A CASE OF SUBACUTE INCLUSION ENCEPHALITIS

BY

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Cases of subacute inclusion encephalitis were first described by Dawson (1933, 1934) in a boy aged 16 and a girl of 5 years in Tennesee. The changes were mainly in the grey matter and inclusions of Cowdry type A were found in neurones and oligodendrocytes. In the next 20 years 18 similar cases had been reported, 12 in males and six in females, all in children or young people in their first two decades of life (Akelaitis and Zeldis, 1942; Brain, Greenfield and Russell, 1948; Malamud, Haymaker and Pinkerton, 1950; Foley and Williams, 1953). In the meantime, a supposedly different condition, subacute sclerosing leuco-encephalitis, with a rather similar clinical picture had been described by van Bogaert (1945). Inclusion bodies were later demonstrated in cases of this disease (van Bogaert, 1958), and the white as well as the grey matter was shown to be involved in cases previously regarded as Dawson's inclusion encephalitis (Foley and Williams, 1953). For these reasons the two conditions are now thought to be identical. The occurrence of inclusions strongly suggests viral origin, but efforts to isolate the virus have hitherto failed (Haymaker, Smith, van Bogaert and de Chenar, 1957). Other attempts to reproduce the disease in animals have yielded only equivocal results (van Bogaert and Innes, 1962).

This type of encephalitis is very rarely diagnosed in this country. Thus the 1960 Registrar-General's records for England and Wales contain only three instances of the condition: all males, aged 19, 11 and 8. Inquiry of the pathologists who performed the autopsies revealed that intranuclear inclusions were found in two of these cases. The following is another rather characteristic instance of the condition.

Case Report

A previously healthy boy was 7 years old in March 1959 when symptoms first appeared. His mother noticed serious deterioration in his hand-writing, and some mental deterioration was observed later at school and at home. He became forgetful and less retentive. At the same time movements of his limbs and head and, later, of his face and mouth became increasingly clumsy. He began to walk, as his mother put it, 'as if he was top-heavy, with his head in front of the rest of the body'. Shortly after, his speech became increasingly slurred and hesitant until it was almost unintelligible. There were increased and distorted associated movements: he grimaced when attempting to speak, and many parts of his body wrenched and twitched when he tried to use his limbs.

During September 1959, he was admitted for a week to the Canadian Red Cross Memorial Hospital, Taplow, when a diagnosis of rheumatic chorea was considered. Within a week or two of his discharge further gradual deterioration set in, involving intellect, speech, limb movements, gait and control of trunk.

By this time he began occasionally to be incontinent of urine and faeces. His legs stiffened and walking became impossible.

When admitted to hospital he was in a state of opisthotonos. Although conscious, he was in a strange mental state. He watched the observer rather like a frightened animal, and never spoke or responded to the spoken word. He followed objects with his eyes and seemed to have fair visual acuity and, probably, a normal visual field. He reacted to noise or touch with a sudden motor-sensory jerk of his whole body, sometimes accompanied by a long scream. When left alone he would curl up on one side or other, and exhibit occasionally a small involuntary convulsive jerk of his body. He resisted in particular any effort to extend the spine. His arms were flexed at his shoulders, elbow, wrist and digits, and held tightly against his chest with considerable resistance to extension. His head was held in a position of moderate extension. His legs were thrust out in extreme extension of all joints and there was great resistance to attempted flexion.

The optic fundi, pupils, pupillary responses and external ocular movements were all normal. So far as could be assessed, sensation was also normal. The tendon reflexes were all remarkably brisk and approximately equal. The plantar responses were extensor.

Six months after the commencement of the illness, he was transferred to St. Mary's Hospital, London.
Investigations. Red blood cells, normal; white blood count, 17,000 and 19,000 per c.mm., with a normal differential count. The erythrocyte sedimentation rate was normal. The skull and chest radiographs were normal. The cerebrospinal fluid was clear, colourless and under normal pressure, with 2 lymphocytes per c.mm., 19 mg. per 100 ml. of protein, and a Lange curve of 5554320. The Wassermann reaction was negative and cerebrospinal fluid culture was sterile. The electroencephalogram (Fig. 1) showed a grossly abnormal record with high voltage delta waves from all areas of both sides, intermixed with theta waves. There was at times, and only during sleep, a simple stereotyped sharp wave complex which was recorded from both frontal areas. The air ventriculogram showed no abnormality.

