Granulomatous meningitis and diffuse parenchymatous degeneration of the nervous system due to an intracranial epidermoid cyst

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This single case report, with detailed clinical and pathological findings, is presented since, to the best of our knowledge, no such syndrome has previously been described. This case showed diffuse degenerative changes in the central nervous system resulting, we believe, from the dissemination throughout the subarachnoid space of the degradative products of an intracranial epidermoid cyst.

CASE HISTORY

N. T., a carpenter born on 29 April 1918, was first seen in consultation with Dr. S. M. Garston on 22 December 1958 when his complaints were of clumsiness of the right hand and recent shortness of breath. Since the age of 16 years he had had occasional major epileptic fits which had been well controlled by treatment with phenobarbitone and phenytoin which he had taken regularly for 20 years. In June 1952 he underwent a partial gastrectomy for peptic ulcer. He made a good recovery and continued to work regularly until December 1958. He was a heavy smoker who showed signs and symptoms of chronic bronchitis and emphysema. He was obese and plethoric, showed early masking of the facies, and an action-type tremor of the right hand. It was felt that he might be suffering from early Parkinsonism but the picture was not typical and he was admitted to the Chester-le-Street General Hospital for further investigation.

On admission, examination confirmed that he was intellectually normal and that he was obese and plethoric and had a hoarse voice. He had an action tremor of both upper limbs, but this was more severe on the right side and there was some accentuation towards the end of movement suggesting early cerebellar disease. He was seen by an ear, nose and throat consultant who found him to have paresis of the left vocal cord suggesting a partial left recurrent laryngeal nerve palsy. The only other neurological abnormality of note was that he had absent reflexes in the lower limbs. Although a chest radiograph was negative apart from a calcified right apical lesion, as were bronchoscopy and sputum cytology, it was felt that he probably had a bronchogenic carcinoma giving rise to a left recurrent laryngeal nerve palsy and to a carcinomatous neuropathy with early cerebellar degeneration. The cerebrospinal fluid showed no pleocytosis but its protein content was 130 mg./100 ml. As no resectable neoplasm in the lung was demonstrated, a course of radiotherapy was given to the mediastinum.

When seen again in March 1959 the patient’s voice was still hoarse but his chest seemed much improved. The shaking of both arms was now worse than it had been and at this stage the patient remarked that both of his parents had shaking of the limbs late in life. He also commented that his own tremor was frequently relieved by alcohol. Hence, despite the mask-like face suggestive of Parkinsonism, it was considered that he might have benign familial tremor. However, evidence of early bilateral cerebellar ataxia was still present. He was treated empirically with benzhexol. In August 1959 he returned complaining of pain in the right arm and forearm and said that the tremor in both hands was becoming much worse. He was therefore admitted to the Newcastle General Hospital. On admission he was still obese and plethoric and had a troublesome productive cough. There was no change in the neurological signs. The upper limbs showed no poverty of associated movements and there was no wasting, weakness, or sensory loss in the arms or legs. Radiographs of the chest were unchanged and radiographs of the skull showed that the sella turcica was within normal limits while the dorsum sellae and posterior clinoid processes appeared to be intact. No pathological intracranial calcification could be detected and there was no bone change in the vault or base of skull. The cerebrospinal fluid was re-examined. The fluid was under normal pressure and was slightly hazy; it contained 32 cells/c.mm. of which 67% were lymphocytes, and its chloride content was 695 mg./100 ml., sugar 67 mg./100 ml., and protein 60 mg./100 ml. The cerebrospinal fluid was sterile on culture, the Wassermann reaction was negative in the blood and cerebrospinal fluid, the serum electrolytes were normal, and the electroencephalogram (E.E.G.) showed only a mild non-specific abnormality. Repeated examination of specimens of sputum failed to reveal any abnormal cytological deposit and no acid-fast bacilli were seen on direct smear or grown on culture. The
E.S.R. was 4 mm. in one hour, the haemoglobin was 17·0 g./100 ml, P.C.V. 49%, W.B.C. 6,400/c.mm., with a normal differential count. After careful consideration no contrast radiological studies were performed.

