

CAVERNOUS SINUS THROMBOPHLEBITIS*

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SEPTIC thrombosis of the cavernous sinus was first described with autopsy findings by Duncan (1821), and the classical description of the clinical signs was made by Bright (1831). Grove (1936), in a review of 400 cases, estimated that the mortality rate of the condition was practically 100 per cent., and Dixon (1926) remarked that reported recoveries were probably errors in diagnosis. With the development of chemotherapy and antibiotics, however, not only has this state of affairs greatly altered, but the condition itself seems to be becoming less frequent, since only four cases have been reported in Great Britain in the past 10 years (Young, 1946; McAllen and Shaw, 1952; Bennett, 1954; Haas, 1955). Of the three further papers published during this time, two refer to cases occurring before 1946 (Reid and McGuckin, 1956; Gregory, 1946), and one was written from Hungary (Miklós, 1950). The rarity of the condition to-day is presumably due to early treatment of facial sepsis with antibiotics. Even so, the death rate is still by no means negligible, and the ever increasing incidence of penicillin-resistant staphylococci, recently estimated at 37 per cent. for out-patients and 57 per cent. for in-patients (Fairbrother, 1956), will add to this. This paper presents two such cases in which the infection followed the development of a sty, one of which proved fatal.

Case Reports

Case 1, a woman aged 24^o, the mother of three children, was admitted to St. Thomas's Hospital on March 14, 1956; 4 days before admission she had complained of some irritation in the right eye without swelling or redness, and 2 days later there was an obvious sty on the lower lid near the inner canthus. Next day the eye was swollen and she was given 600,000 units of a long-acting form of penicillin by injection and 500,000 units in tablets by mouth. That evening she complained of headache. On the morning of the day of admission the eye was extremely swollen and she felt ill. It was thought that this might be an allergic reaction to penicillin and she was given 500 mg. tetracycline. At 2 p.m. the left eye began to swell, and her husband later described it as "going up as I watched". An hour later she was drowsy and disorientated, and on admission at 5 p.m. she was unconscious.

Examination.—She was comatose with marked meningism, and reacted only to painful stimuli by purposeless movements and a high-pitched cry. Temperature (axilla) 104.8° F., pulse irregular 92/min., respirations 18/min. (Fig. 1, opposite). There was severe bilateral proptosis and chemosis, the lids being so oedematous that it was only possible to force them apart by 1 or 2 mm., while between them the oedematous conjunctiva pouted forth. There were signs of a resolving sty on the right lower lid and the surrounding skin was hot and red. The oedema extended across the upper part of the face and temples, and there was a small oedematous area over each mastoid process. The pupils were only visible in part, but were central and reacted to light. No clear view of the fundi was obtained because of oedema and mistiness of the refracting media. The limbs were held in flexion; the tendon reflexes were present and equal and the plantar responses

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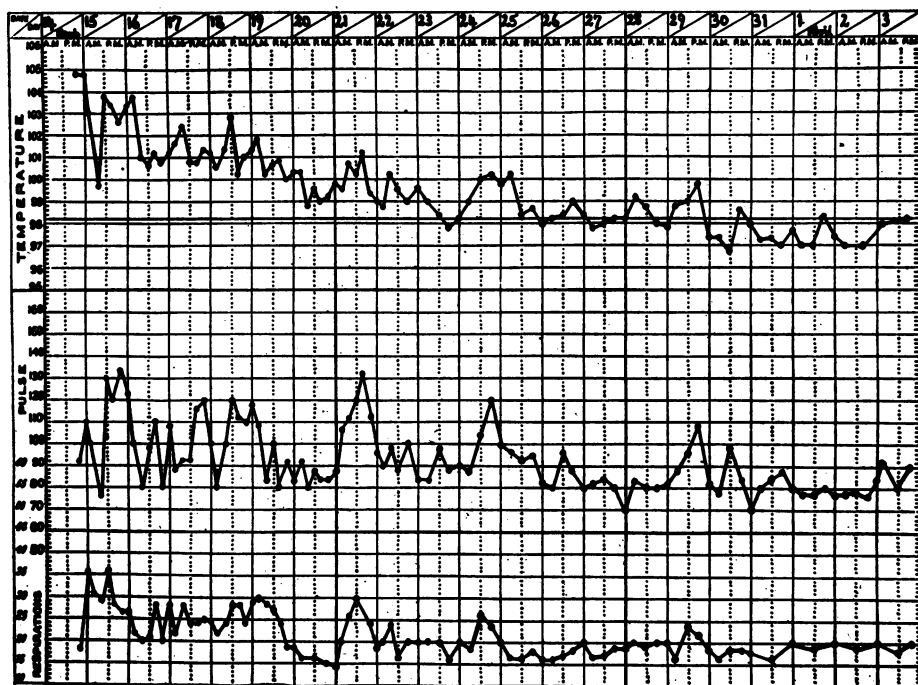


