Case report

Paradoxical embolism in a boy with cystic fibrosis and a stroke

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Abstract
An 11 year old boy with cystic fibrosis suffered a stroke, producing right sided weakness. Four years previously a totally implantable venous access device (Port-a-Cath) had been inserted. Magnetic resonance angiography revealed a filling defect in the left middle cerebral artery. Transoesophageal echocardiography demonstrated a thrombus attached to the tip of the Port-a-Cath and also the presence of a patent foramen ovale. After an initial period of anticoagulation the defect was closed using a septal occlusion device introduced via a cardiac catheter. The boy's neurological signs completely resolved and he remains free from further thromboembolic episodes. Whilst pulmonary embolism has been described before in relation to a totally implantable venous access device, this is believed to be the first description of a paradoxical embolism in relation to such a device.

Keywords: cystic fibrosis; paradoxical embolism; catheterisation

An 11 year old boy with cystic fibrosis was admitted to hospital with sudden onset of confusion and slurred speech. On examination he was found to have a right-sided hemiparesis, expressive and receptive dysphasia. He had originally presented at the age of two days with a meconium ileus and was subsequently found to be homozygous for the AF508 deletion. A sweat test performed at the age of four months confirmed the diagnosis of cystic fibrosis. Since the age of four he had required many hospital admissions for intravenous antibiotic therapy. In February 1992 a Port-a-Cath was inserted via the right internal jugular vein and secured to the anterior chest wall. His lung function was considerably compromised with a forced expiratory volume in one second (FEV1) of 0.63 l (35% predicted) and a forced vital capacity (FVC) of 0.98 l (49% predicted).

A computed tomographic (CT) brain scan performed on the day after admission revealed a poorly defined area of low attenuation in the left temporoparietal region which was suggestive of ischaemia in the territory of the left middle cerebral artery. Magnetic resonance angiography confirmed recent ischaemia in this region with evidence of an embolus in the left middle cerebral artery. A transthoracic echocardiogram was performed which showed an unusual Ebstein's-like deformity of the tricuspid valve; the proximal part of the septal leaflet of the tricuspid valve was displaced apically with a point of attachment in the mid body of the right ventricle. Mild tricuspid regurgitation was also seen but no other abnormalities were apparent.

Ebstein's anomaly is associated with abnormal intra-atrial connections and therefore a transoesophageal echocardiogram was arranged. This was performed under general anaesthesia and demonstrated a small patent foramen ovale, the anterior border abutting the posterior aspect of the ascending aorta. The Port-a-Cath was seen in the right atrium and was noted to impinge against the tricuspid valve during the cardiac cycle. In addition, a large thrombus was seen attached to the tip of the Port-a-Cath in the right atrium.

Despite using intravenous contrast, no right to left shunt was demonstrable during the procedure. Techniques to enhance any right to left shunt such as coughing and the Valsalva manoeuvre were not possible because of the general anaesthetic.

The patient was anticoagulated with warfarin and started on an anti-platelet dose of aspirin. One month later the defect was closed using a 9 mm atrial septal occlusion device introduced via a cardiac catheter (fig 1). By this time the neurological signs had completely resolved and aspirin was discontinued after three months. There have been no further episodes of thromboembolism.

Figure 1 Septal occlusion device clamped across the atrial septum.
Discourse
Paradoxical embolism was first described by Cohnheim in 1877 but until 1930 only post-mortem cases were reported in the literature. In recent years more advanced techniques for detection of a patent foramen ovale have allowed the accurate diagnosis of presumptive paradoxical embolism during life.

Thromboembolism has been described as a complication relating to the use of totally implantable venous access devices but we believe this is the first time that a paradoxical embolism has been described in relation to the use of such a device.

Paradoxical embolism can only be considered proven if a venous thrombus is detected lodged in an intrahemispheric septal defect. This degree of certainty is extremely rare, but has been demonstrated during life using both transthoracic and transoesophageal echocardiography. More often we can assume paradoxical embolism if "Johnson’s triad" exists—that is, (1) venous thrombosis with or without pulmonary embolism, (2) an intracardiac defect with right to left shunting, and (3) arterial embolism without a corresponding source in the left heart or proximal arterial tree.

The reported incidence of a patent foramen ovale varies from 5% to 30%. In younger adults with ischemic stroke, where the cause may be undefined in up to 35% of cases, the incidence of a patent foramen ovale is significantly higher at around 40%. This suggests that paradoxical embolism occurs more frequently than was previously thought.

Paradoxical embolism is more likely in the setting of a chronic cough, as in cystic fibrosis.

Coughing and the Valsalva manoeuvre are used during contrast echocardiography to promote right to left shunting across a patent foramen ovale, and indeed coughing is felt to be the most effective manoeuvre to demonstrate such shunting.