Because of his tremor and because of increasing unsteadiness in walking, the patient remained unable to work but he attended occupational therapy and gained weight. He remained short of breath and had occasional acute respiratory infections which responded to antibiotic therapy. A number of drugs were given, including various anti-Parkinsonian remedies and tranquillizers, none of which produced much improvement in his condition. Gradually over the succeeding year the tendon reflexes in the upper limbs disappeared, his tremor increased, his mask-like face became more obvious and he became increasingly short of breath. Eventually the hoarseness of the voice increased and he was found to have a marked though intermittent laryngeal stridor. Repeat laryngoscopy revealed that both vocal cords now moved poorly, suggesting that, both recurrent laryngeal nerves were involved. Repeated chest radiographs, however, failed to demonstrate any significant change.

In August 1962 he reported that he was becoming increasingly unsteady on his legs and for the first time some wasting of small hand muscles and of the shoulder girdle muscles was observed. There was also loss of vibration sense at the ankles and impairment of position and joint sense in the great toes on both sides, but no other significant sensory loss was detected. He also began to show evidence of slight dementia.

Electromyographic (E.M.G.) examination was carried out upon the left deltoid and left opponens pollicis on 11 April 1962 by Dr. D. D. Barwick. There was some apparent spontaneous fasciculation in both muscles but no fibrillation was observed. The motor unit discharges appeared normal in duration and configuration, though one or two large amplitude potentials were seen. There was a striking reduction in the interference pattern on maximum voluntary contraction and single discharge could be clearly identified, particularly in the thenar muscle. The appearances suggested the presence of a lesion situated proximally in the lower motor neurone. At this stage it was suggested that the patient's clinical picture, which included features of Parkinsonism, slight dementia, amyotrophy, and some evidence of cerebellar degeneration, was somewhat reminiscent of the Guam type of motor neurone disease or of the so-called Parkinsonism-dementia complex.

Over the next year the muscular weakness and atrophy in the upper limbs increased steadily and eventually spread to involve the lower limbs. He continued to have frequent episodes of respiratory infection, often associated with laryngeal stridor. No new neurological features appeared, but on 8 June 1965 he was readmitted, having had an episode of loss of consciousness with difficulty in breathing. On 12 June he complained of severe epigastric pain and his laryngeal stridor became very much worse. He deteriorated steadily over the next few days and eventually died on 14 June. Shortly before his death the cerebrospinal fluid was re-examined; it contained 25 lymphocytes/c.mm. and 136 mg. protein/100 ml.

**PATHOLOGICAL FINDINGS**

**GENERAL** At necropsy the body was well nourished, the only visible wasting being in the thenar muscles, more severe on the left side, and in both shoulder girdles where the trapezius and deltoid were particularly affected. There was marked emphysema of both lungs and the apex of the right lung was bound to the chest wall by firm adhesions over an area of calcified fibro-caseous tuberculosis. An extensive search showed no evidence of a bronchogenic carcinoma or of neoplasia in the abdomen. The heart was markedly enlarged (550 g.) with hypertrophy of both right and left ventricles. There was no valvular abnormality and only a moderate amount of coronary atheroma. The middle and lower thirds of the oesophagus were adherent to the surrounding mediastinal tissues and to the tracheal bifurcation; there was dense fibrous tissue in this region and the lower third of the oesophagus showed extensive chronic ulceration with fibrosis, the ulcerated area being covered by thick yellow necrotic slough in which were large numbers of fungi. The abdominal organs appeared normal.

**GROSS APPEARANCES OF THE CENTRAL NERVOUS SYSTEM**

The scalp was normal as was the skull apart from patchy yellow discoloration of its inner surface strongly suggestive of previous treatment with tetracyline. The dura was normal and the brain, which weighed 780 g., showed moderate atrophy of the cerebellum with a very small symmetrical fissure in the occipital region. Two large atrophic parieto-occipital lesions were found in each hemisphere, the left side being slightly more affected than the right. The surfaces of the cerebrum appeared smooth; there were no visible lesions in the basal ganglia or in the thalamus. The ventricles were of normal size and configuration.

**CHARTS**

Two sets of charts were prepared. The first chart shows the respiratory movements, the second shows the chest movements. These charts illustrate the marked and progressive upper-lung involvement with little evidence of mid and lower lung involvement. The second chart also shows the marked abnormalities in the respiratory movements with no evidence of diaphragmatic contribution.