FIG. 1.—Case 1, temperature chart of the first 3 weeks.

flexor. Examination of other systems revealed no abnormality and the spleen was not palpable.

Laboratory Investigations.—Lumbar puncture: opalescent fluid under high pressure containing 4,000 cells/cu.mm., 95 per cent. polymorphs; protein 400 mg. per cent.; no organisms seen in a stained film, sterile on culture.

Haemoglobin 82 per cent.; Haldane (12.14 g. per cent.); white cells 14,100/cu.mm., 85 per cent. polymorphs.

Right conjunctival swab grew many coagulase-positive *Staph. aureus* sensitive to streptomycin, erythromycin, aureomycin, and chloramphenicol, but resistant to penicillin.

Left conjunctival swab: sterile.

Blood culture: *Staph. aureus* with characteristics similar to that isolated from the right eye.

Urine: protein ++, acetone ++, sugar —, many granular and hyaline casts but no cells, culture sterile.

Electrocardiogram: very marked sinus arrhythmia.

Treatment.—The immediate treatment was streptomycin 1 g. twice daily, penicillin 1 mega unit 2-hrly, and heparin 15,000 units subcutaneously 12-hrly. At the first lumbar puncture 20,000 units of penicillin were administered intrathecally. Some hours later, when the characteristics of the organism became known, she was given erythromycin suspension by nasal stomach tube 200 mg. 4-hrly. On the 7th day streptomycin was reduced to 1 g. daily, and on the 14th day streptomycin, penicillin, and heparin were discontinued. The erythromycin was continued until the 24th day, when the temperature had been normal for a week.

Local treatment to both eyes consisted of adrenaline solution (1/1000) and aureomycin cream (1 per cent.) 6-hrly until the 24th day, and atropine 1 per cent. drops daily from the 7th to the 12th day.

The high-potency vitamin preparation "Parentrovite" was injected on alternate days. Tubefeeding continued until the 12th day, the patient receiving 1,500 calories of protein, fat,

and carbohydrate in the form of "Complan", with a total fluid intake of about 3.5 l. daily.

Progress.—On the 2nd day the oedema had subsided enough to allow the lids to be parted, when it was seen that there was a complete bilateral internal and external ophthalmoplegia, but the mistiness of the media still prevented a clear view of the fundi. In other respects her condition was substantially unchanged and she remained unconscious until the 6th day, when she first began to obey simple commands and rubbed the site of an injection. There was no response to the flashing of a bright light into the opened eyes and it was feared that vision was lost. All the tendon reflexes were absent except at the ankles, and the plantar responses had become extensor; there was still considerable meningeal and cerebral irritation and at frequent intervals she would scream and throw herself around in the bed. At this time the proptosis and lid oedema was beginning to diminish on the right side (Fig. 2).



FIG. 2.—Case 1, one week after admission.

The pupils were dilated—even before the atropine, and were unequal, and inactive to light (Fig. 3).



FIG. 3.—Case 1, one week after admission.

The ophthalmoplegia continued and the corneal reflexes remained absent. The fundi were still not clearly visible, but on the 10th day the right one was seen to be normal.