Any child with an unexplained stroke requires a careful neurological examination, particularly if there are risk factors such as an indwelling venous access device and a chronic cough. If transthoracic echocardiography shows no abnormality then more invasive investigations should be considered such as transoesophageal echocardiography.

Transcatheter techniques such as that used in our patient can offer significant advantages over open surgery in patients with cystic fibrosis. Postoperative recovery is quicker with less interruption to physiotherapy, and the avoidance of sternotomy may have important implications for any proposed heart-lung transplantation.

LETTERS TO THE EDITOR

Surgery and respiratory muscles

In their review of the effects of surgery on the respiratory muscles Siafakas and co-workers have cited my work incorrectly on two occasions. We reported a study of respiratory mechanics after abdominal surgery with measurements of the pressure-volume characteristics of the rib cage and abdomen. This report has been cited to support statements on the effects of surgery on gas exchange efficiency of the lung and of general anaesthesia on the thorax. On neither occasion is this citation appropriate. We found evidence that the abdominal muscles were active in patients after abdominal surgery, that this activity was variable, and that it could possibly explain the patterns of movement otherwise considered to represent "diaphragmatic dysfunction". These observations, along with a short review of the published work on the subject, formed an editorial in which I argued that the concept of diaphragmatic dysfunction was outmoded. This work has been cited in support of the effects of laparoscopic cholecystectomy, which is incorrect. Indeed, there is remarkably little direct evidence that the intercostal inspiratory muscles become more active in the patient after surgery. There is also little direct evidence in humans that the diaphragm is the respiratory muscle most affected by surgery.

Many of the changes in the shape of the thorax caused by the induction of anaesthesia can be attributed to a loss of skeletal muscle tone, with a change in the shape of the vertebral column. If this is prevented, then the changes in thoracic dimensions during induction of anaesthesia are small, variable, and do not require the hypothesis of major movements of intravascular volume as indicated in fig 1 of their review. This is supported by direct measurements of intravascular volume, which do not show these shifts.

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4 Spence HJ, Drummond GB, Wrath PR. Changes in chest wall compartment volumes on induction of anaesthesia with etomidate, propofol, and thiopentone. Br J Anaesth 1996;77:369–73
6 Stoddard MF, Reddy DL, Dawkins PR. The cough test is superior to the Valsalva maneuver in the delineation of right-to-left shunting through a patent foramen ovale during contrast transoesophageal echocardiography. Am Heart J 1993;125:15–9

AUTHORS’ SUPPLY We wish to thank Dr Drummond for pointing out the incorrect citation of his work in our recent review. We apologise for this, especially for quoting his editorial for the effects of laparoscopic cholecystectomy on the respiratory muscles. However, we have extensively discussed the semantics of the term “diaphragmatic dysfunction” in the methodological part of our review, sharing some of Dr Drummond’s views. Furthermore, we have cited the work of Dr Drummond and colleagues in the general discussion of the function of respiratory muscles during surgery, arguing that respiratory muscle dysfunction, in the general sense of the term, could influence functional residual capacity. We believe that this is in agreement with Dr Drummond’s findings that upper abdominal surgery alters the relative activity of respiratory muscles (including the abdominal muscles) leading to changes in the rib cage abdominal configuration (fig 1, Nimmo and Drummond). Similarly, we have cited his work to support the argument that general anaesthesia causes volume displacement between the thoracic and abdominal cavities. Dr Drummond...
The study by Waller and colleagues for their comments regarding our study. We must first emphasise that we were not intending to make any conclusions regarding the relative clinical or financial benefits of either drainage system, and that we were specifically addressing the situation of postoperative air leaks. We have shown that, at resting tidal volume, flutter valve drainage bags maintain a more negative (but not excessively negative) intrapleural pressure than underwater seal systems and are therefore more likely to restore the normal physiology of the pleural space.

The aim of chest drainage in this situation is to restore and maintain the negative intrathoracic pressure necessary for lung re-expansion which will allow reactivation of the surface forces promoting visceral and parietal pleural apposition. This is dependant on removing excess gas or fluid from the pleural space. We therefore consider the exit of air (by which we assume they mean will reduce intrapleural pressure) after removal of air or fluid from the pleural space.

The study concludes that an ideal postoperative drainage system will "allow the maintenance of a negative intrapleural pressure, even in the presence of an air leak". In our view a negative pleural pressure in this situation would only serve to encourage the egress of more air from the damaged lung surface into the pleural cavity, thus worsening the situation.

Whilst accepting that the postoperative situation may differ somewhat from that which pertains in a spontaneous pneumothorax because of the presence of fluid/blood in the pleural cavity, we would expect the same physiological principles to apply, especially in the presence of an air leak. There is a risk that the conclusions from this paper might be extrapolated into general respiratory practice and the scenario of spontaneous pneumothorax. For all of the above reasons we would urge caution before abandoning the standard and well tried technique of drainage of the pleural cavity (underwater seal) in favour of the suggested alternative, at least before data from larger, controlled clinical trials become available.


