Alexander's disease presenting as astrocytoma

T. A. FRENCH¹, B. D. BOWER², AND A. H. CAMERON

From The Children's Hospital, Birmingham

SYNOPSIS A case of progressive fibrinoid degeneration of astrocytes is described. Symptoms began with convulsions at the age of 6 weeks and cerebral tumour was suspected because of enlargement of the head, increased intracranial tension, and marked proliferation of astrocytes in the brain biopsy which was interpreted as an astrocytoma. Fibres and granules staining deeply with PTAH are a constant feature of the few cases so far described. The aetiology is unknown but an inherited metabolic defect of astrocytes may be responsible.

In 1949 Alexander reported a case of mental retardation and hydrocephalus in a young child with changes in the brain described as progressive fibrinoid degeneration of fibrillary astrocytes. We report a similar case presenting as fits in a male infant aged 6 weeks. There were unusually florid histological changes in the brain biopsy which suggested neoplasia.

CASE REPORT

CLINICAL HISTORY The second child of an otherwise healthy family was born at 37 weeks' gestation of a normal pregnancy and of unrelated parents. He was an apparently normal baby with a birth weight of 3.4 kg and cried immediately after delivery. The neonatal period was normal. At 6 weeks of age clonic convulsions affecting the right arm and leg and both sides of the face started, followed two weeks later by frequent infantile spasms of the salaam type. At 9 weeks old he was an irritable, well-nourished baby with bilateral facial twitching and right spastic hemiparesis. The head circumference was 40.3 cm (70th percentile). The fontanelles and fundi were normal.

INVESTIGATIONS EEG examinations suggested gross disturbance of subcortical structures and cortical pathways. The main abnormal pattern consisted of spikes and waves. The abnormalities were some-

times observed on the same side as the clinical attacks, but the degree of alternation was not that seen in the Aicardi syndrome (absence of corpus callosum) (Jeavons *et al.*, 1973). The blood sugar, calcium and urea, the tryptophan load test, urinary amino acid chromatogram, and skull radiograph were all normal. The ventriculogram suggested cortical atrophy, but the ventricles were not dilated. The right ventricular CSF protein at 9 weeks of age was 1.3 g/l and at 10 weeks was 2.7 g/l. Biopsy of the left frontoparietal area was performed at 13 weeks. This showed a conspicuous proliferation of gemistocytic astrocytes. These cells contained numerous granules which stained positively with phosphotungstic acid haematoxylin (PTAH). The appearances were interpreted as a gemistocytic astrocytoma (Fig. 1). Despite anticonvulsants the myoclonic jerks, salaam spasms, and clonic convulsions continued. The skull enlarged rapidly to 45.7 cm (well above 90th percentile) with an increase in fontanelle tension and vomiting. Spastic quadriplegia developed terminally and he died at the age of 18 weeks.

METHODS The brain was fixed in 10% formalin for three weeks. Paraffin sections of 7 μ m were stained with haematoxylin and eosin (HE), elastic Van Gieson (EVG), periodic acid Schiff (PAS), and Martius scarlet blue (MSB). Paraffin sections of 15 μ m were stained with phosphotungstic acid haematoxylin (PTAH), Holzer, cresyl fast violet (CFV), luxol fast blue (LFB), and Lillie's myelin stain. Frozen sections (15 μ m) were stained with oil red O.

NECROPSY FINDINGS (171006) A moderately wasted (3.95 kg; less than 3rd percentile) male infant 58.5 cm

¹ Address for reprint requests: T. A. French, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET.

² Present address: Department of Paediatrics, Radcliffe Infirmary, Oxford.

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FIG. 1 *Gemistocytic astrocytes, containing numerous bodies in their cytoplasm. (Biopsy of frontal cortex). PTAH, $\times 768$.*

in length (3rd percentile), with a symmetrically enlarged head (49 cm: above 97th percentile). All significant abnormalities were in the nervous system. The meninges were slightly thickened over the interpeduncular cistern. Externally the frontal cortex on both the superior and inferior surfaces was creamy-white, semicystic, and partly adherent to the dura mater. Horizontal slicing (Fig. 2) showed widely dilated posterior horns of the lateral ventricles with atrophic white matter, but a normal corticomedullary junction. In the frontal regions the changes were profound. The cortex was thinned and had a fine honeycomb appearance. Changes were most evident in the underlying white matter, which was spongy, some spaces being up to 0.8 cm in diameter, some containing mucoid material and brown pigment. A similar appearance was present in the white matter under the insula on the left, the anterior parts of both internal capsules, and the lateral aspects of the thalami and putamen on both sides. The left choroid plexus was covered by filmy white adhesions; the right was normal. Filmy white membranous material was present in the moderately dilated third ventricle. The aqueduct of Sylvius, midbrain, cerebellum, and spinal cord were macroscopically unremarkable.

