Postgrad Med J (1990) **66**, 747 – 750

Carotid artery stenoses and thrombosis secondary to cavernous sinus thromboses in *Fusobacterium necrophorum* meningitis

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Summary: We report the case of a young man with *Fusobacterium necrophorum* meningitis who developed bilateral carotid artery stenosis associated with thrombosis of the cavernous sinuses. Intraluminal clot was present in the region of the stenoses for which he was anticoagulated. The clinical presentation, problems with diagnosis, the use of anticoagulation and the need for prolonged treatment with metronidazole are discussed.

Introduction

Fusobacterium necrophorum, a Gram negative anaerobe, is an unusual cause of meningitis[1-5] and has a distinct association with the development of cranial nerve palsies. Cavernous sinus thrombosis in association with this infection has only been reported on one occasion,[3] although it is prone to occur during anaerobic septicaemia.[6] Carotid artery stenosis has not previously been recognized in association with this organism. The use of anticoagulation in the treatment of cavernous sinus thrombosis is controversial.[7,8] We describe a patient who was anticoagulated because of the presence of mural thrombi within the carotid artery, to reduce the risk of cerebral embolism. Six months after the infection had resolved there was evidence of partial resolution of the carotid stenoses. This report also demonstrates the need for prolonged treatment with metronidazole to eradicate this infection.

Case report

A 26 year old man, previously well, became ill with pharyngitis, fever and rigors. Despite treatment with erythromycin the symptoms persisted and he was admitted to hospital a week later with meningitis and diplopia. He was pyrexial (40°C), with an exudative pharyngitis, meningism, a tender elongated mass each side of the neck and a right sided VIth nerve palsy. Investigations showed a normochromic, normocytic anaemia (11.1 g/dl), leucocytosis (12.5×10^6/l) with neutrophilia, erythrocyte sedimentation rate 60 mm/h, serum albumin 24 g/l, normal liver function and a normal computed tomographic brain scan. Cerebrospinal fluid (CSF) contained 790 polymorphs/mm^3, protein 110 mg% and glucose 2.6 mmol/l and no organisms were seen. An initial diagnosis of partially treated meningitis was made and he was started on cefotaxime, chloramphenicol (both intravenously) and metronidazole (500 mg three times daily rectally). Shortly after admission, he developed a total ocular paresis of the right eye, proptosis and sensory impairment over the first division of the right trigeminal nerve. Cavernous sinus thrombosis, with involvement of the IIIrd, IVth, first division of Vth and VIth nerves was diagnosed. He also developed pleurisy, and a ventilation/perfusion lung scan demonstrated multiple perfusion defects due to presumed septic emboli.

There was no response to treatment and the neck masses enlarged. Six days after admission an early growth of an anaerobe in the blood culture was seen. Intravenous metronidazole 500 mg three times daily was commenced and by the following day there was some clinical improvement. Repeat CSF examination showed a white cell count of 54 – mostly lymphocytes. Nine days later the anaerobic organism was identified as *Fusobacterium necrophorum*, being isolated from both blood and CSF. Culture of encysted pleural fluid was sterile. The organism was sensitive to penicillin, erythromycin, chloramphenicol, cefotaxime and metronidazole. At this point the patient continued to improve although a low grade pyrexia persisted and there was no improvement in the ocular paresis. In

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Accepted: 20 April 1990

addition, an isolated left side XIIth nerve palsy became apparent.

Intravenous metronidazole was maintained for 3 weeks, stopping when the CSF lymphocyte count fell to 24×10^6/l. One week later, however, the count rose to 120×10^6/l and the metronidazole was restarted for a further 2 weeks, then converting to an oral dose of 400 mg three times a day for 2 months until the CSF returned to normal.

Four vessel cerebral angiography and phlebography studies were performed (4 weeks after admission), because of the rising lymphocyte count and failure of resolution of the cranial nerve palsies, to confirm the clinical diagnosis of cavernous sinus thrombosis and to investigate the possibility of early abscess formation. The angiographic studies demonstrated bilateral, tight carotid artery stenosis in the region of the cavernous sinuses (Figure 1) with mural thrombi (Figure 2). There was marked compensatory dilatation of the vertebrobasilar system with bilateral filling of the middle cerebral zones through the posterior communicating arteries. Fronto-orbital and bilateral internal jugular vein phlebography showed occlusion of the venous outflow tract on the right, including the sigmoid sinus and the upper internal jugular veins and furthermore, occlusion of both cavernous sinuses and the posterior right superior ophthalmic vein. On the basis of the presence of intraluminal clot he was anticoagulated with warfarin which was continued for 4 months.

