ACTINOMYCOSIS OF THE BRAIN

BY

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THE following case of actinomycosis of the brain is described since it presents several interesting features, particularly the involvement of the sphenoid bone, a rare occurrence according to the literature, and the spread of the disease to the venous sinuses. The literature has been examined from these aspects and a summary added of cases of actinomycosis of the brain reported in the ten years following the extensive reviews of the subject by Friedman and Levy (1938) and Cope (1938).

Case Report

A corporal, aged 31 years, was first admitted to hospital on June 30, 1944, complaining of sudden onset of headache nine days previously, with fever for the last five. The only past illness was an attack of malaria in 1930. He looked ill, but nothing abnormal was found on clinical examination; there were 6,000 white blood cells per c.mm. of blood, and the sedimentation rate was 50 mm. in the first hour. He remained in hospital for a month, the symptoms persisting, and all investigations, including blood cultures and smears, sputum examination, lumbar puncture, blood Kahn, and radiographs of chest and sinuses proved negative. The only change noted on clinical examination was the development of a complete right sixth cranial nerve palsy on July 20.

The patient came under the authors' observation on July 28, when he was transferred to a neurosurgical unit for further investigation. Then he looked pale and ill, with temperature 100° F. and pulse 88 per minute. The headache was severe, mainly felt as a throbbing pain over the left side of the head; there was marked neck rigidity, but Kernig's sign was negative. Hirsuties over the body was very noticeable and he had obviously lost weight recently. Examination of the nervous system showed the right sixth nerve palsy, a little weakness of the left arm and left hip, and doubtful diminution of the lower left abdominal reflexes. All other systems were normal, and a full examination of the ears, nose, and throat, carried out by Lieut.-Col. R. B. Lumsden, R.A.M.C., was negative. A lumbar puncture showed a cerebrospinal fluid pressure of 110 mm. Queckenstedt responses were normal, protein 40 mg. per 100 c.cm., there were no cells, the Wassermann reaction was negative, and the Lange reaction 0000000000. A full

x-ray study of the skull and cervical spine was normal; the sedimentation rate was now 100 mm. in the first hour, and the white blood count 11,000 per c.mm. of blood (81 per cent. polymorphs).

The fever continued rising to 102° F. in the evenings, and on Aug. 2 fresh signs of a partial right third nerve palsy developed. A course of sulphadiazine was begun on Aug. 6, after a further examination had revealed nothing new apart from a slight diminution of the reflexes in the left arm and leg. That same evening a complete left sixth nerve palsy developed. On Aug. 7 the patient complained of some tenderness in the right side of the neck and it was noted that the trachea was displaced a little to the left: on Aug. 10 he had pain in his right chest and a pleural rub was heard in the right axilla. By now the third nerve palsy had improved a little but the neck was held very stiffly and the patient was afraid to move it at all; the upper part of the right posterior triangle of the neck was swollen and tender, and it was thought that a hard mass could be felt beneath and behind the sternomastoid. Further radiographs of the chest and cervical spine were negative, as was another ear, nose, and throat examination.

On Aug. 17 the neck was examined under general anaesthesia. Nothing abnormal was felt, the supposed mass being presumably due to muscle spasm. A 3-inch incision was then made along the posterior border of the sternomastoid extending down from the mastoid tip; exploration in all directions and down to the transverse processes revealed no abnormality and the wound was closed. Sulphadiazine was now discontinued, after the patient had had 113 g. without effect on the condition apart from some lowering of the temperature. A blood transfusion of three pints was given on Aug. 27. At this stage, therefore, no definite diagnosis had been reached; the clinical picture suggested an infiltrating lesion at the base of the skull, but whether infective or possibly neoplastic from a small primary in the nasopharynx could not be determined.

At the beginning of September an attack of amoebic dysentery declared itself, for which the patient received a course of emetine. It was interesting to observe that, in addition to its local effect, the emetine seemed to improve the patient's general condition, his neck becoming less stiff and his temperature subsiding.

The signs in the central nervous system remained unchanged, and on Sept. 26 ventriculography was

performed. The cerebrospinal fluid from the right ventricle was slightly blood-stained (protein 40 mg. per 100 c.cm., red blood cells 6,240 per c.mm., white blood cells (lymphocytes) 3 per c.mm.; the fluid from the left showed 20 mg. protein per 100 c.mm. and white blood cells (lymphocytes) 4 per c.mm. The ventriculograms were normal, but it was seen that compared with the radiographs of seven weeks previously there was now destruction of the posterior clinoid processes, erosion of the dorsum sellæ, and opacity of the sphenoidal sinuses.

