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Aetiology of asthma: lessons from lung transplantation

PAUL A. CORRIS JOHN H. DARK

Asthma is thought to result from both genetic and environmental influences. The genetic component is most obviously seen in patients who are atopic and have allergic responses to common antigens. We have done lung transplants in two such patients; and we have also transplanted the lungs from two mildly asthmatic patients, whose death was unrelated to their asthma, into two patients with end-stage cystic fibrosis and primary pulmonary hypertension, respectively. The non-asthmatic recipients of asthmatic lungs developed asthma after transplantation; however, the asthmatic recipients of normal lungs have not developed asthma up to three years after transplantation.

These observations support the notion that asthma is a "local" disease.

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Introduction

Although asthma is due to an interaction of genetic and environmental influences, their relative contributions are unknown.¹ Labile airflow obstruction is characteristic of asthma and is due to bronchial inflammation.² Asthma may be familial, usually in people who are atopic.³ Studies in families suggest that atopy is dominantly inherited,⁴ and molecular genetic linkage studies indicate the gene is located on chromosome 11.⁵

Lung transplantation is an option for patients with end-stage lung disease,⁶ and provides an opportunity to look for disease recurrence in healthy lungs transplanted into patients as a consequence of primary lung disease. We have studied two patients with asthma who required lung transplantation. Both gave long histories of typical asthma but also developed a progressive fixed obstructive defect that deteriorated despite increases in treatment. We have also studied the lungs of asthmatic donors transplanted into two patients dying of cystic fibrosis and primary pulmonary hypertension, respectively. We are not aware of any other non-asthmatic recipients of asthmatic lungs.

Asthmatic recipients of normal lungs

Both recipients were atopic and developed asthma during childhood. They were lifelong non-smokers. They had responded initially to treatment with inhaled steroids and beta-2 agonists. However, over the 5 years preceding transplantation, each developed worsening airflow obstruction which was unresponsive to treatment that included oral steroids. By the time of referral for transplantation, the quality of life of both patients was poor and the rate of decline in lung function suggested a life

ADDRESS: Departments of Respiratory Medicine and Cardiothoracic Surgery, Freeman Hospital, Newcastle upon Tyne, UK (P. A. Corris, FRCP, J. H. Dark, FRCS). Correspondence to Dr P. A. Corris, Department of Respiratory Medicine, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK.

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expectancy of one year or less. Both patients continued to have diurnal variability in peak expiratory flow with an early morning dip characteristic of asthma. At the time of transplantation the first patient, a woman, 28, was receiving 2000 µg inhaled beclomethasone, 20 mg oral prednisolone, 80 µg inhaled ipratropium bromide 4 hourly; inhaled salbutamol 200 µg as required, and a continuous infusion of subcutaneous terbutaline 12 mg over 24 h. The second, a man, 24, was receiving 2000 µg inhaled beclomethasone, 30 mg oral prednisolone, 80 µg inhaled ipratropium bromide and inhaled salbutamol 200 µg as required on a daily basis.

They had successful transplants with heart-lung blocks from donors with no history of asthma. The ages of the donors were 28 and 35, and the cause of death was subarachnoid haemorrhage in both. The patients were extubated within 24 h of surgery, and both were well enough to be transferred from the intensive care unit by 48 h. Peak flow monitoring was begun in the first week after surgery. All asthma treatment was stopped, with the exception of oral corticosteroids as part of routine immunosuppression. Neither recipient showed diurnal variation in peak expiratory flow in the first 6 months following transplantation, and so far neither has developed any evidence of airflow obstruction during 3 years of follow-up. Transbronchial lung biopsies were done at 3-monthly intervals in the first year and annually thereafter. Examination of bronchial tissue has shown no features of asthma (eosinophilic infiltration, basement membrane thickening, or epithelial disruption); but mild CD-8 lymphocytic infiltrates have been found in both cases—a common finding in patients after transplantation. Both patients received standard triple immunosuppression with cyclosporin, azathioprine, and prednisolone for the first 6 months. Subsequently both have been successfully weaned off prednisolone, and have received no further steroid for 2 years. We did histamine challenge tests on both patients 3 years after transplantation and neither showed a 20% fall in FEV₁ after doses of nebulised histamine up to 8 mg.

