because of her diabetes or the effect of the coma on her central nervous system. There is no description of the radiograms of her remaining ankle, which might indicate the presence or absence of osteomyelitis. Nor is there any indication of the degree of pain she was in after fracturing her hip. We know that she has two sons but do not know their degree of support or interest. Her general state is not described, except by the statement that she was obese. What was her psychomotor score? How strong were her determination and will to live? Indeed, how much would she contribute to the process of rehabilitation after surgery? I would certainly ask for an examination by a general physician, including a check on her biochemical and haematological variables, and by an anaesthetist to see whether she could cope with a major operation.

If all of these factors were favourable I would argue for immediate internal fixation of the fracture to relieve pain and facilitate nursing. Of all fractures, around the hip an intertrochanteric fracture heals most readily after internal fixation. With the patient's pain lessened the nurses would be able to protect her pressure points and give her hope for some form of mobility in the future.

Operate to relieve the pain

James Scott

The patient was clearly not very mobile before admission and her general health was poor. Whatever treatment was advised, the fracture of the femoral neck would probably prove to be a preterminal event.

With regard to the pressure sore, it was clearly right that everything should be done to manage it conservatively and to avoid amputation. But during her most recent admission to hospital the decision whether to fix the fracture is probably not the most important aspect of her management. The main purpose of treatment would be to relieve pain.

Her management should be decided after careful discussions with the patient, her family, and the physicians responsible for the care of her diabetes. I would also wish to consult an anaesthetist about her suitability for general or spinal anaesthesia and for continuing pain relief if the decision was taken not to operate.

Very occasionally patients with fractures of the femoral neck do not feel great pain, and a trial of conservative treatment would be appropriate if, despite the fracture, the patient could sit comfortably in a chair. If she could not, internal fixation should be considered because, despite the relative contraindications presented by the infected heel sore and her general medical condition, successful internal fixation would make her more comfortable and might even restore her to the same degree of mobility as before the fracture. If she were to die in the immediate postoperative period she would have been spared the weeks of uncomfortable terminal care resulting from a conservative approach.

The outcome

The decision was taken not to operate and two months later the patient died of pneumonia.

We welcome other reports of difficult cases, which we will then send to experts in the field for their comments.

Grand Rounds—Hammersmith Hospital

Late presentation of Kartagener's syndrome

Consequences of ciliary dysfunction

Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN
Case presented by:
M Perraudeau, *senior house officer*

Chairman: James Scott, *professor of medicine*

Discussion group:
M Walport, *professor of rheumatology*
C Oakley, *professor of cardiology*
S Bloom, *professor of endocrinology*
D Brooks, *senior lecturer, neurology*

Series edited by:
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BMJ 1994;308:519-21

Primary ciliary dyskinesia provides a unique insight into the role of cilia in the human body. It is usually diagnosed in childhood, when prompt treatment of respiratory infections can minimise irreversible damage to the lungs.

Case history

A 48 year old man presented with a four month history of cough productive of green sputum, a two month history of night sweats, and a two day history of left sided pleuritic chest pain. He had previously had recurrent chest infections, recurrent purulent rhinosinusitis, and had produced more than one cupful of sputum a day for many years. He smoked 20 cigarettes a day.

On examination he had a fever (38°C), a regular pulse (100 beats/min), and blood pressure of 130/80 mm Hg. He was not clubbed. His apex beat was localised to the right fifth intercostal space and he had signs of consolidation in the left mid-zone. He had complete situs inversus viscerum.

He had a haemoglobin concentration of 140 g/l and a peripheral leucocyte count of $11{\cdot}8\times10^9$/l with 88% neutrophils. His erythrocyte sedimentation rate (34 mm in the first hour) and C reactive protein concentration (15 mg/l) were raised. Routine biochemistry tests gave normal results. Blood cultures were sterile but sputum culture grew *Streptococcus pneumoniae*. Culture was negative for acid fast bacilli. Chest radiography confirmed dextrocardia, with the aortic arch lying on the right side of the trachea (fig 1). The left lung had three lobes with consolidation in the middle lobe. A gastric air bubble was noted on the right side. The plain film showed no evidence of bronchiectasis but computed tomography of the chest after his pneu-

