ARCHIVES OF DISEASE IN CHILDHOOD

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Annotations

Pulmonary embolism in parenteral nutrition

Parenteral nutrition administered via silicone central venous catheters is a frequently used supportive treatment in paediatric practice and is essential for patients with gut failure. Risks of infection and local line tip thrombosis have been extensively studied but, despite mounting evidence, thromboembolic events have only recently been accepted as a major complication.[1 2] It now appears that major right atrial thrombosis and pulmonary embolism are common and potentially fatal complications of long term venous access/long term parenteral nutrition in childhood.[3]

Concern about the increasing rates of central venous thrombosis in patients receiving parenteral nutrition via central venous catheters has been expressed since the 1970s.[2] In 1981 a retrospective necropsy study showed a 3·7% incidence of pulmonary embolism in children with the presence of a central venous catheter as the most common risk factor for thrombosis in those children with clinically relevant pulmonary emboli.[4] Despite these findings some authors continued to regard central venous and intracardiac thrombi as extreme rarities.[5] Over the same period others reported postmortem diagnosis of pulmonary embolism that had been detected antemortem in only 30% of patients.[4 6] Initial studies into central venous thrombosis using venographic imaging yielded thrombosis rates of 0–66%.[7 8] These studies, which were not designed to detect pulmonary emboli, none the less identified them clinically in 6–10% of cases. In 1992–3 the patients having long term parenteral nutrition at the Hospital for Sick Children, Great Ormond Street, London, were investigated specifically to identify central venous thrombosis, pulmonary embolism, and intracardiac thrombus using echocardiographic and ventilation perfusion scanning.[3] Major thrombosis and/or embolism was identified in 12 of 32 patients and four died as a result of pulmonary emboli. Actuarial survival free of thrombosis was 53% at five years (95% confidence interval (CI) 30 to 77%). Survival free of fatal pulmonary thromboembolic events was 74% at five years (95 CI 48 to 99%). In this study major thrombotic complications in children with long term central access for gastrointestinal disease were much more common than previously recognised. This highlights the importance of an awareness of this diagnosis and the need for further studies into treatment and prevention.

Clinical features

David and Andrew in a review of the literature since 1975 found that 26% of deep venous thrombosis cases in children were secondary to central venous catheters compared with 1–2% in the adult population.[9] Of these, 5·5% were receiving total parenteral nutrition (TPN). Paediatricians, therefore, need to consider the diagnosis of pulmonary embolism in a different population to the adult physician. Some children with pulmonary embolism may present with signs due to the underlying deep vein thrombosis – for example the superior vena cava (SVC) syndrome – or with a chance finding of right atrial thrombus on echocardiography. The classical signs and symptoms of pulmonary embolism such as chest pain, dyspnoea, haemoptysis, syncope, tachypnoea, tachycardia, sweating and fever may occur but even in the adult population have only an 85% sensitivity and 35% specificity.[10] Small emboli may be asymptomatic while significant dyspnoea due to widespread emboli may be attributed to general debility until there is a greater awareness of the possible diagnosis of pulmonary embolism.[3] Children receiving parenteral nutrition who develop unexplained dyspnoea, fever, or exhaustion should be screened for emboli both clinically and with echocardiography and ventilation-perfusion (V/Q) scanning.

Diagnostic tests

The diagnosis of pulmonary emboli depends on visualisation of thrombi and/or unequivocal demonstration of the effects of emboli. The probable source of emboli, that is the catheter, SVC, and right atrium are best initially imaged by transthoracic echocardiography which is non-invasive and can usually be performed without sedation.[11] If further delineation of the SVC and the collaterals which form after blockage are necessary bilateral venography is required. Contrast studies performed via the central venous catheter only image the catheter tip and are not an appropriate diagnostic test for SVC or intracardiac thrombus. Electrocardiograms may show evidence of right heart strain with pulmonary emboli and new changes of this kind should prompt echocardiography; these changes cannot, however, be regarded as diagnostic of pulmonary embolism and have not been validated in children.[12] In addition right heart strain may be caused by other diseases

which complicate parenteral nutrition such as granulomatous pulmonary arteritis due to particulate contamination of parenteral fluids.[13]