The temperature became normal on the 17th day and, although the patient became more restless and noisy for a period, she regained full consciousness on the 20th day. By this time there was only slight proptosis and minimal chemosis of the right eye and she said that she could see a blurred image with it. The left eye however was still considerably swollen, haziness of the ocular media was still present, and there was no perception of light. The complete bilateral ophthalmoplegia was unchanged, but both corneal reflexes had returned. It was not until the 25th day that the left fundus was clearly seen and the appearances of primary optic atrophy noted.

After the temperature had been normal for 10 days the patient passed a moderate quantity of pus per rectum, and on examination was found to have a boggy mass in the recto-vaginal pouch which was slightly tender. Culture of the pus grew numerous Gram-negative bacilli and enterococci but no staphylococci. This abscess caused no further symptoms and rectal examination a month later was normal.

The proptosis and chemosis had cleared completely by the 6th week, but there was still considerable ptosis. By the time of her discharge from hospital this, too, had almost gone (Figs 4 and 5), although it was still more marked on the left. Seven weeks after the onset of the illness external ocular movements were seen for the first time. Starting as a flicker, upwards in the right and lateral in the left eye, these gradually increased in range and direction until at the time of discharge 6 weeks later they were almost full. Both eyes had normal lateral movements, but elevation and depression were still reduced, more so on the left side. The pupils remained fixed and unequal, larger on the right side. Visual acuity in the right eye was 6/12 correctable to 6/9 and N5, and the visual field was full, but the left eye remained amaurotic.

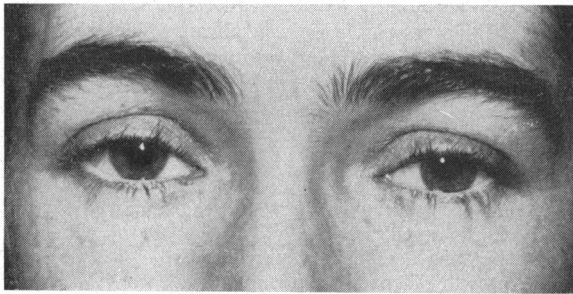


FIG. 4.—Case 1, 3 months after admission.



FIG. 5.—Case 1, 3 months after admission.

In the 9th week after admission, 3 days before she was due to leave hospital, she developed mild frontal headaches on waking, and the cerebrospinal fluid, which had contained only ten white cells/cu.mm. a month before, was found to contain 57 white cells, 70 per cent. being lymphocytes. Culture was again sterile. A few days later the headaches had become more severe and she developed signs suggesting a right cerebellar lesion. Serial electroencephalograms which had been taken since the 5th week of the illness had shown the gradual reappearance of a stable α -rhythm, and there was no change at this time. X-rays of skull and chest, a white cell count, and the erythrocyte sedimentation rate were normal. It was thought that a cerebellar abscess had developed, and she was given a week's course of oxytetracycline 500 mg. 6-hrly, when the headaches disappeared and the localizing signs gradually decreased. On discharge, on June 17, she was found to have, in addition to the eye signs described above, only a minimal inco-ordination of the right arm and leg and slightly increased reflexes in the left leg. The cerebrospinal fluid was perfectly normal, containing only one cell/cu.mm. and 15 mg. per cent. protein. When last seen, some 6 months later, she had remained well and all long tract signs had disappeared, although the pupils remained inactive and the left eye was blind. Her mental state was quite normal.

Case 2, a female infant, 2 weeks old, was admitted to St. Thomas's Hospital on February 20, 1956. After a full-term normal delivery she had been breast fed, and on discharge from the maternity hospital 3 days earlier she had been passed as a normal baby, but her mother stated that the child had had a "bad" eye for a week. The day before admission she had been seen in the hospital eye department when an early stye was noted in the upper lid, but there was no chemosis. Chloramphenicol ointment (1 per cent.) was applied three times daily. The next day the eye was more swollen, but the child remained reasonably well and was taking normal feeds until the evening, when she suddenly became comatose and was brought straight up to hospital.

Examination.—The child was comatose and limp. Temperature (axilla) 96.6° F., pulse 140/min., respirations 28/min. There was proptosis and chemosis of the left eye, and the upper lid had a discharging stye and was moderately oedematous. The right eye was normal. Both pupils reacted normally to light, but the fundi were not seen. There was a monilial infection of the mouth. Otherwise no abnormality was revealed except an enlarged spleen.