Non-asthmatic recipients of asthmatic lungs

A woman, 26, was referred for transplantation with respiratory failure due to bronchiectasis. Investigation showed her to have an abnormally high sweat sodium concentration which, together with the colonising of her respiratory tract with *Pseudomonas aeruginosa*, led to a diagnosis of cystic fibrosis. She gave no history of eczema, hay fever, nor episodic wheezing in childhood, and skin prick testing to common allergens was negative. Lung function tests showed a severe obstructive defect with an FEV₁ of 0.8 L and vital capacity of 1.7 L. There was no adequate acute bronchodilator response to inhaled beta agonists, and a 2-week trial of oral prednisolone 30 mg daily produced no improvement in lung function.

A woman, 24, had progressive dyspnoea on exercise for 5 years due to primary pulmonary hypertension. There was no history of eczema, hay-fever, or wheezing, and lung function showed no evidence of an obstructive defect. Neither patient had increased numbers of circulating eosinophils, nor did any of their first-order relatives have asthma. As far as we can ascertain, therefore, neither patient had any evidence of asthma before transplantation.

Heart-lung blocks came from donors with a previous history of asthma. Death was due to subarachnoid haemorrhage and complications of cranial surgery, respectively, and was unrelated to asthma. The history available before deciding to use the lungs from these donors suggested that the asthma was mild and controlled by the occasional use of an inhaled beta-agonist in both cases. However, after successful heart-lung transplantation had been done, further information became available that one of the donors had been receiving maintenance prophylactic therapy for asthma with inhaled beclomethasone 200 µg twice a day. Both recipients of asthmatic lungs showed diurnal variation in peak expiratory flow of over 30% in the first week after transplantation with early morning dipping, and had airflow obstruction with a good acute response to inhaled bronchodilators, which persisted despite immunosuppressive treatment with cyclosporin, azathioprine, and oral prednisolone. High-dose inhaled beclomethasone (1000 µg twice a day) with nebulised salbutamol 5 mg four times per day were started, and although there was a good response the diurnal variation in peak expiratory flow persisted. The clinical picture has been complicated by the development of nocardiosis in the lungs of the first patient and obliterative bronchiolitis diagnosed on lung biopsy in the second, at 6 and 8 months, respectively. The diurnal variation in peak flow and reversible airflow obstruction began in the first week after transplantation and before any histological evidence of obliterative bronchiolitis. The transbronchial biopsies done before these complications at 1 week, 1 and 3 months after transplantation showed epithelial disruption and a mild eosinophilic infiltrate, but there was no significant basement membrane thickening. Both patients remain alive and well, albeit with compromised lung function, at 15 and 12 months after transplantation, respectively. Quality of life and exercise performance are better than before operation in both cases.

Discussion

We believe that the observations made in these cases can help our understanding of asthma. In two cases, non-asthmatic lungs did not become asthmatic even up to 3 years after transplantation into asthmatic hosts, by which time host lymphocytes and macrophages would have colonised the lungs.⁷ These observations imply that the development of asthma in lungs requires more than the presence of inflammatory cells from an asthmatic host; in contrast with those patients whose asthma was apparently transmitted via bone marrow transplantation.⁸ That the lungs are denervated and patients received immunosuppressive therapy potentially confound the picture. There is, however, no evidence that vagotomy produces lasting objective benefit in asthmatic patients and there are no reported effects on diurnal variability.⁹ Although inhaled and intravenous anticholinergic treatment may reduce the characteristic variation in peak flow in asthmatic patients,^{10,11} the observations made in our two non-asthmatic patients who received lungs from asthmatic donors showed that neither vagotomy nor immunosuppression prevented the persistence of asthma. They continued to show diurnal variation despite receiving prophylactic treatment. The evidence suggests that the airflow obstruction in the lungs of these patients became worse after they had been transplanted.