The differential diagnosis seemed to lie between a diffuse encephalitis of unknown aetiology, one of the lipoidoses or progressive diffuse demyelination, as in Schilder's disease.

After admission he ran an irregular fever of 99°-100° F. (37°-37·8° C.) and was given a course of tetracycline with no effect on the temperature. He then developed cellulitis over the dorsum of the left hand. Tetracycline was replaced with penicillin leading to an immediate and rapid control of the fever. Within a day or two of his admission he was treated with prednisone, receiving between 15 and 40 mg. daily, over a period of ten days. The prednisone was stopped when a case of chicken-pox was discovered in the ward. A few days later the patient developed chicken-pox himself and this led to a great increase of bronchial secretion with impending respiratory difficulty. For that reason he was transferred to the Western Fever Hospital where he remained for a month.

On readmission to St. Mary's Hospital there was serious general deterioration and he died on March 6, 1960, aged 8 years, having been ill for almost exactly one year.

Autopsy. This was performed 16 hours after death. The body build was average, but showed poor nutrition. A patent tracheostomy wound was present in his neck.

The cardiovascular system was normal. The upper respiratory passages, trachea and bronchi contained muco-pus and showed intense mucosal congestion. There was complete collapse of the left lower and the right upper lobes and patchy collapse of the other lobes of the lungs. The left pleural cavity contained 200 ml. of purulent fluid. Microscopy showed extensive pyogenic bronchopneumonia in both lungs. Alimentary, reticuloendothelial and endocrine systems were normal, apart from congestive changes in the liver and spleen. No inclusion bodies were seen in any somatic tissue or organ. The kidneys and ureters were normal. The urinary bladder was small with a thick muscular wall. Both testes, of average size, were undescended and fixed in the inguinal canals. Histologically, they were within normal limits.

Central Nervous System. The brain was heavy, weighing 1.475 g., and showed nothing unusual on external inspection; the meninges were thin and transparent. The main blood vessels and cranial nerves were normal.

After prolonged fixation in formalin, the cut surface did not, at first glance, look very abnormal. Palpation revealed, however, considerable induration of the white
A CASE OF SUBACUTE INCLUSION ENCEPHALITIS

matter over most of the central nervous system. Closer scrutiny showed also that the white matter had acquired an unusual ivory-white tinge. The cerebral cortex was by contrast rather soft. Its brown colour had given place to bluish-grey, and this lent it an appearance of greater translucency. There were also a few darker areas in the cortex, some narrowed parts, and others appearing faintly granular and friable.

The subcortical nuclear formations were paler than usual. The cerebellum showed on its cut surface marked atrophic change, many folia being shrunked, indurated, with blurred demarcation between the grey and white matter. The dentate and the roof nuclei had also lost their sharp outlines and could only be discerned with difficulty.

Representative blocks of the frontal, temporal, parietal and occipital lobes, the basal ganglia, different levels of the brain-stem and spinal cord, and of the cerebellum were embedded in paraffin and celloidin and sections stained by the usual general and neuropathological methods. Frozen material was used for fat staining and for the Holzer, Kulschitsky-Pal and the silver impregnation methods. Inclusion bodies were searched for in haematoxylin and eosin as well as in Lendrum's philoxine tartrazine preparations.

The meninges were of normal thickness. The subarachnoid space contained a few lymphocytes and plasma cells. Though nowhere very numerous, they were more plentiful over the brain-stem and spinal cord than over the cerebral hemispheres. Similar scanty cellular exudate was present in some of the dilated perivascular spaces throughout the nervous system.