Laboratory Investigations.—Lumbar puncture: 210 cells/cu.mm., 51 per cent. polymorphs; protein 80 mg. per cent.; sterile on culture.

White cell count: 16,000/cu.mm., 88 per cent. polymorphs.

Blood culture: Heavy growth of coagulase-positive *Staph. aureus* sensitive to all antibiotics tested.

Treatment.—The immediate treatment was streptomycin 250 mg. twice daily and sulphadiazine 250 mg. 6-hrly; 2 days later she received in addition 5,000 units penicillin intrathecally and oxytetracycline 50 mg. 6-hrly. Local treatment to the eyes consisted of sulphacetamide drops (10 per cent.) 2-hrly.

Progress.—The day after admission she appeared to be better and was taking feeds well, but the temperature had risen to 100° F., and on the evening of the second day she had several left-sided epileptic fits. A second sample of cerebrospinal fluid proved sterile, and the fits were controlled with paraldehyde and phenobarbitone, but her condition steadily deteriorated and she died 2 days later.

Post-mortem Examination.—There was thrombophlebitis of the left cavernous sinus and considerable haemorrhage around the neighbourhood of the inferior saggital sinus which extended up the medial side of the hemispheres. The superior saggital and lateral sinuses were normal, but several cortical veins were thrombosed. Multiple areas of

softening, consistent with venous infarction, were seen throughout both hemispheres. There was no evidence of septicaemic spread in any other part of the body.

Discussion

It is important to distinguish between three varieties of cavernous sinus thrombosis since they arise in different ways and have substantially differing prognoses. Two main groups are clearly identifiable:

- (1) The aseptic or "marasmic" form, which may occur in the same types of case as does thrombosis in the veins of the limbs or pelvis;
- (2) The sinus thrombosis of septic origin.

A further distinction should be made in this latter group, between those cases in which the cavernous sinus thrombus is infected from the start either because the site of infection is adjacent to the sinus or because the thrombus arises by septic emboli, and those cases in which the thrombus in the cavernous plexus is initially free from bacteria, but is liable to develop infection later unless the original septic condition is overcome. It is in this last group, described by Cavenagh (1936) as a chronic compensatory form of the disease, that the great majority of recoveries were recorded before the days of antibiotics.

The second group comprises the acute forms of cavernous sinus thrombophlebitis which used to be almost universally fatal. Eagleton (1926) states that these "present little difficulty in diagnosis; they are early accompanied by chemosis and exophthalmos, first of one eye and then of the other, associated with profound pyaemia, and followed by death from sepsis or a complicating meningitis". In the present examples, there can be little doubt as to the diagnosis in the first case, for it followed this description accurately except for the outcome, and the second case was proved at *post mortem*. However, it is perhaps a sign of the times that, at an early stage, when the oedema was beginning to appear in the second eye, a tentative diagnosis was made in the first case of penicillin-sensitivity. A somewhat similar error was made in a child aged 3 by suspecting nephritic oedema following suppurative otitis media (Reid and McGuckin, 1946). The speed at which the condition progressed was remarkable; one can appreciate the force of the statement "death regularly follows from sepsis in 6 to 48 hours after the involvement of the second eye" (Smith, 1918).

The positive blood cultures obtained from both patients is a frequent finding, Eagleton (1926) citing evidence of blood-stream infection as one of the points upon which the diagnosis rests. On the other hand, the fact that in each case repeated cultures of the purulent cerebrospinal fluid proved to be sterile came as somewhat of a surprise. It appears, however, that this is the usual finding, although it has not been stressed before. Thus in 98 cases collected from the English and American literature since 1920, blood cultures were taken in only 62, but 43 of these (69 per cent.) proved to be positive,

and if one included a further twelve in whom there was evidence of metastatic abscess formation, despite one or more negative blood cultures, the proportion rises to 89 per cent. In only 37 were cerebrospinal-fluid cultures recorded, but 30 of these (81 per cent.) were sterile. Of 26 patients who had both fluids cultured, only two had positive results in both.