The decision to use lungs from asthmatic donors was not taken lightly, but our information suggested that the donors were only mild asthmatics and in view of the shortage of donor lungs we felt it was ethically acceptable to use them. Quality of life and exercise performance in the recipients remain better than before transplantation in both cases. These observations show that the asthmatic human airway has the capability to remain asthmatic despite as drastic an environmental change as transplantation into another person receiving immunosuppressive therapy. In two cases we have shown that the non-asthmatic airway does not develop asthma even when transplanted into atopic asthmatic hosts and exposed to the new hosts' inflammatory cells. We believe these observations support the importance of inherited factors in determining the behaviour of the asthmatic airway and the value of continued efforts to find a gene and its product if a cure is to be found for this common disease.

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SHORT REPORTS

Sphincter stenosis and gallstone migration through the biliary tract

CARLOS A. HERNÁNDEZ MARKUS M. LERCH

We have investigated whether stenosis or insufficiency at the duodenal papilla results from the passage of a gallstone through the biliary tract. In three groups of patients after cholecystectomy we studied meal-stimulated pancreatic enzyme activity in T-drain bile from the common bile duct. Group A had gallbladder stones only; group B had gallbladder stones and bile duct stones; and group C had an episode of acute gallstone-induced pancreatitis, which was taken as direct evidence for gallstone migration into the duodenum. Reflux of pancreatic juice into the common bile duct was absent in group A, was occasionally found in group B, and was strikingly increased in group C. We conclude that passage of a gallstone through the biliary tract causes functional stenosis of the sphincter of Oddi and allows for a common channel between the pancreatic duct and the common bile duct. It does not cause sphincter insufficiency as previously assumed.

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Eugene Opie suggested in 1901 that reflux of bile into the pancreas is the critical event in the pathogenesis of acute gallstone-induced pancreatitis. His hypothesis was based on the post-mortem observation that an impacted gallstone at the duodenal papilla had created a communication between the common bile duct and the pancreatic duct through which bile could enter the pancreas. His patient died from acute

necrotising pancreatitis.¹ While the belief that the passage of a gallstone through the biliary tract can cause pancreatitis is now universally accepted,² the mechanism by which the stone triggers pancreatitis is still a matter of controversy.³ The common channel hypothesis has been questioned for several reasons. Often, there is no impacted gallstone found in patients with gallstone-induced pancreatitis.⁴ Moreover, most patients with gallstone-induced pancreatitis do not have a common biliary-pancreatic conduit long enough to allow communication between the pancreatic duct and the bile duct.⁵ Two theories have been proposed to reconcile these apparently incompatible observations with Opie's bile-reflux hypothesis. First, oedema and inflammation induced by passage of a stone might cause stenosis of the sphincter of Oddi. Thus, the presence of an impacted stone would not be required.⁶ The alternative theory implies that the damage caused by the passage of a gallstone leads to insufficiency of the sphincter and therefore allows for reflux of duodenal contents and bile into the unprotected pancreatic duct.⁷ We have investigated whether stricture or insufficiency of the sphincter results from gallstone migration.

We selected 21 subjects from all patients who had undergone a cholecystectomy within a 7-year period. This group had a common bile duct T-drain in place from which bile was flowing freely at seven days after the operation. The T-drain had been inserted at or near the insertion of the ligated cystic duct and its proximal and distal arms never exceeded 1.5 cm in length to allow sufficient distance from the sphincter and the papilla. None of these patients had undergone an endoscopic examination, papillotomy, or duodenotomy. Patients were excluded if an intra-operative or postoperative cholangiogram failed to show a common biliary pancreatic conduit (3 patients) or when cholangiometry did not clearly indicate patency of the duodenal papilla (1 patient). Patency was assumed when at least 20 mL of normal saline from a cholangiometer at a pressure of 30 cm H₂O was cleared through the T-drain in 1 min. The remaining 17 patients had all fully recovered from cholecystectomy done seven days earlier and were on a normal diet that was withheld for 8 h before the test.