The chief changes in the cerebral cortex were microglial and astrocytic proliferation and hypertrophy. Most of the microglial cells were scattered diffusely and fairly uniformly. They had small darkly-staining round, oval, rod-shaped or undulating nuclei. No cytoplasm was visible with ordinary stains, but fat stains showed that many contained fine droplets of sudanophil material, and that these droplets tended to coalesce and form larger particles filling the otherwise scarcely discernible cytoplasm. In addition to the diffusely scattered microglia, there were also occasional stars and clusters formed by these cells (Fig. 2). These cellular groups were often located in the vicinity of a degenerate capillary or neurone, represented, perhaps, by vaguely defined debris of PAS positive material. The proliferated cortical astrocytes (Fig. 3) were mostly hypertrophied fibre-forming cells with a fair amount of homogeneous cytoplasm and stout fibillary processes demonstrable by appropriate stains. The cortex showed spongy degeneration in some areas.

It was difficult to estimate the degree of neuronal loss. That some was present was clear from the reduced depth of the cortex and the degenerative changes exhibited by some of the nerve cells. However, many were morphologically sound. Since a number of the large astrocytes possessed condensed nuclear chromatin resembling neuronal nucleoli, it was not always possible to distinguish one type of cell from the other. The difference between them emerged clearly enough in appropriately stained sections, such as Bielschowsky or Holzer preparations, which showed that the neuronal population was considerably depleted.

The white matter presented even more conspicuous changes than the cortex, and these were fairly uniform throughout the central nervous system. The chief features were gliosis (Fig. 4) and sudanophilic breakdown of myelin. In haematoxylin and eosin preparations there were many large fibre-forming fibrillary astrocytes, with a considerable amount of homogeneous cytoplasm (Fig. 5). The fibrillary processes were more delicate than in the cerebral cortex and ramified to form a very dense fibrous network. Although no mitotic figures were seen in any of these cells, several were binucleate and others were obviously undergoing division and fission. In addition, the white matter contained numerous microglial cells, the actual proportion between the two types varying from area to area. Frozen sections treated with one of the Sudan stains showed that most of the microglia were compound granular corpuscles heavily laden with sudanophil material. Fine droplets of neutral fat were also demonstrable in the cytoplasm and fibrillary processes of astrocytes. A notable feature of this very abundant sudanophil material in the white matter was its diffuseness (Fig. 6); there was no apparent tendency for it to condense in certain areas or around blood vessels, as is frequently the case in other conditions. Appropriately stained preparations showed on naked-eye examination a diffuse loss of myelin. There was little sparing of any particular part of the white matter, such
FIG. 3.—Astrocytic gliosis in the cerebral cortex.
(Holzer × 340.)

FIG. 4.—Fibrous gliosis of the white matter of the cerebral cortex.
(Holzer × 2.)
A CASE OF SUBACUTE INCLUSION ENCEPHALITIS

Fig. 5.—Astrocytic and microglial hyperplasia in the cerebral white matter.
(H. and E. × 155.)

Fig. 6.—Marked deposition of sudanophil material in the cerebral cortex and white matter.
(× 150.)
as the subarcuate fibres. Higher magnification showed myelin sheaths in various stages of degeneration. They presented uneven staining, 'varicosities', beading and the formation of many 'myelin balls'. Axis cylinders showed fragmentation, uneven thickness and curling. They appear to have been as heavily involved as the myelin sheaths.

All subcortical nuclear formations presented the same pattern of change as the cerebral cortex. In brief, this consisted of astrocytic and microglial gliosis with a certain amount of neuronal loss. Some formations were heavily involved. This applies particularly to the inferior olives where almost all neurones had disappeared, and the olivo-cerebellar tracts which showed marked pallor of myelin staining (Fig. 7). Focal clustering of microglia and perivascular cuffing by lymphocytes and plasma cells were more conspicuous in the brain-stem than the cerebral cortex.

The white matter displayed, as stated already, notable morphological uniformity throughout the entire nervous system. However, the posterior columns of the spinal cord showed a substantially deeper tinge of myelin staining than the lateral and anterior columns.

The cerebellum presented marked atrophy of all its elements (Fig. 8), Purkinje cells, granular layer, white matter and dentate nucleus. The molecular layer was the seat of marked isomorphous, 'perpendicular', fibrous gliosis associated with proliferation of the Bergmann glia. A few clusters of microglial cells were also present in this layer.