**FIG. 1. Coronal section at the level of the anterior temporal lobes showing the destruction of the basal ganglia on the left side by the epidermoid cyst and its extension into the medial temporal lobe and the Sylvian fissure (×4/5).**
1,510 g., showed slight flattening of all its convulsions. A small fresh blood clot lay antero-superiorly to the optic chiasma and was roughly 2 cm. across; it lay adjacent and was attached to a white crumbling growth which involved the inferomedial surface of the left frontal lobe and the inferomedial tip of the left temporal lobe. This growth was white and pearly in appearance and was strongly suggestive to the naked eye of an epidermoid cyst. Small, white, granular deposits of the growth extended in the subarachnoid space into the commencement of the Sylvian fissure and several minute pearly deposits were present over the lateral and inferior aspect of the anterior third of the left temporal lobe, well separated from the main mass. Coronal section of the brain showed that a cyst full of white, soft material occupied the greater part of the left frontal lobe, being 6 cm. in its greatest diameter across and from above downwards. The cyst burrowed posteriorly into the anterior half of the medial end of the left temporal lobe (Fig. 1) and basal ganglia as far as the posteroinferior limits of the globus pallidus and the ansa lenticularis. It destroyed the greater part of the left caudate nucleus and lentiform nucleus and pushed into and distorted the left internal capsule. The pituitary gland appeared normal but the anterior hypothalamus was severely distorted by the cyst and the left amygdaloid nucleus could not be identified. There was obvious shrinkage of the superior vermis with thickening of the overlying meninges. The medulla was flattened anteriorly with almost total loss of the olivary eminences, the cervical cord was flattened and small and the entire spinal cord was somewhat shrunken. Anterior nerve roots were apparently normal to the naked eye, but the posterior roots were extremely thin from the upper cervical to the mides-dorsal region.

**HISTOLOGY OF THE CENTRAL NERVOUS SYSTEM**

Histologically the frontal lobe lesion was a typical epidermoid cyst (Fig. 2). No actual formative layer of basal epithelium was found in any of the sections, the cyst being lined by a thin fibrous and glial wall internal to which was an eosinophilic mass of squamous epithelial cells with large quantities of keratin and numerous lipid masses, the great majority extracellular and mixed with cholesterol crystals. Keratin, squamous cells, and much degenerative hyaline and lipid material were present in the subarachnoid space over the postero-inferior surface of the frontal lobe; over the anterior third of the temporal lobe hyaline and lipid material to a thickness of 100 μ was present patchily in the subarachnoid space (Fig. 3). In these areas the pia-arachnoid was heavily infiltrated with mononuclear cells, the great majority having the appearance of lymphocytes. Macrophages containing lipid material were also numerous, and occasional multinucleated giant cells with large, well-defined empty spaces in the cytoplasm in processed sections, strongly suggesting that lipid masses had been removed during preparation, were easily found in many areas of the subarachnoid space (Fig. 4). The underlying temporal cortex down to the third or fourth neuronal layers showed vascular proliferation, neurone loss, and considerable astrocytic proliferation. At further distances from the cyst it became progressively more difficult to identify lipid degenerative or keratin masses in the subarachnoid space but some sudanophilic material was present at the level of the superior colliculus and over the superior cerebellar vermis and very similar lipiddi-staining material was present in the aqueduct and in parts of the third ventricle. Over all areas of the brain there was considerable patchy infiltration of the subarachnoid space with lymphocytes, macrophages and occasional giant cells and some fibrous arachnoid thickening. Changes in the cortex generally were limited to cuffing of an occasional cortical arteriole and vein by lymphocytes and a very slight amount of subpial astrocytic proliferation. Throughout the lateral, third, and fourth ventricles there was a well-marked granular ependymitis and severe inflammatory change was present in all areas of the subarachnoid space below the level of the tentorium. This inflammatory change tended to be focal but some increase of mononuclear cells was present in every area examined. Dense collections of cells were present around, and actually infiltrated many of the emerging nerve roots, both cranial and spinal. In addition, many of the small arteries and veins in the subarachnoid space were surrounded by thick collars of mononuclear cells and the walls of some veins were infiltrated by mononuclear cells. The appearances, therefore, were of a widespread chronic granulomatous meningitis, to which was added evidence of unusual parenchymatous lesions.
FIG. 3. Left temporal lobe showing degenerative material and chronic inflammatory cells in the subarachnoid space. The cortex shows astrocytic proliferation with gliosis. Haematoxylin and eosin (× 90).

