Alexander's disease with Rosenthal fibre formation in an adult

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SUMMARY The case of a woman who had a mild mental and physical handicap all her life is described. At the age of 39 years she began a progressive deterioration which terminated with her death after a year. CT scanning revealed basal ganglia calcification and at necropsy there was evidence of widespread generalised myelin loss with extensive Rosenthal fibre formation. The hypothesis that this may be an adult form of Alexander's disease is discussed.

Alexander's disease is a primary leucodystrophy of unknown aetiology. The typical clinical features are of infantile onset, megalencephaly, dementia and increasing spasticity. Progression is inexorable, leading to death within months to a few years from the onset. Histologically, the principal abnormalities are widespread demyelination and extensive Rosenthal fibre formation. Cases with similar pathological features occurring in adults have been reported before but review of their clinical features reveals a remarkably heterogeneous group. Our patient differs from all those described previously in her clinical presentation and in the pathological abnormalities found at post mortem.

Case report

MG was born in 1937 after an uneventful pregnancy. There was no parental consanguinity, or family history of neurological disease and she had a normal male sibling. She is said to have been blue at the time of birth and there may well have been a period of perinatal hypoxia. Motor milestones were all delayed but she learned to walk eventually, although always with an abnormal gait, tending to drag her left leg. Mentally she was mildly retarded. She attended a normal school, however, and eventually learned to read and write. She was unable to work regularly and lived in a protected home environment.

At the age of three, she developed generalised convulsions, but these were never difficult to control. Her condition remained static and she did not come to medical attention again until the age of 39 years when she developed progressive ataxia and dysarthria. Her intellect and memory deteriorated rapidly and she became incontinent. Examination revealed no significant abnormalities outside the nervous system. The head circumference was at the upper limit of normality at 56 cm. She would occasionally answer simple questions appropriately and there was a spastic and cerebellar dysarthria. She was unable to cooperate with more formal assessment of higher cerebral function and appeared grossly demented. Her gait was ataxic and she spent long periods, sitting, grinding her teeth only responding to painful stimuli. The fundi, eye movements and pupillary reactions were normal. The jaw jerk was exaggerated and the tongue was very spastic. Examination of her limbs revealed a moderately severe spastic quadriaparesis with exaggerated reflexes and bilateral extensor plantar responses. There was mild cerebellar ataxia, but no evidence of extrapyramidal dysfunction.

Routine haematological and biochemical investigations were normal as were the serum calcium, phosphate and a 24 hour urinary calcium estimation. VDRL and TPHA were negative in blood and CSF. A chest radiograph was normal but plain radiographs of the skull revealed some calcification in the region of the head and body of the caudate nuclei. A CT scan was of poor quality, with movement artefact despite heavy sedation, but it confirmed calcification in the caudate nuclei. There was slight dilatation of both lateral ventricles, the third and fourth ventricles but no other significant abnormalities. At lumbar puncture, the CSF was clear, colourless and under normal pressure. There was no pleocytosis and the protein, sugar and IgG/albumin ratio were normal. Several EEGs were performed. These were dominated by generalised fast activity which was thought to be drug induced, underlying which was widespread nonfocal theta and delta activity. No focal or paroxysmal features were observed.

She deteriorated progressively and steadily with no suggestion of relapse or remission and died from a terminal pneumonia, twelve months after the beginning of her decline, at the age of 40 years.
Pathological findings
Necropsy showed a thin, middle aged woman with extensive pneumatic consolidation of both lower lobes of the lungs, the bladder mucosa was congested and covered by flecks of pus but no other abnormality was seen outside the nervous system. The brain and spinal cord were removed for further examination and suspended in formol-saline. The fixed brain weighed 1600 grams; it was firm and rubbery in texture with a normal gyral pattern and external appearance. Consecutive slices 1 cm thick were cut, which showed no significant ventricular dilatation. The white matter of the cerebral hemispheres was greyish and gritty in texture with small particles of calcium visible macroscopically in the basal ganglia. There was no atrophy of the hippocampal regions; the structure of the pons, cerebellum, medulla and spinal cord appeared normal. Representative blocks were taken from each slice and sections stained with haematoxylin and eosin, Loyez stain for myelin and cresyl fast violet. Selected material was also stained by Holzer’s method for glial fibres, phosphotungstic acid haematoxylin, the periodic acid Schiff reaction, the Von Kossa method for calcium, and the glial fibrillary acid protein (GFAP) technique. Small portions of formalin fixed material were processed for electron microscopy. Frozen sections were processed by the acid cresyl violet and toluidine blue acetone methods for sulphatide and with the oil red 0 stain for lipid.