Six months later the cranial nerve palsies were almost completely resolved. There was some vertical diplopia, the right pupil reacted sluggishly to light and the tongue still showed minimal atrophy. Repeat carotid angiography (Figure 3) at this time portrayed considerable improvement of the left internal carotid artery but the right was still markedly stenosed, although the intraluminal clot had resolved and the flow across the posterior communicating arteries had reversed to normal.

Discussion

Fusobacterium necrophorum infection, first described by Lemiere,[9] usually commences in the oropharynx with early invasion of the local veins leading to the formation of septic emboli. Several cases of meningitis due to fusobacterium infection have been reported,[1-5] five of which had cranial nerve palsies and have involved the third, fourth, sixth and twelfth nerves. The ocular palsies, as in our patient, can be accounted for by cavernous sinus thrombosis. For an explanation of the isolated twelfth nerve palsy we would postulate involvement in the generalized inflammation as the nerve loops around the internal jugular vein in the neck. Indeed, the internal jugular vein is invariably palpable[10-12] and it is a common error to mistake this for lymphadenopathy.

Carotid artery stenosis has not previously been described in association with fusobacteria infections presumably because angiography has not been indicated. It has, however, been described on

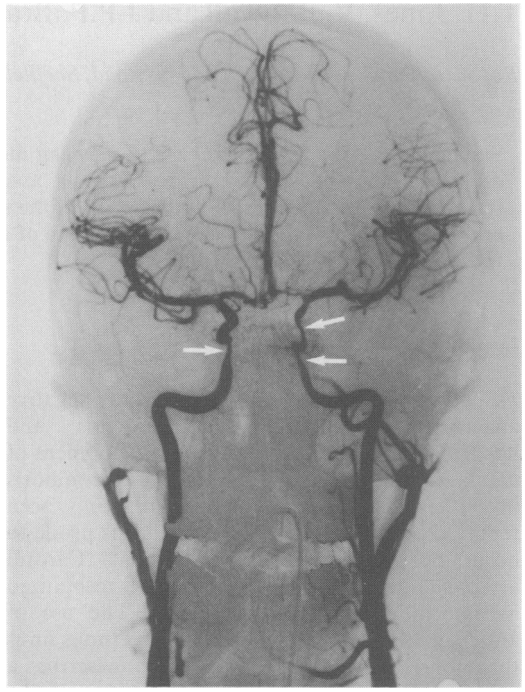

Figure 1 Bilateral carotid angiography 3 weeks after the onset of the illness. Simultaneous bi-carotid injection demonstrating marked constriction of the pre-cavernous parts of the carotid syphons (arrowed), most severe on the right side.

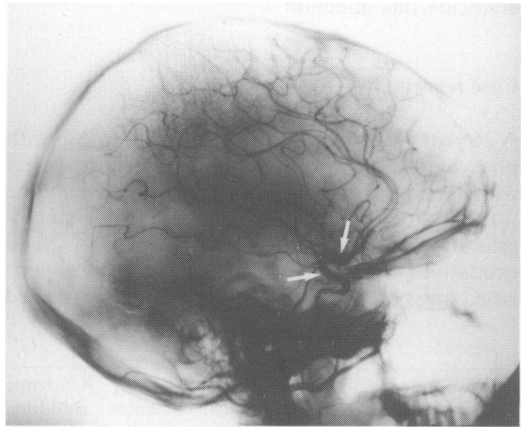

Figure 2 Right carotid syphon with filling defect indicating intravascular clotting (arrowed).