FIG. 4. Inflammatory infiltration of a thick vein wall and nerve roots at lower medullary level. Note the multinucleated giant cell with a clear cytoplasmic area. Haematoxylin and eosin (× 140).
In all sections of the cerebellum and particularly in the superior vermis, there was extensive loss of Purkinje cells (Fig. 5) and marked degeneration of the few which remained. These latter were vacuolated with loss of Nissl substance and pale and irregular nuclei. The overlying molecular layer was in places thin and everywhere showed slight microglial increase and many areas showed perivascular cuffing of superficial veins and arterioles by lymphocytes. The shrunken inferior olives showed severe loss of olivary neurones (Fig. 6) with microglial and astrocytic proliferation. Within the spinal cord there was uniform and fairly severe demyelination of the dorsal columns (Fig. 7), this loss extending from the lowest sacral segments. At all levels of the cord, in addition, there was considerable and often severe loss of anterior horn neurones. This loss was particularly marked in the lower cervical, upper dorsal and lumbar segments (Fig. 8) but was present at every level of the cord. This neurone loss was accompanied only by a very occasional glial star; there was a modest increase of microglial cells throughout the anterior horns and in the many sections examined an occasional small capillary was surrounded by chronic inflammatory cells. In all sections of the cord both anterior and dorsal nerve roots could be found with either perineuronal lymphocytic cuffs or with actual infiltration of the roots by mononuclear cells and some totally demyelinated nerve roots were present. Inflammatory infiltration of dorsal nerve roots extended to the limits of the arachnoid reflection; in one instance inflammatory infiltration and degeneration largely destroyed the proximal half of a dorsal root ganglion, with replacement of neurones...
by fibrous tissue, lymphocytes, and macrophages containing lipid material (Fig. 9), the distal half of the ganglion being normal in appearance. Examination of numerous sections of voluntary muscle revealed grouped fibre atrophy suggesting uniform atrophy of subunits, most severe in the thenar muscles of the hands but present also in trapezius, deltoid, quadriceps, and sternomastoids. The median and ulnar nerves on each side showed replacement of groups of nerve fibres by hyaline fibrous tissue of whorled arrangement (Fig. 10).

Although this suggests atrophy of groups of nerve fibres, its significance remains in doubt as the radiculitis and motor neurone loss would appear unlikely to give rise to such circumscribed lesions.

DISCUSSION

In retrospect it is clear that had this patient been subjected to detailed contrast neuroradiological studies such as angiography, air encephalography, or ventriculography, the clinical picture would have been clarified at an earlier stage of his illness. That the presence of an intracranial space-occupying lesion was never suspected in his case, despite the long history of major epileptic seizures beginning in early adult life, can be attributed to several factors. First, headache was never a feature of the illness; secondly, when seen and when examined on subsequent visits, no physical signs were ever elicited to suggest the presence of a focal lesion in one cerebral hemisphere and the E.E.G. failed to demonstrate any focal abnormalities; thirdly, despite persisting but remarkably variable abnormalities in the cerebrospinal fluid, the clinical picture from the outset was so suggestive of degenerative disease of the central nervous system and the evidence of respiratory disease was so prominent that attention was throughout focused upon the possibility that the neurological findings might be the result of occult malignant disease; and finally, when the...
passage of time indicated that bronchogenic neoplasm was unlikely to be the primary disease, the association of dementia, extrapyramidal signs, cerebellar ataxia, amyotrophy, and peripheral neuropathy favoured the presence of diffuse degenerative changes in several systems of the neuraxis. Furthermore, in the later months of life, his respiratory difficulties gave rise to increasing concern and difficulties in management.