FIG. 2 *Horizontally sliced brain to show dilated lateral ventricles with cystic and spongy degeneration of frontal areas.*

HISTOLOGICAL FINDINGS The conspicuous histological features were proliferation of astrocytes, often gemistocytic, PTAH positive bodies, and demyelination. The PTAH positive bodies were in the cytoplasm of the large astrocytes, giving them a coarsely granular, deeply eosinophilic appearance in the haematoxylin and eosin preparations (Fig. 1). Others appeared to be extracellular and especially frequent in a perivascular, subpial (Fig. 3) or subependymal position. They were cresyl violet, MSB and PAS negative. The distribution of the histological changes was variable both in severity and in composition in different parts of the neural axis.

In the cerebral hemispheres the changes were most severe in the frontal lobes, where both grey and white matter were affected with widespread loss of neurones and a replacement by a loose web of glial fibres and young capillaries (Fig. 4). There were perivascular macrophages and conspicuous proliferation of gemistocytic astrocytes with PTAH positive bodies in the cytoplasm. Posteriorly, the changes were less striking with preservation of the cortex and subcortical white matter but the deeper white matter was involved. Similarly, the thalamus and lentiform nuclei were relatively spared but showed similar changes at their margins. In the cerebellum the granular layer was thinned and the Purkinje cells and large cells of the dentate nuclei were swollen with conspicuous nucleoli. In the brain

stem there was proliferation of subependymal glial cells particularly round the fourth ventricle with the production of glial granulations. Fibres staining deeply with PTAH were particularly striking in the subpial zone arranged at right angles to the surface. There was patchy proliferation of astrocytes, microglia, some of which were of the compound granular corpuscle type, and capillaries. Similar, but less severe, changes were present in the spinal cord. In all areas there was a conspicuous absence of inflammatory cellular response. Glial fibres were seen in varying numbers in different areas, being more common in the more severely destroyed brain. Sudan stains for phagocytosed lipid were positive (Fig. 5). No significant histological features were seen outside the nervous system.

DISCUSSION

This rare lesion of the nervous system was first reported in 1949 by Alexander. Further cases have been described since (Stevenson and Vogel, 1952; Crome, 1953; Wohlwill *et al.*, 1959; Freide, 1964; Iri and Matsuyama, 1966; Schochet *et al.*, 1968; Herndon *et al.*, 1970; Sherwin and Berthrong, 1970; Garret and Ames, 1974). Eight resembled the present case with onset in infancy and were dead by the age of 3 years. The case of

FIG. 3 Bodies arranged at right-angles to the surface in the subpial zone. PTAH, $\times 480$.

FIG. 4 *Frontal white matter to show loss of normal architecture with cystic degeneration and proliferated glial fibres and capillaries. H and E, $\times 19$.*

FIG. 5 *Frontal cortex to show conspicuous phagocytosed lipid. Frozen, oil red O, $\times 768$.*

Stevenson and Vogel (1952) had an encephalitis-like illness and lived till the age of 7 years with mental retardation. Herndon *et al.* (1970) described a boy whose symptoms started at 1½ years. The diagnosis was made by brain biopsy at 8½ years, and he was alive at 10 years. Three older cases have been recorded with onset at 7 years (Vogel and Hallervorden, 1962), 32 years (Seil *et al.*, 1968) and 23 years (Herndon *et al.*, 1970). In all, except for the biopsy case of Herndon *et al.*, the diagnosis was established by necropsy and diagnostic histological findings (see below).

The reported cases do not appear to form a consistent clinical pattern but the commoner features have included macrocephaly, convulsions, spastic pareses, and mental retardation. Our case was the most rapidly progressive.

In the infantile cases there has been a male preponderance (nine males and two females). Only the case of Wohlwill *et al.*, (1959) had a significant family history: the parents were normal but three of the eight sibs died in childhood with 'hydrocephalus'. Mental retardation was noted in a cousin of one case (Schochet *et al.*, 1968) and in an uncle of another (Garret and Ames, 1974). Sherwin and Berthrong's case (1970) had a normal dizygotic twin brother. No significant history in the pregnancies, including drug therapy, was recorded in any case.