A few days later a mass began to develop beneath the previous operative scar in the neck, and by Oct. 13 it was obviously fluctuant. Aspiration yielded 25 c.cm. of thick, creamy, offensive pus which on full bacteriological examination showed Gram-positive cocci and short Gram-positive bacilli in the films, and non-hæmolytic *Staphylococcus aureus* on culture aerobically and anaerobically. The blood sedimentation rate had risen to 144 mm. per hour; the white blood count was 8,800 per c.mm. A diagnosis of osteomyelitis of the base of the skull secondary to sphenoidal sinus infection was made, and on Oct. 21 a sphenoidal canula was passed into each sinus. The left return was clear, but opalescent fluid was obtained from the right side which on culture grew *B. subtilis* and a non-hæmolytic streptococcus. This latter organism, and the staphylococcus grown from the neck abscess, were both penicillin-sensitive, and an intramuscular course of 1,320,000 units of penicillin was given from Oct. 23 to Nov. 3. After this treatment, washings from the sphenoidal sinus grew *B. coli* only: the neck had become less rigid, no mass could be felt, and the scar was sound. A further blood transfusion of two pints was given.

On Nov. 8, the patient suddenly developed a series of generalized epileptic fits which were controlled by phenobarbital. An intracranial abscess was suspected and the ventriculogram repeated. The right ventricle was not found, but the left was entered easily and a radiograph showed it to be normal in size and position. The cerebrospinal fluid from this side showed a raised protein of 70 mg. per 100 c.cm., red blood cells 675 per c.mm., and white blood cells 15 per c.mm. (88 per cent. lymphocytes, 12 per cent. polymorphs). Over the next few days the patient's condition deteriorated; he became mute, and the left-sided weakness progressed to a complete hemiplegia with bilateral papilloedema. He died on Dec. 5, just over five months after the onset of symptoms.

Eight lumbar punctures were performed during his illness and, with the exception of the last cerebrospinal fluid, all had normal protein, cell, and chloride contents; the Queckenstedt responses were normal, and the cerebrospinal fluid pressures within normal limits. The last puncture, done on Nov. 25, showed a cerebrospinal fluid pressure of 300 mm. with 80 mg. per 100 c.cm. protein, 10 lymphocytes per c.mm., chlorides 800 mg. per 100 c.cm., and normal sugar.

AUTOPSY

Head.—The posterior third of the superior longitudinal sinus was distended and occluded by a soft, purulent thrombus, extending to the torcular Herophili and

continued into the right lateral sinus, where the periphery of the clot was undergoing organization, though bearing signs of previous infection. This clot ultimately merged into a thick white cord of fibrous tissue, filling the right sigmoid sinus without adhering to its walls, and reaching as far as the jugular bulb. The right superior petrosal sinus was similarly occluded by organized thrombus; the right inferior petrosal and straight sinuses, and the sinuses on the left side were healthy.

The pituitary gland was embedded in a mass of fibrous tissue riddled with tiny yellow spots and obliterating the right cavernous sinus. When this was stripped away, the floor of the sella turcica was seen to be severely eroded, with a worm-eaten appearance, and in the centre of the floor was a rounded pit 8 mm. in diameter and 8 mm. in depth, oozing with thin greenish-yellow pus. This hole did not communicate visibly with the naso-pharynx or sphenoidal air-sinus. The posterior clinoid processes were eaten away completely, and the whole basi-sphenoid bone was bright red and roughened with osteomyelitis, thin pus welling up through the lacunæ to its upper surface (Fig. 1, p. 166). The ethmoidal and sphenoidal air-spaces contained a little muco-pus; the frontal sinuses and maxillary antra were clear: the middle ears and mastoid processes were normal.

Yellow nodules similar to those around the pituitary were present in the soft tissues surrounding the right atlanto-occipital joint, and extended into the right hypoglossal canal. The right atlanto-occipital joint showed signs of previous infective arthritis, with thickening and opacity of the synovial layer. It was not possible to trace any visible connexion between these lesions and the nasopharynx, nor to demonstrate a primary focus in the nasopharynx or buccal cavity.

The dura mater was densely adherent over the parietal occipital aspect of the right cerebral hemisphere, and beneath it lay a subacute subdural empyema, loculated by adhesions. After the slimy greenish-yellow pus was washed away, numerous broad and deep pressure-indentations up to 15 mm. in depth were observed in the cortex. The pus extended down into the right Sylvian fissure and the under-surface of the right frontal lobe and uncinatæ fissure. The pons was flattened by intracranial pressure, but the anterior surface of the brain stem was not grossly infected. The cerebral convolutions on the left side were markedly flattened by pressure.