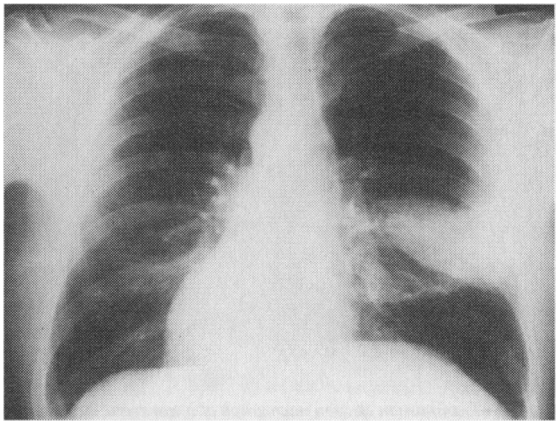

FIG 1—*Chest radiograph showing dextrocardia with the aortic arch lying on the right side of the trachea and consolidation in the left mid-zone*

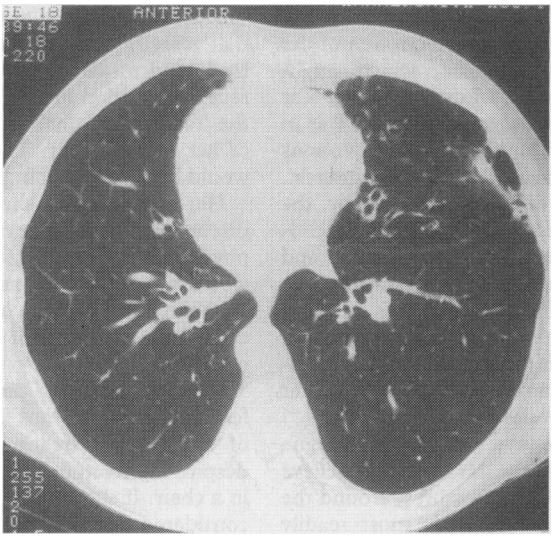

FIG 2—*Computed tomography of the chest showing dilated basal bronchi consistent with bronchiectasis and residual scarring in the left mid-zone*

monia had resolved showed bronchiectasis in the left middle lobe and right lower lobe (fig 2).

Kartagener's syndrome with an acute left sided pneumonia was diagnosed clinically. He was treated with intravenous benzylpenicillin and physiotherapy and advised to stop smoking. His symptoms rapidly improved and he was discharged taking low dose antibiotics in rotation.

He had further tests to confirm the diagnosis. Lung function tests showed mild airways obstruction (forced expiratory volume in one second/vital capacity was 62% predicted). The saccharin test of mucociliary clearance gave a time of 60 minutes (normal result less than 15 minutes). Nasal cilia (obtained by the brush technique and analysed by light microscopy and photometric techniques) were totally immotile. Analysis of a fresh semen ejaculate showed a viability of 40%, but all the sperm were immotile. Transmission electron microscopy of the nasal cilia and sperm tails showed an identical ultrastructural defect—namely, complete absence of the inner and outer dynein arms on the microtubular doublets of the axoneme (fig 3).

Comment

The triad of bronchiectasis, sinusitis, and situs inversus was first described by Siewert in 1903,[1] although its usual eponym, Kartagener's syndrome, derives from the Swiss paediatrician who described four cases with similar features in 1933.[2]

By the 1960s over 300 cases had been reported and the concept of a disease with congenital and generalised non-functioning of the cilia evolved. Men with bronchiectasis and sinusitis were noted to have immotile sperm with generalised defects in sperm tails and the cilia in the respiratory tract.[3] About half of these men also had situs inversus and so fitted the criteria of Kartagener's syndrome. Since not all those affected had situs inversus the term immotile cilia syndrome was proposed.[4] However, further work showed that cilia are often not completely immotile but show abnormal and ineffective motility. Therefore the syndrome is also referred to as primary ciliary dyskinesia.[5]