The pathological findings explain almost all of the symptoms and signs which this man demonstrated. Epilepsy from early life, progressive and largely unilateral Parkinsonian-type tremor almost certainly resulted from the epidermoid cyst itself which encroached upon the uncus and also distorted and actually destroyed part of the basal ganglia. It also compressed the upper brainstem unilaterally. The late development of dementia could be accounted for by the widespread arachnoiditis and superficial cortical degenerative changes. The cerebellar ataxia was fully explained by the severe cerebello-olivary degeneration. The muscular wasting and weakness was clearly the result of extensive anterior horn cell loss, while the loss of deep tendon reflexes and impairment of deep sensation could be explained by lesions in the posterior roots and by dorsal column demyelination. This latter change, and possibly some of the muscle wasting, may have been due to the extensive radiculitis; this also involved cranial nerves, and involvement of vagus rootlets was presumably responsible for the vocal cord paresis.

This man, therefore, presented an extraordinary constellation of severe neurological abnormalities, all of which were adequately accounted for by the necropsy findings. The exact cause of the lesions may not be so certain, but the logical explanation would appear to be that the chronic arachnoiditis,
cerebellar degeneration, and the lesions of the cranial nerves, anterior and posterior roots and probably of the anterior horns were due to toxic degenerative products from the epidermoid cyst which had continually leaked into the subarachnoid space over a period of many years. Certainly the variable abnormalities of the cerebrospinal fluid could be explained in this way. We cannot be certain whether the toxic substance responsible for these degenerative changes was keratin, cholesterol, or some other degradative product of the neoplasm. Long-term animal experiments utilizing repeated injections of keratin or cholesterol into the subarachnoid space followed by neuropathological study would be required to answer this question.

We know of no degenerative central nervous system disease which produces a combination of neuronal defects and changes such as we found in this case, for the degeneration involved the anterior horn cells of the spinal cord, the dorsal nerve roots, the portions of the dorsal root ganglia lying nearest to the subarachnoid space, the inferior olives, and the cerebellar folia. Dorsal column demyelination was presumably secondary to the other lesions, while superficial degeneration in the cerebrum was presumably the result of the granulomatous meningitis. This chronic degenerative process is in certain respects similar to that of superficial haemosiderosis of the nervous system of which we have previously reported an example (Tomlinson and Walton, 1964). In this latter condition bleeding occurs into the subarachnoid space slowly and over a long period of time and the resultant siderosis produces extensive degeneration of cerebellar folia, less severe but marked degeneration of superficial cortex, degeneration of cranial nerves, of the white matter at the periphery of the spinal cord, and sometimes anterior horn cell degeneration. In haemosiderosis the entire appearance can be accounted for by a progressive degenerative change resulting from chronic bleeding into the subarachnoid space. The principal clinical features of this disorder are progressive dementia, nerve deafness, cerebellar ataxia, amyotrophy, and signs of long tract degeneration in the spinal cord. In the case now reported there was a similar slow dementing process, cerebellar ataxia was prominent, and amyotrophy and evidence of dorsal column degeneration with areflexia eventually appeared but nerve deafness was never observed. Nevertheless, the clinical and pathological similarities between the two disorders are sufficient to make us feel that most of the clinical abnormalities we observed in our patient, apart from those attributable to the presence of the neoplasm in the left cerebral hemisphere, were the result of the long-standing dissemination of a toxic and irritative substance throughout the subarachnoid space.

SUMMARY

The case is reported of a man, who died at the age of 48 years, who had suffered from occasional attacks of major epilepsy from the age of 16 years. At the age of 40 he developed signs suggestive of Parkinsonism with a mask-like face and immobility and a predominantly right-sided tremor of action type. Subsequently bilateral cerebellar ataxia appeared and steadily worsened, the deep tendon reflexes were progressively lost, muscular wasting appeared in the upper limbs and impairment of deep sensation in the lower, while progressive dementia also developed in the last few months of life. At necropsy a large epidermoid cyst was found in the left frontal lobe extending deeply into the hemisphere. Histological examination of the central nervous system revealed a widespread granulomatous meningitis and ependymitis, cerebellar degeneration with marked loss of Purkinje cells, a widespread radiculitis involving also posterior root ganglia, dorsal column demyelination in the spinal cord, and severe loss of anterior horn cells. It is suggested that these pathological changes and the resultant clinical syndrome were due to the chronic dissemination of a toxic degradative product of the intracranial neoplasm throughout the subarachnoid space.

REFERENCE