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Recurrent chest infections, ciliary abnormalities and partial complement deficiency in a Jordanian family

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ABSTRACT Four girls born to second cousin parents developed chronic chest infection and bronchiectasis in infancy. Three were studied in detail: they all had the same HLA haplotype, all showed random orientation of cilia or compound cilia in the respiratory tract, and all had low levels of the C1 and C2 components of the complement system. Although the cause of the respiratory disease in this family remains unclear, it is suggested that the low C1 levels may have contributed to the disease in two of the children while the low C2 levels were artefacts and the ciliary abnormalities were secondary to chronic chest infection.

We have recently encountered a Jordanian family in which four children born to second cousin parents suffered from recurrent chest infections and bronchiectasis. An inherited abnormality was suspected and, because primary defects in host defence often have a genetic basis,[1-3] we have investigated defence mechanisms against infection as fully as possible in this family.

Case histories

CASE 1

This girl (As J, aged 10 years) had had a productive cough and catarrh since infancy. At 8 years she had been admitted to a sanatorium with suspected, but unconfirmed, pulmonary tuberculosis. At 9 years she had undergone a left pneumonectomy. On examination she was a small, thin child with scattered crackles and wheezes over the right hemithorax. Her chest radiograph showed absence of the left lung, right middle lobe collapse and bronchial wall thickening at the right base. The maxillary sinuses were opaque and the frontal sinuses were absent.

CASE 2

This girl (Kh J, aged 9 years) had been short of breath and had had a productive cough since infancy. On examination she had finger clubbing and central cyanosis. There was dullness to percussion and widespread crackles were heard over the left hemithorax. The chest radiograph showed a con-

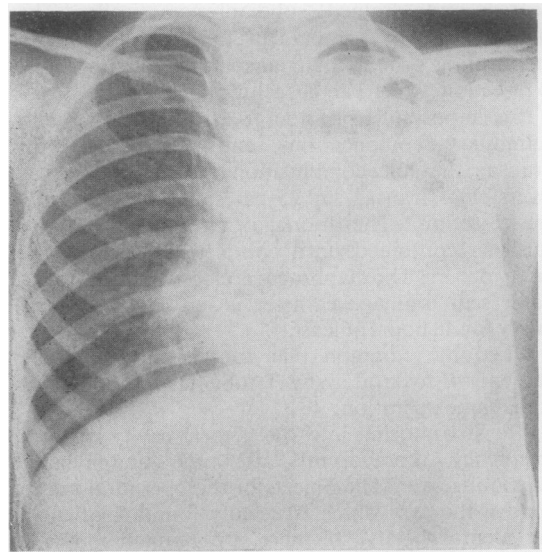

Fig 1 *Chest radiograph of patient 2. There is contraction of the left lung with widespread cavity formation, together with some consolidation in the right lower zone.*

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tracted left lung with multiple cavities in the upper zone (fig 1). The maxillary sinuses were opaque and the frontal sinuses were absent. In view of the severity of the disease affecting the left lung, left pneumonectomy was carried out.

A boy (Fi J) died aged 6 years and was not seen by us. He had had a productive cough throughout his life. Shortly before his death he had developed a swelling of the right jaw and hilar lymphadenopathy for which he had received radiotherapy.

CASE 3

In this girl (Ey J, aged 5 years) a productive cough and sinusitis had been present since infancy. On examination she had finger clubbing and there were coarse crackles and wheezes over both sides of the chest. The chest film showed moderately dense shadowing involving both lower lobes, the middle lobe and the lingula, with dilated bronchi visible at both lung bases (fig 2). The maxillary sinuses were opaque.

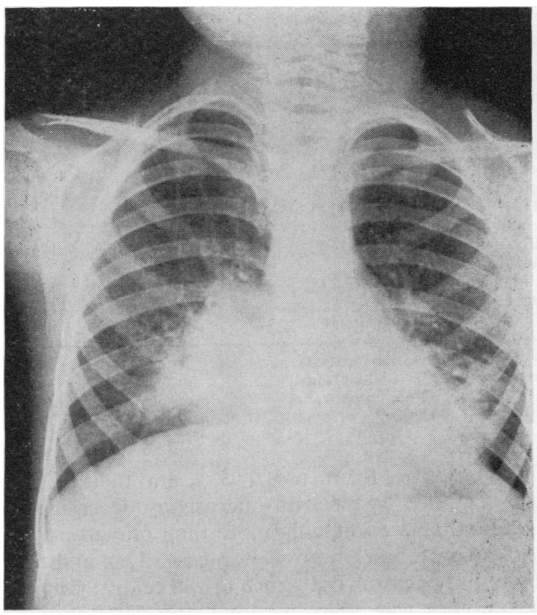

Fig 2 *Chest radiograph of patient 3. There is bilateral consolidation involving both lower lobes, middle lobe, and lingula.*

CASE 4

Qu J (a girl, aged 3 years) had had a productive cough and sinusitis since infancy but was less severely affected than her sisters. She had finger clubbing and there were coarse crackles and wheezes over the whole chest. The chest film showed shadowing in the middle lobe and in both lower lobes with dilated bronchi in the lower lobes. The maxillary sinuses were opaque.