The V/Q radionuclide scan is the most accurate non-invasive test for detecting pulmonary emboli with a positive predictive value of 88% in adult populations.[14] Using the generally accepted criteria of high probability scans only reflecting true pulmonary embolism, sensitivity is 41% while specificity is 97%. In combination with echocardiography it is the most appropriate screening test in an at risk population such as patients receiving parenteral nutrition but clinicians should be aware that false negative may occur. $^{81}Kr^{m}/^{99}Tc^{m}$ methylmalonic acid has been recommended in children due to its very low radiation dose (approximately 20 mrad effective dose equivalent).[15]

Pulmonary angiography is the most accurate diagnostic test available and has shown a reasonable correlation with V/Q scans in one small paediatric population on parenteral nutrition.[3] The relatively high radiation dose necessary for pulmonary angiography prevents its use as a screening test but should not discourage its use in making the diagnosis where this will change management. The other risks of pulmonary angiography are due to sedation or anaesthesia which may be required; embolism if unstable right atrial thrombi are dislodged; and pulmonary hypertensive crisis in the case of chronic obstruction. These risks must be weighed against the benefits and angiography should be restricted to specialist centres where experience in catheterisation and interpretation of pulmonary angiograms are available. If surgery for right atrial thrombectomy or pulmonary embolectomy are considered V/Q scanning may underestimate proximal pulmonary arterial thrombosis and angiography is essential unless contraindicated.[16 17] Some surgeons advocate bronchial arteriography, pulmonary angioscopy, or high resolution computed tomography to assess the extent of distal thrombus in cases of chronic embolism.[16 17]

Mechanisms of thrombosis

Thrombus around central venous catheters can be divided broadly into two types: a fibrin sheath that forms around the tip of most catheters or the more serious catheter associated thrombus which may also be adherent to the SVC or atrium and may obstruct the SVC and tricuspid value or embolise to the pulmonary artery. It is not know if the fibrin sheath is the substrate for these larger clots or what triggers the development of the latter group. One study has shown that hypertonic TPN solutions induce monocyte/macrophage procoagulant activity in vitro, and in a small in vivo study, while lipid emulsions return coagulation to normal.[18] Others have seen that lipid infusions activate platelets by increasing thrombin production.[19] Fat emulsions have been shown to accumulate in pulmonary capillaries where it is suggested that they may cause V/Q mismatch.[20] Although this is very unlikely to be the cause of the major clinical emboli described in some studies it could initiate embolus formation if coagulation is activated. Instances of thrombosis have been reported in children who have never received lipid and may complicate central venous lines placed for indications other than TPN administration.[2 3 6]

Berant *et al* have recently demonstrated that antiphosphatidylcholine antibodies are produced after lipid infusions in susceptible individuals and speculated that a variant of the antiphospholipid syndrome may be induced.[21] Interactions between particulate contaminants of infusions and endothelial cells have been suggested as aetiological factors in adult respiratory distress syndrome and multi-organ failure and might also initiate coagulation.[22] This problem may now be solved by the use of 1·2 micron filters in conjunction with lipid containing TPN solutions but deserves separate prospective evaluation.[23] The presence of an intravascular foreign body is the likely origin of emboli with possible triggers to thrombosis being sepsis or the constituents of TPN solutions.

Treatment/prophylaxis

Treatment of embolism complicating parenteral nutrition must now consider primary prophylaxis as well as acute treatment and secondary prevention. More information is available to guide treatment than primary prevention.

ACUTE PULMONARY EMBOLISM

Acute massive pulmonary embolism causing cardiovascular collapse should initially be treated with resuscitation and ventilation. For the 10% who survive the initial collapse the choice between catheter mediated clot disruption, thrombolysis, and surgical embolectomy is dependent on the emergency facilities available. The more usual situation facing the clinician with a patient on long term TPN is the accumulation of small asymptomatic emboli with or without a right atrial thrombus. In the light of recent studies it is difficult to justify simple observation of asymptomatic emboli unless coexistent disease precludes active therapy.

(1) Anticoagulation

Guidelines are now available for the use of heparin intravenously in children for 7–10 days with warfarin instituted within 48 hours.[9] Heparin requirements may be high due to rapid heparin clearance in the young[24] or extensive thrombus[25]; frequent monitoring is required and haematological advice should be obtained. The long term use of heparin may cause osteoporosis and cannot be reliably administered via TPN solutions if cyclical infusion is used. Warfarin treatment should aim to achieve an international normalised ratio (INR) of 2–3 and should continue for the duration of central venous catheterisation unless unacceptable bleeding occurs. Oral anticoagulation for patients with gut failure may be problematic due to poor absorption but reports suggest that even those with short bowel syndrome (with as little as 12 cm of small intestine) should reach therapeutic levels.[26] Warfarin interactions must be remembered in particular with vitamin K in TPN solutions or in supplemented feeds (if some oral nutrition is possible).