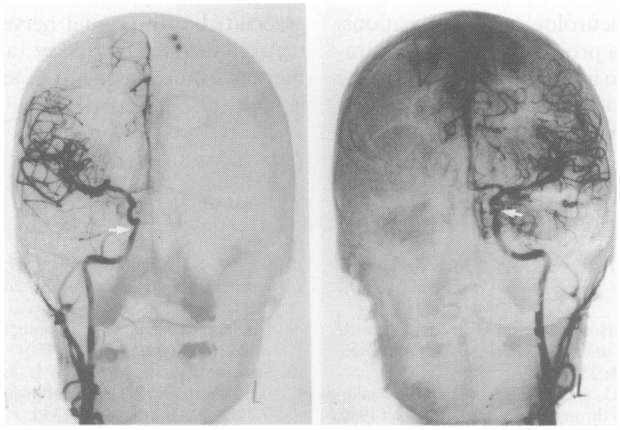

Figure 3 Bilateral carotid angiography 6 months after initial studies showing some resolution of the constrictions of the carotid syphons (arrowed). The remaining narrowing is more marked on the right side.

two occasions in relation to cavernous sinus thrombosis, one secondary to an anaerobic streptococcus[6] and the other *Aspergillus fumigatus*.[13] The narrowing of the carotid arteries, which is mainly confined to the region of the cavernous sinuses, most probably occurred as a result of inflammatory involvement of the artery wall. The presence of intraluminal clot emphasizes that in this group of patients there is a risk of thromboembolism. There is one case reported of a patient with cavernous sinus thrombosis, who developed a hemiparesis,[6] no angiography was carried out. After anticoagulation our patient did not develop any embolic events. Whether or not warfarin prevented further narrowing or helped with regression of the stenoses is difficult to assess. Clearly, however, this case does demonstrate that anticoagulation should be considered as part of the management of patients with cavernous sinus thrombosis in this type of infection. The role of anticoagulants in cavernous sinus thrombosis has not been fully assessed and as a result is controversial. Cavernous sinus thrombosis is rare and therefore management can only be based on experience of isolated cases. A review of Parsons and colleagues[7] suggests that there may be a risk of exacerbating haemorrhagic lesions in the brain with anticoagulation, although no such complication has definitely been reported in this group of patients. On the other hand, a more recent review of such patients treated with antiocoagulation concluded that although there was no reduction in mortality, there was a reduced morbidity, in particular from stroke, ophthalmoplegia, blindness, focal seizures, vascular steal syndrome and hypopituitarism.[8] The fusobacterium produces a coagulase enzyme encouraging clot formation which acts as a barrier to antibiotics. Use of anticoagulation may therefore, in addition to reducing the risk of embolic events, enhance the efficacy of the antibiotics. The demonstration of mural thrombi with the potential risk of embolism in this case, provides further evidence for anticoagulation in this group of patients.

This case also illustrates that the bacteriological diagnosis is difficult and delayed, a high proportion of blood and cerebrospinal fluid cultures being sterile.[14] It may be prudent, as in this case, to maintain cultures for an extended period of time. It is also important to note that though the cerebrospinal fluid may initially show a polymorphonuclear response this changed to a lymphocytic response during treatment.[4] The lymphocyte count becoming elevated on stopping metronidazole and resolving on its re-introduction is an interesting feature.

Metronidazole, intravenously, certainly is the drug of choice in this infection even though the organism was found to be sensitive to cefotaxime, chloramphenicol and erythromycin to which, even in combination, there was little clinical response. This finding is in agreement with previous reports.[12] Metronidazole achieves high levels in the cerebrospinal fluid and is bacteriocidal. There is a definite risk of relapse if metronidazole is stopped too early,[4] and we would advocate a treatment course of at least 5 to 6 weeks based on our experience. The response to therapy should be monitored by cerebrospinal fluid examination.

In conclusion, we have reported a case of *Fusobacterium necrophorum* meningitis in which the patient developed bilateral carotid artery stenosis with mural thrombi, associated with cavernous sinus thrombosis and cranial nerve palsies. Early anticoagulation should be contemplated in the presence of cavernous sinus thrombosis, provided there are no contraindications, to reduce the risk

of stroke and other neurological complications. The infection requires a prolonged course of intravenous metronidazole to be eradicated and response to treatment should be assessed by examination of the cerebrospinal fluid. In cases of meningitis associated with cranial nerve palsies intravenous metronidazole should be added to the initial therapy as the likelihood of an anaerobic infection is high.

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