Intranuclear inclusions were seen in oligodendrocytes of the cerebral white matter, in the Purkinje cells (Fig. 9) and in neurones of anterior horns of the spinal cord. They were eosinophilic with a slight purplish tinge in haematoxylin and eosin sections and varied in size, the large ones almost completely filling the nucleus. Some showed a distinct surrounding 'halo'. An occasional nucleus contained several inclusions. Similar but less
distinct inclusions were present in the cytoplasm of some of the affected cells.

The neurochemical findings are given in the Table.

Discussion

The clinical course and pathological findings in the present case are quite characteristic of subacute inclusion encephalitis, but it should be noted that actual inclusions have not been found even after prolonged search in every otherwise unequivocal instance of the condition. Some patients show very conspicuous changes in the electroencephalogram, complexes of high voltage sharp 'K' waves, but this also is not a constant finding: the electroencephalogram of the present case, although grossly abnormal, did not show any specific evidence of subacute inclusion encephalitis.

Special staining methods may help to reveal the inclusions, but they can be readily seen in well-differentiated haematoxylin and eosin sections. It used to be thought that the condition was one of the 'leuco-encephalitides', i.e. that it affected chiefly or exclusively the white matter. However, it has come to be recognized that both grey and white matter are always involved, and the disease is thus a 'pan-encephalitis' (Tariska, 1960). The only condition that might be histologically mistaken for it is leucodystrophy or the sudanophilic form of Schilder's disease. The chief distinguishing features are, of course, the inclusions, if found, and the tendency to sparing of the subacute fibres in leucodystrophy. Clinically, Schilder's disease is often hereditary, conforming to the recessive mode of transmission, while subacute inclusion encephalitis is entirely sporadic. Most cases are recognized by the insidious onset of changes in behaviour and intellectual impairment, jerking and twitching of limbs at regular intervals and difficulty in speech. Occasionally the disease is ushered in by hallucinations, insomnia or an attack of unconsciousness. Examination of the cerebrospinal fluid shows only one characteristic finding, a parietic type of colloidial gold curve: otherwise it is clear with perhaps slightly increased pressure and few cells. All aspects of the condition have recently been fully and ably reviewed by Lóránz, Nagy and Tariska (1962).

The neurochemical findings in this case indicate widespread sudanophilic breakdown of myelin and are compatible with subacute inclusion encephalitis, without being in any way specific for the condition.

| CHEMICAL CONSTITUENTS OF THE BRAIN (g/100 g. tissue) WITH NORMAL VALUES IN PARENTHESIS |
|-----------------------------------------------|-----------------|-----------------|
|                               | White Matter    | Grey Matter     |
|                               | Wet             | Dry             | Wet             | Dry             |
| Total phospholipid            | 3-31 (21-8)     | 7-8 (22-1)      | 2-35 (22-1)     | 2-9             |
| Sphingomyelin                 | 0-27            | 1-7             | 0-45            | 2-9             |
| Total cholesterol             | 3-38            | 13-9 (14-0)     | 0-784           | 4-0             |
| Esterified cholesterol        | 1-1             | 3-8 (0-3)       | 0-08            | 0-5             |
| Total hexosamine              | 0-43 (0-29)     | 0-43 (0-29)     | 0-74 (6-5)      | 0-74 (6-5)      |
| Neuraminic acid               |                 | 0-16 (0-25)     | 0-16 (0-25)     |                 |
| Water                         | 75-8 (67-9)     | 84-5 (84-2)     |                 |                 |

Normal values taken from Sziwowski and Cumings (1961).
Summary

A boy of 7 developed a progressive encephalomyelopathy leading to total dementia with pyramidal signs and evidence of generalized involvement of the central nervous system. The electroencephalogram was grossly abnormal but not characteristic for any particular disease. The patient died a year after the onset of the disease. Pathologically, there was generalized encephalomyelitis with marked gliotic changes, particularly in the white matter. Inclusions were found in many neurones and oligodendrocytes.

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REFERENCES