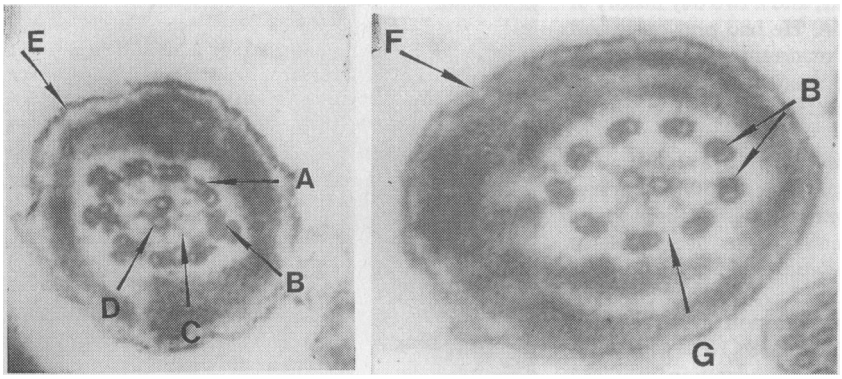

FIG 3—*Transmission electron micrograph of a transverse section through a normal sperm tail (left) and cross section through patient's sperm tail showing complete absence of inner and outer dynein arms (right). A=dynein arms, B=microtubule doublets, C=radial spokes, D=central sheath, E=outer membrane, F=sperm tail membrane, G=nexin links*

The clinical features of primary ciliary dyskinesia have been ascribed to primary ultrastructural defects in cilia. Ultrastructurally cilia and spermatozoa are similar. The axoneme is the key component of the cytoskeleton and has a characteristic nine plus two array of microtubules (fig 3). The nexin links and spokes seem to provide structural rigidity to the axoneme. Dynein arms extend from one side of a doublet in a clockwise direction when viewed from the base toward the tip of the cilium. They contain most of the ATPase activity of the axoneme and are important in releasing energy for sliding and bending of microtubules and ciliary motion.[6]

The tracheobronchial tree is ciliated to the level of the respiratory bronchioles, each ciliated cell having about 200 cilia. Mucociliary transport in the respiratory tract is important for normal respiratory function and resistance to respiratory infection.

The typical clinical picture of primary ciliary dyskinesia is a chronic productive cough, which can usually be traced back to early childhood or infancy; chronic rhinitis often with nasal polyposis (so that an affected baby may be born with a running nose); chronic or recurrent maxillary sinusitis; and frequent ear infections in childhood. Bronchiectasis is not present at birth but may develop early, sometimes even in childhood. The most common respiratory pathogens are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Colonisation with pseudomonas is much less common than in cystic fibrosis. Most men are sterile and many women have a lowered fertility. About half of patients have situs inversus viscerum.

Patients with suspected primary ciliary dyskinesia should have their mucociliary clearance measured and the cilia should be examined by microscopy. Nasal mucociliary clearance can be measured by the saccharin test, in which a saccharin particle is placed on the anterior end of the inferior turbinate and the time taken for the subject to notice the taste is recorded. This test requires some patient cooperation and is not reliable in children under 10 years old.

Nasal cilia are easily accessible and can be obtained from the inferior turbinate without anaesthesia by a non-invasive brush technique. Ciliary beat frequency can then be assessed by light microscopy and photometric techniques and the cilia fixed for electron microscopy. The motility of sperm can be examined simply in men, and electron microscopy may show the characteristic ultrastructural defects.

RATIONALE OF TREATMENT

Treatment of primary ciliary dyskinesia is aimed at relieving symptoms and preventing complications. Early recognition facilitates prompt antibiotic treatment in patients with recurrent infections and is the key to minimising irreversible lung damage. Physiotherapy with postural drainage and stopping smoking are also important. Coughing should not be suppressed since it acts as a substitute for mucociliary clearance; huffing from mid to low lung volume with a forced expiratory manoeuvre helps improve clearance.[7]

Despite the chronic respiratory disease, life expectation seems to be normal. Infertile patients may benefit from advanced micromanipulation techniques

that allow non-motile or poorly motile sperm to penetrate the oocyte.

The prevalence of primary ciliary dyskinesia has been estimated to be 1 in 16 000.[8] Segregation analysis of proband sibships is consistent with autosomal recessive inheritance[9] but the ultrastructural abnormality is variable. The most common abnormality is absence or reduced number of dynein arms. Defects in the radial spokes, nexin links, cilial length, and orientation of the cilia have also been described.[3] There are thus likely to be several genes which may cause the manifestations of the disease. However, no clinical differences have emerged to distinguish different defects.