(2) Thrombolysis

Systemic thrombolysis has been used for right atrial thrombus with on going emboli and for extensive pulmonary thromboemboli. The success of thrombolysis is dependent on the presence of fresh clot and is only appropriate with prompt diagnosis and initiation of treatment. The relative advantages of different thrombolytic agents and paediatric dosage has been reviewed elsewhere.[10] Successful use of both urokinase and tissue plasminogen activator (t-PA) in central venous thrombosis and pulmonary embolism in children has been documented, although numbers are too small for useful comparison of the two agents.[27–29] t-PA has some theoretical advantages: it has a short half life (allowing surgical intervention), it is minimally dependent on plasminogen concentrations which are low in the neonate, and it is non-antigenic. The dosage of thrombolytic agents should be tailored to the individual patient but t-PA is normally used at 0·1–0·5 mg/kg body

weight per hour, the dose being increased gradually if clot dissolution does not occur.[10] Some cases of streptokinase resistant clots responding to t-PA have been reported.[3 30] The principal complications of thrombolysis are bleeding and the detachment of mobile right atrial thrombi causing pulmonary arterial obstruction. In five recent cases where t-PA was used two patients were affected by these complications while three responded fully without side effects (I D Sullivan, personal communication).

(3) Surgery

Surgery for acute pulmonary embolism has a high mortality but may be life saving if severe haemodynamic compromise is present. Removal of right atrial clot as an elective procedure to prevent embolisation has been used with success in adults and children[3 31 32] but lower risk or greater success than thrombolytic treatment alone has not been established. Increasing experience of appropriate thrombolysis has favoured this more conservative approach. There remains an undisputed place for surgery in those patients with a contraindication to thrombolysis such as recent surgery or intracranial haemorrhage.

CHRONIC PULMONARY EMBOLI

Patients with recurrent small emboli may develop extensive obstruction to pulmonary flow. They may be detected by screening tests, investigation into the cause of gradually worsening dyspnoea, or by an acute on chronic thrombotic episode such as a right atrial clot. In the latter situation use of thrombolysis is only applicable to cases where the great majority or all of the clot present is thought to be fresh (one week). If the patient has symptoms attributable to chronic emboli, which will require surgical intervention, intracardiac clot can be removed at the same procedure with negligible increase in risk. Surgical thromboendarterectomy for extensive symptomatic chronic emboli has been used in adults and in some children with great success but requires detailed preoperative assessment and experienced perioperative care.[3 16 17] All patients should remain on anticoagulation for the duration of central venous catheterisation after surgery (or thrombolysis) and if any underlying clotting defect is suspected haematological advice should be taken with a view to lifelong anticoagulation.

PROPHYLAXIS

Primary prevention of TPN or catheter related pulmonary embolism remains controversial. Clinical experience, although unproved, suggests meticulous catheter care can reduce all line related complications to a minimum. It has been shown that having more central venous lines segregates with a lower risk of thrombosis and this may reflect prompt and appropriate line replacement.[3] Current prophylactic regimens, flushing with heparin containing solutions, are designed to protect the catheter rather than the patient. Two trials have examined the prophylactic use of anticoagulants in adult patients with central venous catheters. The first specifically looked at 51 patients on TPN who were randomised to receive 5000 IU heparin every six hours or no heparin and a reduction in frequency of clots on venography (via the catheter) was seen in the treated group.[33] The second study in 80 patients evaluated thrombosis using venography in the presence and absence of very low dose warfarin (1 mg/day in adult patients) and showed a statistically significant reduction in thrombosis without the induction of a haemorrhagic state.[34] Some authors have advocated prophylaxis since the 1980s. Future studies assessing prophylaxis should span the various dosage regimens: the upper therapeutic range (INR 2·5–3·5); the 'lower dose' warfarin which reduces bleeding risk but can be too low to prevent emboli from mechanical heart values (INR 2–2·5); and the very low doses which do not alter clotting tests.[34 35]

Implications

It should now be accepted that children receiving parenteral nutrition are at risk of major thrombosis. Widespread availability of V/Q scanning and echocardiography should facilitate their use in screening at risk populations for thromboembolism. Pending further research screening should be at six monthly intervals unless there is a clinical suspicion of intracardiac or pulmonary clots. Multicentre studies to assess thrombosis rates and management strategies have been called for on many occasions. The British Society of Paediatric Gastroenterology and Nutrition is now proposing a national register to confirm the extent of thrombotic complications. Consideration should be given to extending this survey to include a randomised controlled study of warfarin prophylaxis using a range of dosage regimens. The issue of dose is particularly important in children where one of the aims of treatment is to restore a normal active lifestyle with its attendant cuts and bruises. Until such information is available an increased awareness of this diagnosis will probably make the greatest difference to outcome.