The whole of the right temporal lobe was bulkier than the left, and the posterior part of its under-surface was gummed to the tentorium cerebelli. On this being stripped away, a broad yellow area was revealed, midway between the temporal and occipital poles, and extending from the right crus laterally for 6 cm. Section of the brain showed this yellow plaque to be the inferior wall of a subdural abscess 12 mm. in depth, of fairly recent origin, and more acute than the subdural empyema. The white matter of the adjoining right temporal lobe was grossly swollen by oedema, causing medial displacement and undue exposure of the right hippocampus, while the cavity of the inferior ventricular horn was reduced to a mere slit (Fig. 2, p. 166). There was no evidence of ventriculitis, however, and the rest of the ventricular system was normal in appearance.

HISTOLOGY

Right cavernous sinus.—The blood spaces were replaced by a mass of granulation tissue, in parts breaking down into small abscesses. In the centre of some of these were colonies of *S. actinomyces* (Fig. 3, p. 167). The wall of the carotid artery at this level was intact.

Right temporal lobe.—The abscess lay between the surface of the cortical grey matter and the pia-arachnoid; in the pus lining its walls were colonies of *S. actinomyces* (Fig. 4).

BACTERIOLOGY.—Direct smears of the subdural pus showed a rich mixed flora—streptococci in chains, staphylococci, gram-negative diplobacilli, diphtheroids, and scanty fine filaments with metachromatic granules. On culture, *Staphylococcus aureus* and hæmolytic streptococci were grown aerobically, coliform bacilli and diphtheroids anaerobically. Culture on Saboraud's medium yielded a growth of long branching gram-positive filaments, morphologically *S. actinomyces*.

Thorax.—The heart was normal. The right lung contained several small abscesses, of a fairly chronic nature. In each lung were scattered a few smooth-walled cysts, apparently of congenital origin.

HISTOLOGY.—Some of the lung abscesses were acute, associated with hæmorrhage, and obviously embolic in origin; the more recent, on gram-staining, showed a mixed bacterial flora. Others however, were surrounded by granulation tissue, or even dense fibrosis with numerous giant cells, and were weeks or months old. In one of these a colony of *S. actinomyces* was found (Fig. 5).

Abdomen.—The spleen was enlarged and congested. The colon contained a few amœbic ulcers. The other organs were normal.

SUMMARY AND DIAGNOSIS

The chronicity of the lesions suggests that the infection was actinomycotic from the outset. After infection of the basisphenoid bone, spread occurred to the soft tissues around the sella turcica, with involvement of the right cavernous sinus, progressive thrombosis along the superior petrosal and right lateral sinuses, and recurrent metastatic abscesses of the lungs. Infection of the meninges resulted in a subdural empyema and subpial abscess. The congenital cysts of the lungs and the amœbic dysentery were coincidental lesions.

Comment

This case illustrates several clinical characteristics of actinomycosis. The long course of the disease, the temporary improvements with actual remission of clinical signs in the nervous system, is well exemplified here as is the difficulty of diagnosis and of isolating the causal agent even when suspected, the picture being apparently dominated by the secondary pyogenic invaders which are mainly responsible for toxicity of the disease process.

The spread of the infection from the basisphenoid to the atlanto-occipital joint accounted for the

pronounced neck symptoms and signs, and a septic embolism to the lung was responsible for the attack of pleuritic pain. The marked signs in the central nervous system which developed in the last days were presumably due to the extension of the subdural empyema. The findings on lumbar puncture were very interesting: despite the extensive intracranial infection the spinal fluid remained normal in all respects, with the exception of the last examination ten days before death, which showed only a slight increase of protein and cells. It should also be noted that the Queckenstedt response on the right side remained normal despite the presence of organized thrombus in the transverse sinus on that side: the absence of adhesions between the thrombus and the sinus wall, however, suggests that occlusion to blood-flow was not complete.

The marked changes in the sphenoid bone and the venous sinuses require further comment.

The sphenoid bone may be secondarily eroded as a result of intracranial invasion of actinomycosis from neighbouring structures such as the jaws, but primary infection of the bone is rare, and reports of only three previous cases could be found in the literature. Beevor and Buzzard (1903), Stevenson and Adair-Dighton (1911), and Kramer and Som (1935), each described a case of extensive osteomyelitis of the bone with meningitis and changes in the cerebrospinal fluid. Kramer and Som's case was similar to the one reported here in that a sphenoid infection had been diagnosed during life, but *S. actinomyces* was not detected in the sphenoidal washings, and at autopsy no obvious communication could be traced between the meninges and the sinus. In their case, however, serial sections demonstrated a sub-epithelial actinomycotic abscess in the wall of the left sphenoid sinus and colonies in the marrow spaces of the bone and in the thickened dura covering the basisphenoid. No other focus was found in the buccal cavity or nasopharynx of these cases; and they, together with the one described here, are considered primary sphenoid infections. This does not exclude the possibility that there may have been a focus elsewhere in this region at a previous date, since, as pointed out several times before, the spread of actinomycosis is characterized by healing of the track behind the advancing lesion.