Although ultrastructural abnormalities often occur in both cilia and sperm flagella, patients with ultrastructural axonemal anomalies of only one cell type have been reported.[9,10] Men with primary ciliary dyskinesia should therefore have seminal analysis before being told they are infertile.

SITUS INVERSUS

Situs inversus occurs randomly in about 50% of patients with primary ciliary dyskinesia but may also occur without associated respiratory disease. Parents of children with primary ciliary dyskinesia usually have no history of chronic lung disease. The risk of another child being affected is about 25%.

The causes of lateralisation of organs are unknown but a network of genes and their products is likely to be involved. Ciliary function may be critical to the directional organ movements that produce lateralisation. Brown *et al* suggested that handedness may be signalled by a molecule which is itself handed and can be fixed in a particular orientation in relation to the anteroposterior and dorsoventral axes.[11] Cells may become polarised with respect to the midline, perhaps as a response to a diffusible substance produced by midline cells. Dynein is capable of asymmetrical transport and Brown *et al* postulated that situs may be associated with a defect in cytoplasmic rather than ciliary dynein. However, this does not explain why patients with defects of the microtubules other than the dynein arms also develop situs inversus.

Discussion

MW: These patients are teaching us something about left-right asymmetry. The obvious explanation is that if your cilia don't beat then your heart doesn't move to the correct side. It may not be as simple as that. In Polynesian bronchiectasis there is bronchiectasis and ciliary dysfunction but no situs inversus. An alternative hypothesis is that dynein has a role in intracellular asymmetry. In this hypothesis the molecule can be visualised as an F shaped structure which orientates according to the polarity of the cell and sets up intracellular gradients. Interestingly, it is very common for only one of conjoint twins to show abnormalities of symmetry.

CO: Not all patients with dextrocardia and situs inversus have Kartagener's syndrome; but all patients with isomerism (whereby you have mirror image structures) have complex cardiac defects.

JS: The cilia and the dynein always have the same geometric relationship, which may imply an asymmetrical moiety. Is there one dynein gene?

MW: There seems to be one dynein gene. However, there are probably several different mutations within this gene.

SB: If it produces infertility why is it so common?

MW: Theoretically, primary ciliary dyskinesia ought to breed out, but that is going to take a long time as it is a rare recessive. Selection against the homozygous is very slow and inefficient. The genetics of our patient's family are interesting because he has a nephew with Kartagener's syndrome and no dominant examples of this syndrome have ever been described. There is no history of consanguinity in this family.

DB: Is there an increased incidence of left handedness in these patients?

MW: As far as we know there is not, and this implies different genes for cerebral lateralisation.

I thank Dr Kevin Lindsay, Queen Charlotte's and Chelsea Hospital, for the sperm tail analysis and electron micrographs, and Professor Cole and Dr Charlotte Raynor, Royal Brompton National Heart and Lung Institute, for the nasal ciliary studies.

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ANY QUESTIONS

What are the long and short term hazards of exposure to trichlorotrifluoroethane and perchloroethylene, which are used in dry cleaning processes?

The toxic hazards of both these dry cleaning solvents have been reviewed in some detail. Trichlorotrifluoroethane, which is also known as FC 113, has low toxicity in humans. It is, however, one of the solvents with ozone depleting potential listed in the Montreal Protocol to be phased out in the European Union by the end of this year. The main health effects of perchloroethylene are on the central nervous system and include headache, drowsiness, and dizziness. These are minimal below an exposure level of 100 ppm and should not occur at or below the current exposure limits in Britain. Perchloroethylene causes hepatocellular carcinoma in mice, but this is not considered relevant to humans as the metabolic pathways involved in the breakdown of perchloroethylene in humans are different from those in mice. It has been suggested recently that there is an association between exposure to perchloroethylene and loss of pregnancy in women employed in the dry cleaning industry. The epidemiological studies that have reported this have weaknesses in their methodology and are not supported by animal data. If modern dry cleaning installations are operated correctly exposure to the solvent is kept well below British occupational exposure limits, minimising any risk to health.—DAVID GOMPERTZ, *Institute of Occupational Health, Birmingham*

Health and Safety Executive. *Tetrachloroethylene.* London: HMSO, 1987. (Toxicity review No 17.)