Pathologically, the brains have been larger than normal, but despite the clinical picture no evidence of obstructive hydrocephalus has been found.

Microscopically, the striking constant feature consisted of characteristic eosinophilic bodies which stained consistently with the PTAH stain but not regularly with others. They have been typically present in the subpial, subependymal and perivascular positions, at right angles to these structures in the brain and spinal cord. Their large number and apparent extracellular, as well as intracellular, location contrasts with the less frequent and intracellular bodies of similar nature which may be found in subacute sclerosing encephalitis, and progressive multifocal leucoencephalopathy. Their characteristic appearance has been seen in the optic nerves (Stevenson and Vogel, 1952) and in the peripheral nerves (Crome, 1953). Alexander believed that it was due to fibrinoid degeneration of fibrillary astrocytes. The astrocytic proliferation

in the present case, with large numbers of the PTAH positive bodies in the gemistocytic astrocytes, accords with his conclusion. Crome believed that they were more likely to be products of myelin breakdown, as his case showed extensive demyelination and the bodies were seen in the peripheral nerves, where astrocytes are not present. Demyelination has been a variable feature and in Alexander's case it was not conspicuous. There is no evidence that it is the primary process. Neuronal loss has also been variable; it was striking in Crome's case and in the frontal cortex of our case. Inflammatory changes have not been conspicuous. The cyst formation in the distorted and partly collapsed white matter of the cerebrum, especially in the frontal regions (Fig. 2) appear to have been secondary features and were unusually prominent in our case. The appearances (Figs. 2 and 4) might be confused with the effects of cerebral birth injury and ischaemia. The absence of haemosiderin and the presence of PTAH positive bodies indicate the correct diagnosis. Especially in a small biopsy the proliferation of gemistocytic astrocytes, when conspicuous, as in this case, may be confused with an astrocytoma. Again, the presence of the typical intracellular and extracellular bodies should make this pitfall avoidable.

Alexander (1949) noted the resemblance of the PTAH positive bodies to the fibres described by Rosenthal (1898) in syringomyelia and intramedullary ependymoma, and the relationship between the two bodies has been more recently discussed by Hallervorden (1961). Rosenthal fibres are commonly seen in astrocytomas, especially those of pilocytic juvenile type (Russell and Rubenstein, 1959). They are also seen in areas of old reactive gliosis, in central pontine myelinolysis (Tihen, 1972) and after vincristine therapy for reticulum cell sarcoma (Mastri and Sung, 1973). Electron microscopy shows them as osmiophilic bodies and has established that they occur only in the cell bodies and processes of astrocytes. Those that appear to be extracellular in the perivascular situation, for example, are found to be within the cytoplasm of astrocytic processes. They are not seen in phagocytic cells or oligodendrocytes (Herndon *et al.*, 1970). Rosenthal believed them to be degenerative glial fibres and this is widely accepted. An origin

from myelin breakdown products is unlikely because of their presence in glial tumour cells. Electron microscopy has confirmed the close similarity between the fine structure of Rosenthal fibres and the characteristic bodies of Alexander's disease (Schlote, 1966; Schochet *et al.*, 1968; Herndon *et al.*, 1970; Garret and Ames, 1974). Both are seen as dense osmiophilic bodies closely related to the cytoplasmic filaments of astrocytes. The bodies consist of tightly packed aggregates of fine granules approximately 20 nm in diameter and are not membrane bound. Histochemistry (Herndon *et al.*, 1970) indicated that they consist of protein which Freide (1964) has called neurokeratin.

Although demyelination does not seem to be the primary defect in Alexander's disease, the large number of unmyelinated axons suggests that defective myelination may occur. Astrocytes have metabolic and structural supporting functions for neurones and oligodendroglia. The lesion may be a metabolic one in the astrocytes with the consequent accumulation of the PTAH bodies and the defective nutrition of oligodendrocytes and hence defective myelination. In Alexander's disease of infantile type the changes are widespread and the clinical features profound. In the cases with later onset there may be a less severe enzyme defect in the astrocytes which does not manifest itself until there is an increased need for glial fibre production stimulated by central nervous system disease. A similar mechanism is postulated for those cases of multiple sclerosis with Rosenthal fibre formation (Herndon *et al.*, 1970).

It may be concluded that the cases of Alexander's disease reviewed above appear to form a rare clinical and pathological entity the cause of which remains undetermined. The histological features appear to be of a degenerative nature perhaps due to a metabolic defect of glial function. A suggestive family history is confined to the case of Wohlwill *et al.*, (1959) and there is no record of cousin marriages.

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