The involvement of the intracranial venous sinuses was an important feature of the case reported here. The predilection of actinomycosis for the region of the sella turcica, whether by direct extension or metastasis, is well known, and several case reports draw attention to collections of pus or granulomatous masses around the pituitary region, and some to abscesses within the gland itself. The descriptions

FIG. 1 (left). Osteomyelitis of basisphenoid. Note the extensive erosion and the organized thrombus in the right lateral sinus.

FIG. 2 (above).—(left).—Right temporal sub-pial abscess with surrounding oedema.

FIG. 3 (top left).—Section through the right cavernous sinus. The carotid artery is cut longitudinally. The arrow marks a colony of *S. actinomyces* lying within a small abscess, x 30.

FIG. 4 (top right).—*S. actinomyces* in wall of sub-pial abscess, x 140.

FIG. 5 (lower left).—Embolus in right lung. Note the chronic inflammatory thickening of the abscess wall, x 30.

would suggest that the cavernous sinus was involved in several instances, but thrombosis of the venous sinuses has received scant attention in the literature, only six references to this complication being found.

In Ponfick's (1882) second case, the cavernous sinus was filled with pus and the left transverse sinus occupied by a gelatinous mass which was continued through the bulb into the left jugular vein with thrombosis of adjacent neck veins. Moosbrugger (1886) described the findings in a man of 27 whose primary focus was in the upper jaw: at autopsy the right transverse sinus contained a whitish purulent clot. Horn (1913) described a very unusual case of an otitis media due to actinomycosis. His patient developed meningitis and signs of a cavernous sinus thrombosis. A right mastoid exploration was done and the sigmoid sinus found filled with yellow debris; the thrombosis extended backwards to the region of the torcular and down into the internal jugular vein which, at the operation, was ligated just above the clavicle and excised. At autopsy there was a purulent meningitis, pus in both orbits, and septic thrombosis of the right sigmoid sinus and jugular vein, both transverse sinuses, the posterior part of the longitudinal sinus, and both cavernous sinuses. Bell's (1922) patient had an acute meningitis with death in fourteen days: at autopsy a basal meningitis was found, the pituitary surrounded by pus and both cavernous sinuses filled with pus from which the fungus was grown. The case described by Friedman and Levy (1937) had yellow pus in the left cavernous sinus and coagulated bloody material in the longitudinal sinus; the tissues around the pituitary were softened and four abscesses were found in the anterior lobe of the gland. Gonzalez Torres (1939) re-examined a museum specimen with meningitis and a mass of actinomycotic granulation tissue in the left middle fossa involving the Gasserian ganglion and the pons; there were extensive thromboses of the venous sinuses including the superior longitudinal sinus and the left sigmoid sinus.

Bearing in mind the chronic nature of the infection, the cavernous sinus may be thrombosed without producing the classical signs of this complication—collateral channels can be used or only a partial thrombosis of the sinus occur as in this case. The discrete abscesses in the pituitary gland described in some cases may have followed retrograde thrombosis from the cavernous sinus. In this connexion it may be observed that in Turner and Reynolds' (1931) study of 21 cases of septic thrombosis of the cavernous sinus due to the common pyogenic bacteria, secondary involvement of the pituitary gland was found in four.

Not only may these thromboses be an important factor in the intracranial spread of the infection, but actinomycotic metastatic abscesses in the lungs may arise. They were present in the case reported here, and in the case described by Bell (1922). Multiple lung abscesses were also found in Kramer and Som's case although only gram-positive cocci were seen in the sections, and actinomycotic pulmonary abscesses were present in the case reported by MacFee (1932), where a basal meningitis followed actinomycosis of the jaw. No mention is made in these latter two cases of the condition of the venous sinuses, but the lung abscesses were presumably due to venous embolism.