Fa J, a baby girl, died aged 6 weeks and was not seen by us. She weighed 900 grams at birth and failed to thrive, but she had no evidence of chest disease and her chest film was normal.

Fy J, a boy, aged 8 months, was not seen by us. He was the twin of Fa J. He was well and had a normal chest film at 8 months of age.

The father, aged 36 years, and mother, aged 30 years, were second cousins. Both had been healthy throughout their lives and the father was normal on physical examination. The mother was not seen by us, but both parents had normal chest radiographs.

Investigations

Cases 1-4 were investigated. All were below the twenty-fifth percentile for height and below the tenth for weight. Electrocardiograms were normal. All four had an elevated ESR (38-65 mm/hr) and a raised leucocyte count (12·7-17·5 $\times$ 10^9/l). Serum electrolytes, glucose, alkaline phosphatase, SGOT, bilirubin, and albumin were all normal. Total globulin, IgG, IgA, and IgM levels were normal or elevated. The sweat sodium concentration was normal on two to five occasions in each child and faecal fat excretion was normal in the three children in whom it was measured.

MICROBIOLOGY

Haemophilus influenzae was found in the sputum of all four children and *Streptococcus pneumoniae* was cultured once from the sputum of case 1. *Candida albicans* was cultured from case 1 and *Aspergillus fumigatus* from case 2 on one occasion each. Repeated cultures of sputum for *Mycobacteria* spp were negative.

SEROLOGY

Rheumatoid factor, antinuclear factor and autoantibodies to smooth muscle, reticulin, mitochondria, thyroid cytoplasm and gastric parietal cells were absent. Isohaemagglutinin (anti-B) titres were normal and serum precipitins to *Aspergillus fumigatus* and *Candida albicans* were not detected in any of the four cases. Serological tests for syphilis were negative. Immunisation with TAB vaccine, tetanus toxoid, and influenza vaccine produced adequate increases in specific antibody titres in all four cases.

TISSUE TYPING

Case 1, 3, and 4 were of haplotype HLA a_1b_{12}/a_1b_{12} and their father was HLA a_1b_{12}/a_1b_5. All four children were of blood group A rhesus positive.

Table 1 *Lymphocyte and neutrophil studies*

Investigation	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Control*
Total lymphocyte count × $10^9.l^{-1}$	4·8	3·9	5·8	6·8	
Lymphocyte transformation to PHA:		10948			10631
difference in counts per minute from unstimulated cells	86185		59623	84810	10652
Delayed PPD: 1 TU	+	—	—	—	
hypersensitivity PPD: 100 TU	+	—	+	—	
skin testing *C albicans**	+	+	+	+	
Latex phagocytosis: percentage of cells with over 10 particles/cell	94%		87%	74%	
Nitroblue tetrazoleum test: percentage of cells containing formazan deposits	21%		8%	18%	
Neutrophil glycolytic pathway enzymes: units/minute/10^9 wbc					
Myeloperoxidase	96·3		85·7	68·6	88·9
Glucose 6-phosphate dehydrogenase[4]	13·7		7·3	13·7	13·9
Phosphoglyceromutase[5]	29·2		27·9	23·3	23·9
Pyruvate kinase[5]	32·6		25·3	30·5	37·7
Lactate dehydrogenase	29·1		28·6	86·0	15·3

PHA = phytohaemagglutinin, greatest response to 0·2 or 0·5 mitogenic units/ml.
* = *Candida albicans*, Hollister-Stier antigen.

Table 2 *Further neutrophil function studies in case 1*

	Case 1	*Control*
1 Adherence to nylon wool	Normal	
2 Polymorph chemotaxis and migration into skin window[6]	Normal	
3 CO_2 production from yeast stimulated polymorphs after two hours. Counts/minute[7]		
polymorphs alone	561	397
polymorphs + yeast	1493	1990
4 Quantitative NBT* reduction: μmol formazan per ml blood[8]	0·0083	0·0089
5 Killing of *Staphylococcus aureus*: organisms/ml[9]		
at start	11 × 10^6	11 × 10^6
after two hours	3 × 10^6	6 × 10^6

*NBT = nitroblue tetrazoleum.