The site of infection was in both cases a simple sty. Although these are so common, they very rarely cause cavernous sinus thrombophlebitis. In the 98 cases mentioned above, the original infections were: furuncles of face 53 (nose 25, lip 9, forehead 7, eyebrow 5, cheek 4, chin 3); ear infection 14; sinusitis 13; dental sepsis 8; styes 3; tonsillitis 3; erysipelas 1; facial injuries 1; unstated 2.

One remarkable report deserves special mention: Barnshaw (1939) described a girl of seven who developed typical acute cavernous sinus thrombophlebitis with staphylococcal septicaemia following a sty and made an uninterrupted recovery with expectant treatment only.

The organism responsible in both cases recorded in this paper was *Staphylococcus aureus*. This was the organism found in 70 per cent. of the series described by Shaw (1952). In the 98 cases mentioned above, an organism was isolated in 73: *Staph. aureus* in 67 (92 per cent.), *Strept. pyogenes* in four (5 per cent.), pneumococcus in one (1 per cent.), and *Staph. albus* in one (1 per cent.). In view of the rising incidence of penicillin-resistant staphylococci, it is not surprising that cases have been reported due to such organisms (McAllen and Shaw, 1952; Haas, 1955). Both these patients gave cause for considerable anxiety during the course of their illness, and one died later from a cerebral abscess 3 months after an apparently full recovery. In addition, at least five patients have been reported to have died despite penicillin. Three had staphylococcal infections (Abraham, Gardner, Chain, Heatley, Fletcher, and Jennings, 1941; Wolfe and Gain, 1945), and in one the organism was not determined (Fox and West, 1947). In the third a haemolytic streptococcus was grown from nasal discharge (Bennett, 1954), but since treatment was ineffective despite being started comparatively early and this organism is so rarely penicillin-resistant, it is conceivable that a penicillin-resistant staphylococcus was also present.

Such observations suggest that in dealing with a case of acute cavernous sinus thrombophlebitis, one ought not to rely on penicillin alone until the results of bacteriological investigations become known, a matter of at least 12 hours, but should give in addition a broad-spectrum antibiotic as soon as specimens have been taken for culture.

Although heparin was administered in the first case, there is as yet no general agreement on the value of anticoagulant drugs in the treatment of this condition. Lyons (1941) was the first to employ heparin, and it has been given since in several cases. The natural history of the condition, with its progressive thrombophlebitis, would suggest that treatment aimed at preventing further extension of the clot would be of value. On the other

hand, some authors have not used heparin because they consider that the thrombus acts as a protective barrier (Reid and McGuckin, 1946). Such an argument should not be accepted without criticism, since untreated cases usually progress towards a fatal termination with metastatic abscess formation. The thrombus is surely the essential feature of the disease, and one of the criteria of pathogenic staphylococci is that they produce coagulase; moreover, a blood-clot is renowned for the ease with which it becomes infected and for its excellence as a nutritive medium for bacterial growth. As for the suggestion that anticoagulants would encourage wide dissemination of the pathogen, one must remember that, when antibiotics are used, a bacteraemia is less hazardous to life than multiple septic infarcts, which are almost invariably found *post mortem* in fatal cases (Dixon, 1926). Another point was raised by Shaw (1952), who suggested that anticoagulants will give the antibiotic better access to the organisms.

Despite such arguments it is difficult to assess the practical value of anticoagulants in the treatment of the disease, since the past 15 years have also seen the development of antibiotics. It seems, however, that about half the cases treated with sulphonamides or antibiotics as well as anticoagulants have shown evidence of septic emboli, and while a similar proportion of complications has been found in those treated without anticoagulants, several of these died. In the second case described in this paper, when no anticoagulant was used, there was at *post mortem* no sign of active sepsis, but there were multiple cerebral infarcts caused by extension of the thrombosis. On balance then, there does not appear to be any good reason why anticoagulants should not be used, and on general principles they appear to be fully justified.

In the series of 98 cases taken from the literature, eight were treated with antibiotics and anticoagulants with only one death, and that occurred from a cerebral abscess 3 months after apparent full recovery; eighteen cases were treated with antibiotics alone, of which five died in the acute illness. These figures are not conclusive as the recent introduction of anticoagulant therapy might cause a higher proportion of cures by this means to be reported.

