffer from an excess respiratory morbidity (3). Defects of the ciliary axoneme have been reported in the Maori of New Zealand (4,5). North American Indians are believed to be a population group similar in some ways to Polynesians. We retrospectively identified Cree Indian children living on Canada's James Bay who had 'native lung' and examined the ultrastructure of their respiratory cilia to determine whether these children had axonemal defects similar to those seen in Polynesians.

### PATIENTS AND METHODS

Moose Factory General Hospital is the major referral hospital for the west coast of James Bay and the Ontario communities on Hudson's Bay. The majority of the regional population (approximately 12,000) is Cree. Approximately 3000 people live in the twin communities of Moose Factory and Moosonee in Ontario.

All pediatric hospital admissions to the Moose Factory General Hospital with a discharge diagnosis of pneumonia were reviewed for the period 1983 to 1985. Native lung was defined as three or more documented episodes of pneumonia in a Cree child, at least one of which was severe enough to require hospitalization. All patients so identified were contacted and asked to participate in this study.

After written informed consent was given by the parent or guardian, a nasal brushing from the child was obtained for the evaluation of ciliary ultrastructure. To minimize patient discomfort a modification of the nasal brushing technique for obtaining ciliary specimens, as described by Rutland and Cole (6), was used. Two per cent lidocaine was first instilled into the nostril, and a cytology brush was pulled along the inferior nasal turbinate. No child complained of discomfort, and there was no nasal bleeding. A tracheal brushing was obtained in one child who underwent fiberoptic bronchoscopy as part of an assessment for possible foreign body aspiration.

Samples were immediately immersed in 3% glutaraldehyde with 0.2 M cacodylate buffer at pH 7.4 and stored at 4°C until analyzed. The specimens were later washed in the same buffer, immersed in 1% buffered osmium tetroxide, dehydrated in graded alcohols and embedded in resin, thin-

sectioned and stained with uranyl acetate-lead citrate for transmission electron microscopy. Control specimens obtained from one of the investigators were processed at the same time for comparison.

At the time of this study, one of the authors was on faculty at Queen's University, Kingston, Ontario, and this study was approved by the Queen's University Institutional Review Board for Human Research.

### RESULTS

Examination of recorded data from hospital in-patient and out-patient charts identified 10 children who met the diagnostic criteria for recurrent pneumonia and who lived in Moose Factory or Moosonee. Their age ranged from 20 months to 17 years (mean age 4.3 years), and seven were male. All 10 children had recurrent otitis media (two to 18 episodes, mean 5.0), and four were known to have a family member with tuberculosis. No patient had clinical evidence of bronchiectasis such as chronic sputum production or digital clubbing. Although all had been diagnosed with purulent rhinitis at some time in the past, no sinus radiographs or computed tomographic scans were available that would permit diagnosis of sinusitis. There were no records of family size, type of home heating or exposure to environmental tobacco smoke in the majority of the charts, but tobacco smoke exposure is almost universal in Canada's northern regions. No child had situs inversus on chest radiograph.

Evidence from sweat testing, tuberculosis testing and blood counts was obtained from the hospital charts when recorded. Quantitative immunoglobulins were completed on only one patient. Although it was hoped to exclude cystic fibrosis, immunodeficiency, aspiration or other causes for recurrent pneumonia, equipment for performing these studies is usually not available at Moose Factory. All children received Bacille Calmette Guérin vaccinations at birth. Follow-up radiographs taken when the child was well were generally unavailable.