Table 3 *Levels of activity of the components of the complement pathway in cases 1, 3, and 4 on two occasions, six months apart.*

	Case 1		*Case 3*		*Case 4*	
C1	39%*	59%	45%*	5%	30%*	9%
C4 (functional)	500%		500%		400%*	
C4 (antigenic)	175%	82%	125%	66%	138%	64%
C2	54%*	19%	60%*	20%	74%*	19%
C3 (mg dl^{-1})	130	110	140	135	140	100
C5		91%		91%		112%
C6		198%		215%		163%
C7		92%		95%		157%
C8 + C9		43%		88%		67%
Factor B		51%		80%		69%
Factor D		47%		60%		61%
β1H		114%		104%		152%
C1 inhibitor (immunochemical)	95%	260%	95%	260%	105%	115%
Total classical pathway activity	70%	82%	63%	17%	16%	21%
Total alternative pathway activity	100%	46%	105%	67%	111%	47%

* = "Target" formation (see text).
Normal ranges: C3 = 60-180 mg dl^{-1},
Other components = 60%-180% of normal human serum[10]

LYMPHOCYTE AND NEUTROPHIL STUDIES

Details of the investigations carried out and of the results obtained are given in tables 1 and 2. The only abnormality detected was a rather reduced lymphocyte transformation to phytohaemagglutinin (PHA) in case 2. She was tested on a different occasion from the other three cases and her PHA response was similar to that of her control.

COMPLEMENT STUDIES

Sera from cases 1, 3, and 4 were studied on two occasions each. Low activities of C1 and C2 were found in comparison with normal laboratory control sera, while activities of the alternative pathway and of C3 and subsequent components of the complement system were normal (table 3).

MICROSCOPY

Sections from the pneumonectomy specimens of cases 1 and 2 showed dilated bronchi with chronic inflammatory cell infiltration and loss of epithelium. There was no evidence of cartilage deficiency or of proximal bronchial stenosis.

Nasal biopsies from cases 1, 3, 4, and their father were examined by electron microscopy. Occasional compound cilia containing more than one group of 9 + 2 microtubules were seen in cases 1, 4, and the father, and occasional absence of the central pair of microtubules was seen in case 1 (fig 3). Random orientation of the cilia was seen in cases 1, 3, and the father (figs 4, 5). Tissue preservation did not permit adequate examination of radial spokes or, in cases 1 and 4, of dynein arms, but the latter structures were identified in case 3 and the father (fig 4, insert).

Discussion

Interest in this family centres on the combination of abnormal cilia and deficiencies in the complement system. A number of different abnormalities of

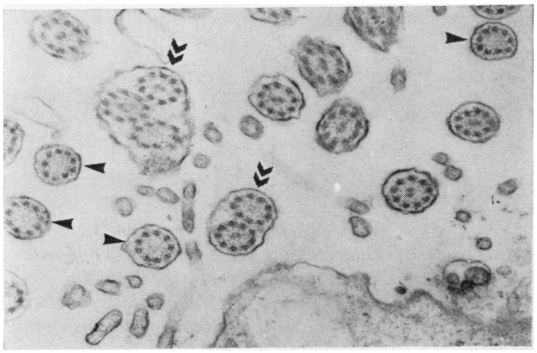

Fig 3 *Nasal biopsy of patient 1. Compound cilia containing more than one group of 9+2 microtubules are seen (double arrowheads) and some cilia lack the central pair of microtubules (single arrowheads). Electronmicrograph original magnification × 39 500.*

respiratory tract cilia have been reported in association with chronic chest infections or with bronchiectasis. A lack of axonemal (dynein) arms on the outer microtubular doublets of the cilia of patients with Kartagener's syndrome have been described, often in association with male infertility and with immotile spermatozoa which also lack dynein arms.[11-13] The term Immotile Cilia Syndrome has been proposed to include such cases, and also incomplete forms of Kartagener's syndrome with absent ciliary dynein arms.[13 14] Absent radial spokes in the immotile nasal and bronchial cilia of a family with recurrent respiratory infections has been reported recently.[15]

In the family that we have studied dynein arms and radial spokes were present in the cilia of at least some members, but all showed other ciliary abnormalities including random orientation, compound cilia and absence of central microtubules, alterations which have been reported in patients with bronchial carcinoma and with asthma and in animals exposed to carcinogens or to 50% oxygen.[16-20] Thus the abnormal cilia in the children may have been coincidental or secondary to their recurrent infections. The healthy father of our patients also displayed random orientation of cilia and compound cilia, and it is therefore likely that some additional defect existed in the children to account for their chronic respiratory infection. The only abnormalities found apart from those affecting the cilia were in the complement system.