The mechanism of the ophthalmoplegia usually found in one or both eyes at the height of the illness, and which in a few cases may only partially resolve, is largely a matter of speculation. Smith (1918) considered that the cause was involvement of the nerves within the cavernous sinus, and stated that the third nerve was most frequently implicated, but that sixth nerve palsies were also often seen, while neuralgic pain might occur in the distribution of the ophthalmic division of the fifth nerve. In the more acute cases he considered that the rising intra-orbital pressure might cause displacement and fixation of the globe and its muscles before any distinct nerve palsies could be recognized. *Post-mortem* reports have been of little assistance, since most record only macroscopic findings. Walsh (1937),

however, reported microscopic findings in six patients. In every case infection of the orbital tissues was found with inflammatory cell infiltration of the muscles; in one case the nerves of one cavernous sinus were invaded with inflammatory cells, and similar changes were seen in the gasserian ganglion in another. In the first patient described above, the return of ocular movements was long delayed as compared with cases recorded in the literature, in which a few days to a week or two seems to be the rule. In our case this took 7 weeks, and although after a further 3 months the external ocular movements are nearly full, the pupils remain inactive. In most recorded cases the pupillary responses were never lost.

Out of the sixty cases which recovered in the above series of 98, blindness in both eyes was the sequel in only one, and blindness in one eye in three. No satisfactory explanation has been suggested for the site or nature of the lesion, or why it should occur in only a few patients. In the present case, disturbance of the refracting media, preventing a clear view of the fundi, persisted in the left eye until the 25th day, when optic atrophy was clearly developing, the original stye having been on the right side. Such a marked disturbance of ocular media has not previously been recorded. Although one might expect to see thrombosis of the retinal veins in cavernous sinus thrombosis, this does not usually occur. One report (Bennett, 1954) records, however, that a few hours before death in the acute illness there were "choked discs and enormous thrombosis of all visible retinal veins". Papilloedema has been reported in a few patients, but the usual description is one of venous congestion with some blurring of the disc. Nicholson and Anderson (1944) reported detailed ophthalmoscopical findings in one patient who developed optic atrophy in the right eye; at the height of the illness the veins were engorged and the arteries were collapsed with extensive sheathing, the disc was moderately swollen, and there was diffuse retinal oedema; 2 months later there was marked optic atrophy. They considered that there had been an inflammatory reaction in the arterial walls, possibly spreading from the cavernous sinus along the arterial wall by direct extension. One suggestion made about the present case was that there might have been an acute glaucoma during the first week of the illness, but the shape of the disc does not support this view. There remain then two possible causes, a "toxic neuritis" of the optic nerve caused by the adjacent purulent inflammation, or an inflammatory arteritis. Histological study of *post mortem* material might give the answer, but opportunities are now exceedingly rare.

A cerebral abscess as a complication or *post mortem* finding is well recognized, being reported in seven out of the series of 98 cases; in five of these it did not appear for from 3 to 6 months after apparent recovery (Lewis, 1934; MacAllen and Shaw, 1952; MacNeal, Frisby, and Blevins, 1941; Wolfe and Gain, 1945). Although the frontal or temporal lobes provide the commoner sites, two cases have been reported of cerebellar abscesses: one on the surface of an hemisphere, the second deep in the midline. In

the first case presented here there was no proof that a cerebellar abscess was present, and, in view of the apparent recovery, the lesion might possibly have been a thrombosis or thrombophlebitis of the veins on the right cerebellar hemisphere.

Summary

(1) Two cases are described of cavernous sinus thrombophlebitis; each arose from a styte, the causative organism being *Staph. aureus*.

(2) In the first patient the complications included meningitis, septicaemia, an abscess in the pouch of Douglas, and possibly a cerebellar abscess. The second patient, an infant of 2 weeks, died.

(3) The diagnosis, treatment, and complications are discussed with reference to the literature.

(4) It is concluded that, in the present state of knowledge, initial treatment should consist of penicillin, a broad-spectrum antibiotic, and anticoagulants.

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