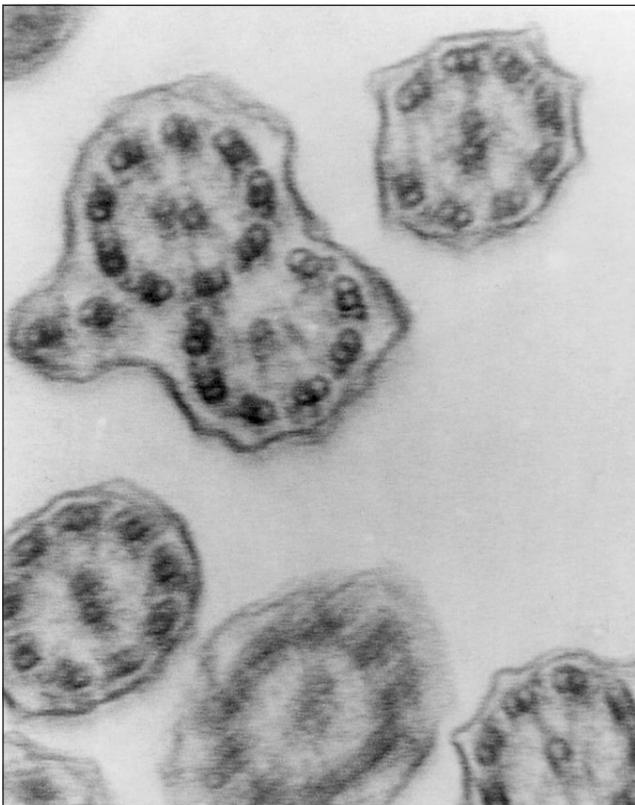
Six patients (five boys and one girl, mean age 7 years 2 months) consented to examination and nasal brushing. All came from homes with at least two smokers but none of the children were active smokers. One child had been diagnosed as having asthma but was not on medication for this. Two had otitis media, and five of the children had a nasal discharge at the time of recall examination. Three of the children were on antibiotics, and one was on decongestants. Compliance with taking prescribed medications was difficult to assess accurately.

A minimum of 30 cilia were examined for four of the patients, and the percentage of abnormal cilia as well as the types of abnormalities seen are presented in Table 1. Overall 21% of the cilia counted were abnormal but these abnormalities were characteristic of acquired ciliary defects and not

**TABLE 1**  
Ciliary abnormalities in children with 'native lung'

Patient	Age (years)	Sex	Percentage abnormal cilia	Ciliary abnormalities seen
1	14.3	F	28	Megacilia, abnormalities of central microtubules, tubular additions and deletions
2	6.3	M	10	Megacilia, partial loss of dynein arms
3	8.0	M	16	Tubular additions and deletions, partial loss of dynein arms
4	9.0	M	30	Megacilia, partial loss of dynein arms, tubular additions
5	2.5	M	Small sample	Megacilia, partial loss of dynein arms
6	4.9	M	No cilia seen in sample, few cells obtained	

F Female; M Male

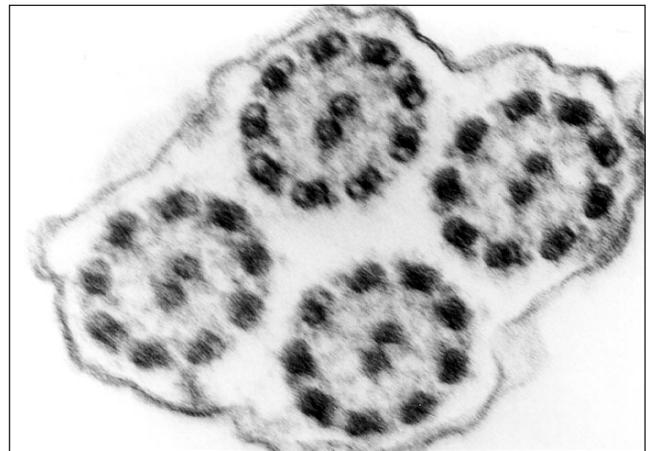


**Figure 1** Acquired ciliary abnormalities in a Cree girl with recurrent chest infections (patient 1). A compound or megacilium is seen as well as additions and deletions of peripheral microtubular doublets and central microtubules. Note the variability in orientation of the central microtubules and that the dynein arms appear to be normal (uranyl acetate-lead citrate stain, original magnification 60,000 $\times$ )

primary ciliary dyskinesia. Control specimens, processed at the same time as test samples, had abnormalities in only 3% to 7% of cilia counted. Figures 1 and 2 show the axonemal ultrastructure of cilia from patients 1 and 2, respectively. These multiple and varied ciliary abnormalities with prominent megacilia or fusion cilia are most characteristic of inflammatory airway changes (7).

## DISCUSSION

The ciliary axoneme consists of pairs of microtubular doublets surrounding a pair of central tubules. In the axoneme, nexin links bridge neighbouring doublets and stabilize the cilium, dynein arms provide the energy for the doublets to slide over each other, and radial spokes span the



**Figure 2** Typical compound or megacilium from a brushing taken from a six-year-old boy (patient 2). This abnormality is characteristic of acquired ciliary defect secondary to inflammation (uranyl acetate-lead citrate stain, original magnification 60,000 $\times$ )

distance between the outer doublets and central sheath. In 1976 Afzelius (8) described absence of dynein arms on the microtubular doublets in the airway of patients with Kartagener syndrome. Later studies have indicated that although there is no coordinated mucociliary transport in patients with Kartagener syndrome, the cilia do retain a dysfunctional motility (9). Because of these data, in 1981 Sleight and others (10) proposed that the name of the syndrome be changed to 'primary ciliary dyskinesia'.