The levels of C2 detected were compatible with heterozygous C2 deficiency on only one of the two estimations in each child.[21] The usual association of C2 deficiency is with connective tissue disorders although not all heterozygous C2 deficient subjects have an associated disease state.[21 22] Reduced C2 levels have been described in some patients with recurrent bacterial upper respiratory tract infections.[23] Heterozygosity for C2 deficiency might have occurred in all three children together with their common HLA haplotype since the C2 gene locus and HLA are closely linked.[24] However, without known homozygous C2 deficiency in a family member the so-called "heterozygous C2 deficiency state" cannot be diagnosed with certainty in the presence of other abnormalities in the complement system and in the absence of HLA haplotypes a_{10} or b_{18}.[22]

Consumption of C2 as a result of active inflammatory or immune complex disease is unlikely since levels of C2 are relatively unaffected in comparison to levels of C4 or C3[22] which were normal or elevated in our patients. It is therefore likely that the low C2 levels were an artefact, possibly the result of storage.

The levels of C1 detected were compatible with heterozygous C1 deficiency on both measurements in cases 3 and 4.[24] However, without parental data it is impossible to be certain whether the reduced C1 activity was primary in these two children or whether it was secondary to their recurrent infections. The presence of "targets" on the C1, C4, and C2 plates

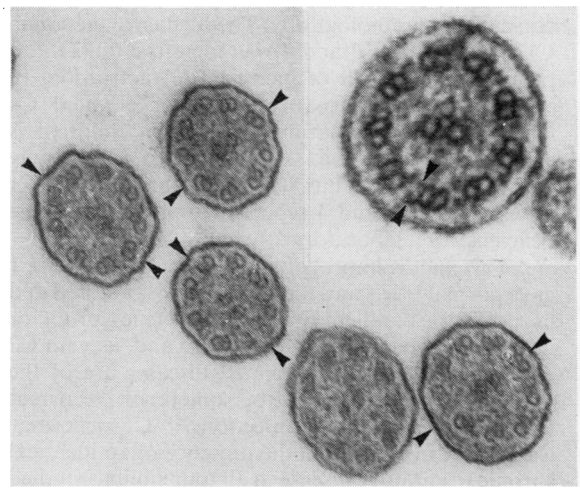

Fig 4 *Nasal biopsies of the father and patient 3 (inset). The father's cilia show random orientation, as shown by the alignment of the central pair of microtubules indicated by arrowheads. Dynein arms, indicated by arrowheads in the inset, are present in patient 3. Electronmicrographs original magnifications × 134 000 and (inset) × 192 000.*

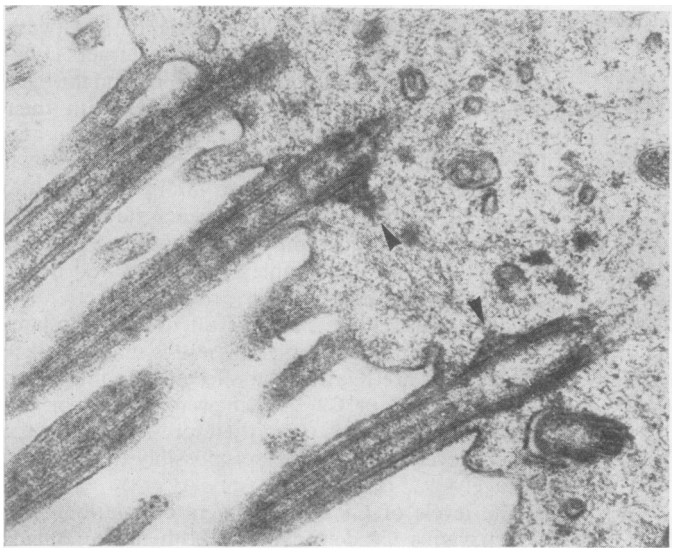

Fig 5 *Nasal biopsy of patient 3. Adjacent cilia are orientated in opposite directions as shown by the direction of the lateral spurs (arrowheads) on the basal bodies. Electronmicrograph original magnification × 50 000.*

suggests either that activated C1 was present in the test serum or that some form of competitive inhibition was taking place.[10] That C1 activation could be responsible is suggested by the finding that "target" formation only occurred on the first estimation when the children had active infection clinically.

At the time of the second estimation "targets" were absent and all the children had improved clinically and radiologically. The further reduction in C1 levels in cases 3 and 4 was therefore unlikely to have been the result of increased C1 activation. In addition the presence of normal or elevated C4 levels on both estimations, in all the children, is against C1 activation since activated C1 rapidly consumes C4.[25,26] Thus it is likely that the low C1 levels in cases 3 and 4 represented either a genuine deficiency or a laboratory artefact.

An artefact is improbable since serum from case 1 gave normal levels and the three sera were stored and processed in parallel. However, deficiency of C1 or its subcomponents is extremely rare and, as with C2 deficiency, the usual associated diseases are of the immune complex type with, sometimes, recurrent upper respiratory tract infections.[21] C1 deficiency was absent in case 1 and the presence of an identical chronic respiratory disease in all four siblings studied suggests that the low C1 levels in cases 3 and 4, even if genuine, were not directly responsible.

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