Summary of the Literature

Extensive reviews of the literature of actinomycosis of the nervous system up to 1937 have been made by Friedman and Levy (1937), who found 108 cases recorded and listed seventy-six references, and by Cope (1938), who gave eighty-five special references and two additional ones in his general list, and divided them as far as possible according to the mode of invasion. Five additional references to cases recorded over this period, which do not appear in the lists of these authors, may be added. The case described by Beevor and Buzzard (1903) has already been mentioned: Letulle and others (1911) recorded a case of pleuro-pulmonary actinomycosis with a cerebral abscess which ruptured into the ventricle; Belkowsky (1911) a case of chronic pachymeningitis giving rise to several abscesses in the neck and diabetes insipidus; Topley (1912) a basal meningitis with multiple cerebral abscesses following a primary focus in the abdomen—probably the appendix; and Klemmer's (1923) second case was that of a young man with actinomycosis of the lung who over a period of eight years developed several metastases and finally succumbed to a cerebral abscess.

Over the last ten years, reports of twelve further cases have been found and are included in the following summary of the modes of invasion of the nervous system by the fungus. This may occur by one of three routes.

Primary.—With increasing knowledge of the disease it is apparent that several of the so-called primary cases hitherto reported were secondary to foci elsewhere in the body, the original lesion healing completely, or being discoverable only after diligent search. Although some authors deny that the infection can ever be primary in the nervous system, there is a small group of cases which can be classified as such. Cope (1938) drew attention to six cases in the literature where a so-called actinomycoma was discovered in the region of the third

ventricle, no other focus being found. Since then Orr (1945) has added one further case to this group. Macroscopically the appearance is that of a gelatinous tumour-like mass, firm in consistency, varying in size up to about one inch in diameter, situated in the third ventricle. It is clearly defined from the surrounding tissues and, as in Orr's case, may be pedunculated and produce the syndrome of intermittent obstruction usually associated with colloid cysts of that region. Microscopically, mycelial strands are recognized within degenerate cell masses lying in a gelatinous matrix. It is suggested that the portal of entry may be via the perineural spaces of the olfactory nerves.

Direct extension.—The disease may spread by extension from neighbouring parts from lesions in the paranasal sinuses, ear, pharynx, face, and jaws, and give rise to a basal meningitis which may be associated with cortical abscesses. The spread is usually along connective-tissue planes, entrance to the cranial fossæ being gained through the various foraminæ. There are, however, cases on record where undoubtedly direct spread through the bone has occurred, as in the case reported here. Friedman and Levy (1937) found twenty-three cases on record of spread by direct extension. Since that date Eckoff (1941) has described two cases of direct extension from the jaws. Harley and Wedding (1946) reported a remarkable case of a young soldier aged 19 years who had chronic sinusitis and developed a bilateral uveitis associated with alopecia, poliosis, and dysacusia, an unusual but previously described syndrome. In addition, he had symptoms of meningoencephalitis with a mild lymphocytic reaction in the cerebrospinal fluid. *S. actinomyces* was recovered from the spinal fluid and the aqueous humour.

Metastatic.—Most commonly the disease reaches the cranium through the blood stream from other foci in the body, particularly the lungs, and gives rise to cerebral abscesses, or meningitis (again usually basal), or both. Of the 108 cases of actinomycosis of the nervous system which they collected from the literature, Friedman and Levy ascribed sixty-two to this group.

Eight more cases belonging to this group have been reported in the last ten years. Zeitlin and Lichtenstein (1937) have recorded a case of basal meningitis and frontal abscesses (one of which had ruptured into the ventricle) from a lung primary; Morrison and others (1938) described a ventriculitis and basal meningitis following primary actinomycosis of a finger, a small abscess in the right lung being found at autopsy; and Burgstein (1940) a case of meningitis secondary to a lung lesion. Kulkov

(1942) reported a left subdural empyema in a young woman which followed a primary lesion in the cheek and numerous sinuses over the body, an area of consolidation of the right upper lung being disclosed at autopsy; and Kasten (1945) described a case of basal meningitis and multiple frontal lobe abscesses following a lung primary, there being an additional lesion in the left kidney, the symptoms of which first brought the patient under observation.

Gonzalez Torres (1939) has made a histopathological study of two museum specimens of cerebral actinomycosis, one with cerebral abscesses and the other a granuloma of the middle fossa involving the left Gasserian ganglion and the pons with meningitis; the origin of the infection in these two cases was not stated. Similarly Aranovich (1942) reported an embolic hæmorrhagic meningoencephalitis but the post-mortem was limited to the head.

Summary

1. A case of actinomycosis of the sphenoid bone with involvement of the intracranial venous sinuses and development of a subdural empyema, subpial abscesses, and embolic abscesses in the lungs is described.

2. Three previous cases of sphenoid osteomyelitis have been recorded, and six autopsy reports describing involvement of the intracranial venous sinuses in actinomycosis of the nervous system have been found in the literature.

3. The ways in which actinomycosis may spread intracranially are summarized, and references to twelve fresh cases reported over the last ten years are added.

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