Primary ciliary dyskinesia is believed to be an autosomal recessive disorder with incidence of about 1 in 20,000 people in Europe and North America. The hallmark of primary ciliary dyskinesia is absence of mucociliary transport in association with specific and consistent ultrastructural defects in the ciliary axoneme in affected patients (7). Situs inversus (Kartagener syndrome) is thought to occur in approximately half of patients with primary ciliary dyskinesia.

Infectious and inflammatory processes also produce axonemal abnormalities and slow mucociliary clearance (7,11). The two most common among the nonspecific abnormalities are megacilia (multiple axonemes within a common cell membrane) and an abnormal number of microtubular doublets. Abnormalities, such as partial loss of dynein arms or peripheral doublets, megacilia or loss of cilia, are frequently observed in adults with chronic bronchitis and children with recurrent or persistent lower respiratory infections (12,13). Disorganized axonemes with extra or missing microtubules

are commonly seen during an acute airway infection and in chronic rhinitis or asthma (14). Compound cilia are rarely seen during an acute infection, and normal cilia are always present in the same specimen. Ultrastructural changes observed in this study were most consistent with acquired ciliary defects.

There are a number of limitations that suggest caution in the interpretation of these data. The first is the definition of 'native lung'. We would have liked to have rigorously ruled out any other cause for recurrent chest problems, such as asthma, aspiration, immunodeficiency or cystic fibrosis, but this could not be arranged. It would also have been useful to study tracheal mucus transport in these children but, again, this was not possible at Moose Factory General Hospital. We noted that seven of 10 children identified as having native lung were male. This is consistent with the increased incidence and severity of lung disease reported in male Canadian aboriginal children (1).

In nasal specimens taken from healthy children, the percentage of abnormal cilia is about 3% and 7% (15,16), much less than the 21% abnormal cilia that we observed. However, it has been reported that ultrastructural abnormalities of nasal cilia persist in a large proportion (32%) of cilia even 12 weeks after an upper respiratory tract infection in more than one-quarter of children (17). These acquired ciliary abnormalities return to normal during convalescence (18).

It has recently been recognized that disorientation of the central ciliary microtubules may be another cause of primary ciliary dyskinesia (19,20). In normal biopsy specimens, ciliary deviation is generally less than 20%, while in patients with symptoms characteristic of primary ciliary dyskinesia, and perhaps in Young's syndrome (21), there is increased ciliary disorientation. However, de Jongh and colleagues (21) have speculated that in Young's syndrome, disorientation of the ciliary tip may be partially due to abnormal mucus. Although one of the patients studied (patient 1) had disorientation of the central ciliary microtubule, we are reluctant to presume that it was the cause of her respiratory infections because ciliary disorientation is common in patients with acute respiratory infections, but these abnormalities return to normal with resolution of inflammation (18). It may also be that in some patients, ciliary disorientation may be secondary to chronic airway inflammation. Furthermore, it may be more difficult to ascertain accurately the orientation of the central microtubules in specimens obtained by brushing compared with biopsy specimens.

It has been suggested that bronchiectasis in Polynesians of New Zealand may be due, in part, to abnormal cilia. Wakefield and Waite (4) examined the ciliary ultrastructure of 12 Polynesians with bronchiectasis. Although all patients had varying degrees of dynein arm deficiency, in only two patients was this the only ciliary abnormality seen. In the other 10 patients there were a wide variety of acquired ciliary defects including distorted cilia and megacilia indicative of chronic inflammation. None of these patients had dextrocardia.

When the data reported here are pooled with those of the

New Zealand studies (4) it appears that native lung in Cree children or Polynesians is not caused by congenital abnormalities of the ciliary axoneme. These patients do seem to have a large number of acquired ciliary defects which suggests that either there is a greater exposure to irritants and infections leading to childhood chronic bronchitis or there may be an increased susceptibility to injury or a diminished capacity for repair in the respiratory cilia of some aboriginal children.

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