AUTHORS' REPLY

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Aspergillus fumigatus: re-invention of the wheel

The paper by Murayama et al contains the unwary statement that their study may have been the first to demonstrate the suppressive effects of Aspergillus products on antifungal host defences by both human alveolar macrophages and PMNs. A search for Aspergillus in the eThorax website would have saved both them and your referees from accepting this. In a series of papers published in the 1980s Maura Robertson and I showed this in animal and human cells, demonstrated the paradoxical effect of complement and, perhaps more importantly, showed that the substance produced by the spores had similar effects on soil protozoa, thus explaining the biological paradox as to why an organism that gains nothing from colonising animal lungs should have developed such exquisite antiphagocytic properties. Some of this work was summarised in our paper published in the Lancet in 1989. These effects are discussed in at least one well known textbook of respiratory disease.

It is to be hoped that the “wheel reinventing” tendency of authors who search the literature back only five years and the short memory or ignorance of referees may be alleviated by use of your new web site.

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AUTHORS’ REPLY

We agree with Dr Roberts that the Internet raises special issues for patients with rare diseases and that the problem is often too much information rather than too little. With respect to lymphangioleioymomatosis (LAM), our approach in Nottingham has been to produce a four page fact sheet for patients which we have given to patients in the LAM Trust and to some of the doctors looking after the patients. The fact sheet was pilotled amongst a few patients with LAM and modified in the light of the feedback we received. Several patients have obtained the fact sheet from the LAM Foundation in the USA which goes into slightly more detail than our document, particularly with respect to prognosis; as might be expected with a rare disease. As far as further information whilst others do not.

Whether specialist registrar trainees should be deciding what patients with a rare disease should be encouraged to read is more debatable since some will never have met a patient with the disease in question. It seems more appropriate to us for fact sheets and information to be provided by people with some knowledge and expertise of managing patients with the particular disease, in conjunction with the patients themselves. The British Thoracic Society is planning to develop an orphan disease register and to encourage research into rare disorders. One of their requirements will be to consider what information is required and how it should be presented and piloted.

C M ROBERTS
Programme Director, North Thames East Respiratory Medicine STG, Whipps Cross Hospital, London E11 1NR on behalf of the North Thames (East) respiratory trainees


AUTHORS’ REPLY

We thank the editors for the opportunity to respond to the concerns raised by Professor Seaton. His group and Drs Mullbacher, Eichner et al in Australia are pioneers in studies of the antiphagocytic activity of Aspergillus products and they have done some excellent work. We cited some of their original articles in our previous paper. Professor Seaton et al have shown that spores and spore diffusates of A fumigatus suppress the production of superoxide anion and hydrogen peroxide by rodent phagocytes and that diffusates of A fumigatus spores inhibit phagocytosis of antibody coated radiolabelled sheep red blood cells by mouse peritoneal exudate cells. They have also performed experiments using human cells and have shown that spore diffusates of A fumigatus reduce the migration of human polymorphonuclear leukocytes and decrease the capacity of mouse peritoneal exudate cells to spread on glass. They have measured the ability of human pulmonary macrophages to bind and kill A fumigatus spores and have examined the effects on killing of heat labile serum components. However, they have not presented data on the suppressive effects of Aspergillus derived products on polymorphonuclear leucocyte mediated damage to A fumigatus.

It has been considered that selective protection against Aspergillus spores by mononuclear phagocytes and against hyphae of Aspergillus by polymorphonuclear phagocytes are critical host defences in humans. Since Aspergillus spores enter mainly through the respiratory tract and proliferate in mycelial form in human tissues, our study has focused on interactions between Aspergillus spores and human alveolar macrophages, and also between Aspergillus hyphae and human polymorphonuclear leucocytes. In our study we showed that A fumigatus culture filtrate suppressed not only human polymorphonuclear leucocyte mediated A fumigatus hyphal damage but also inhibition of spore germination of A fumigatus by human alveolar macrophages, and suggested that A fumigatus culture filtrate suppressed, not only human polymorphonuclear leucocyte derived products on human polymorphonuclear leucocyte mediated hyphal damage of Aspergillus and also on inhibition of spore germination of A fumigatus by human alveolar macrophages.

TAKOKU MURAYAMA
RYOICHI AMITANI


NOTICE

The Dr H M (Bill) Foreman Memorial Fund

The Trustees of the Dr H M (Bill) Foreman Memorial Fund invite applications for grants relating to study in respiratory disease. Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own for study in respiratory disease, and also for support for clinical research abroad. Intending applicants should write for further details to Dr Brian Davies, Lindoahugh Hospital, Penarth, Vale of Glamorgan CF64 2XX, UK.
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