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Human herpesvirus-6 infections

Human herpes virus-6 (HHV-6) was first discovered by Salahuddin and colleagues in 1986 after identifying herpes-like particles in the peripheral blood of patients with AIDS and lymphoproliferative disorders.[1] In the subsequent decade, it has been found to be clinically ubiquitous. However, although improved methods of diagnosis of HHV-6 infection have led to a better understanding of the spectrum of disease caused by the virus, there is still controversy about many of the associations.

Microbiology

Structurally, the double stranded DNA virus shares many characteristics of the other human herpes viruses, having the greatest homology with cytomegalovirus.[2] There are two distinct but closely related types: type A (characterised by the U1102 strain) and type B (characterised by the Z29 strain).[3 4] HHV-6, like HIV, shows tropism for CD4 cells,[5] and as with other herpes viruses, HHV-6 has been shown to cause persistent, asymptomatic infection.[6] The site(s) of latency have not been clearly established, but latent virus has been identified in kidneys, bronchial glands, monocytes and salivary glands.[6 7]

The virus can be isolated by tissue culture using continuous cell lines such as cord blood lymphocytes.[1 3] However, in the clinical setting, serodiagnosis and polymerase chain reaction (PCR) of blood, cerebrospinal fluid, or other sterile site are the most commonly utilised methods of diagnosis. Of the various serodiagnostic assays, the enzyme linked immunosorbent assay (ELISA) and neutralisation methods have been shown to be more sensitive than immunofluorescence.[7–10] No significant cross reactivity between HHV-6 and other human herpesviruses has been detected.[11] PCR, when available, provides a rapid method for determining the presence of HHV-6 DNA. However, as detailed below, a positive result may indicate either an acute infection, reactivation, or subclinical persistence of the virus.

Epidemiology

Horizontal person to person transmission is the most likely route of infection, although this is yet to be firmly established. Oral secretions appear to be the most probable source, as the virus has been detected in the saliva of a significant proportion of healthy adults.[6] Sexual transmission is thought not to be important.[7] The virus has been detected in donated organs,[12–14] and although transfusion associated infection is possible, it has not yet been reported. Vertical transmission (mother to fetus) and reactivation in pregnancy have been documented serologically but no syndrome of congenital infection has yet been described.[15] Breast milk does not appear to be an important source of infection.[16]

The virus has been identified in populations world wide. Estimates of seroprevalence, however, vary around the world, partly due to differences in the method of the assay.[1 7 8 17–21] Seroprevalence rates using immunofluorescence appear to be lower than those determined by neutralisation or ELISA, even in the same population.[22] At birth, most children are IgG antibody positive due to maternal immunoglobulin (approximately 70% by immunofluorescence, 95% by neutralisation).[20–22]

Antibody levels reach a nadir at 4–7 months, then increase throughout infancy so that by 12 months, two thirds have been infected, peak levels being reached at 2 to 3 years. Recent seroepidemiological studies of adult populations from the United States, Japan, and Europe report rates from 80% to almost 100%,[6 20–22] indicating that some waning of antibody may occur and that reinfection and reactivation may not occur frequently.

Disease associations

EXANTHEM SUBITUM

Of the many reported disease associations of HHV-6, exanthem subitum (or roseola infantum) is one of the few in which a causal link has been proved. Yamanishi *et al*, in 1988, were the first to make the association by isolating HHV-6 from the blood lymphocytes of four children with exanthem subitum and showing concurrent seroconversion to HHV-6.[21] Others have confirmed this finding.[8 16 23–25] Asano *et al*, in a study of 176 infants with confirmed HHV-6 infection, clarified the clinical features of exanthem subitum.[26] In addition to the well characterised rash, other features included erythematous papules on the mucosa of the soft palate called Nagayama's spots (in 65% of children), bulging fontanelle (26%), seizures (8%), diarrhoea (68%), cough