Histological preparations showed changes most marked in the white matter of the cerebral hemispheres. There was extensive reduction of myelin in the centrum semi-ovale with patchy sparing of the subcortical arcuate fibres (fig 1). In the myelinated tracts of the internal capsule and the cerebellar peduncles myelin reduction was minimal but there was diffuse reduction of myelin in the cerebellar white matter (fig 2). Myelin stains of the pons, medulla and spinal cord appeared normal. The myelin deficient areas contained numerous hypertrophied astrocytes and fibrils staining positively by Holzer’s method. A notable feature was the presence of very large numbers of homogeneous eosinophilic bodies lying amongst the glial fibres including the subependymal regions but particularly prominent around blood vessels (figs 3, 4). These stained positively with Holzer’s stain and with the GFAP method. Electron microscopy of formaldehyde fixed material showed these bodies to consist of amorphous aggregates of osmiophilic material in association with tightly packed glial filaments (fig 5).

The staining characteristics confirmed that these were Rosenthal fibres as described in Alexander’s disease and other conditions. The distribution of the Rosenthal fibres was much more extensive that the absence of myelin. Many were present in the sub-pial area of the spinal cord, the pons and the internal capsule which contained relatively normal amounts of myelin.

No sudanophilic or metachromatic material was identified in any section. Axon stains showed many surviving axons, marked disruption was present only in the areas of most severe myelin loss and gliosis. The neurons of Ammon’s horns appeared normal and prominent neuronal loss was restricted to the substantia nigra where there was free pigment present within macrophages and lying free in the brain substance. Areas of calcification were examined microscopically; coarse blocks of calcium were found in the thalamus and basal ganglia. Finer perivascular deposits were present in cerebral cortex.

Discussion
The history of this woman’s illness is biphasic. She appears to have had a mild physical and mental handicap from the time of birth but this was a static deficit until her terminal decline began, relatively suddenly, at the age of 39 years. The deficit which was present throughout her life may have been related to perinatal hypoxia although no specific features were found in the brain, macroscopically or histologically, to suggest this. Alternatively, her longstanding motor and intellectual deficit may have been the early manifestation of the pathological process which led to her eventual death. Indeed the widespread calcification most marked in the basal ganglia would favour a chronic rather than an acute process.

Histologically, in the areas where there was loss of myelin with secondary gliosis, this appeared to be a diffuse process and we found no suggestion of the formation of gliotic plaques as are found secondary
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Fig 2  Sagittal section of the left cerebellar hemisphere. Myelin stains densely in the peduncle but the corpus medullare stains poorly. Loyez ×2·5.

Fig 3  Section from frontal white matter showing perivascular collection of eosinophil bodies. Haematoxylin and eosin ×240.
Fig 4. Eosinophil bodies abutting the median raphe of the spinal cord. Haematoxylin and eosin x240.

Fig 5. Electron micrograph showing granular osmiophilic material in association with glial filaments x31 000.

to circumscribed areas of demyelination in multiple sclerosis. The history of her illness is also very much against this diagnosis and the whole disease process seems more in keeping with a primary leucodystrophy.

The formation of Rosenthal fibres is a non-specific process. They were first reported in 1898 as a focal phenomenon, occurring in cases of syringomyelia and intramedullary ependymoma. They have subsequently been described occurring focally in a variety of degenerative and neoplastic lesions including astrocytomas, optic nerve gliomas and plaques of demyelination in multiple sclerosis. Focal formation has also been described in areas of longstanding reactive gliosis around craniopharyngiomas and haemangioblastomas. More widespread formation has been described in gliomatosis, central pontine myelinolysis, vincristine therapy, radiation therapy and encephalomalacia. Diffuse Rosenthal fibre formation, with and without demyelination, has been reported in two patients. This was associated with widespread inflammatory cell infiltration of the nervous system and was regarded as an anomalous response to the inflammatory infiltrate in patients somehow "programmed" to react in this way.

Widespread diffuse Rosenthal fibre formation particularly in the subpial, perivascular and subependymal zones, associated with diffuse demyelination and preservation of neurons, is the histological appearance characteristic of Alexander's disease. The typical clinical features are infantile onset, megalencephaly, progressive spasticity and dementia, leading to death in months to years. Recently, a specific CT scan appearance of well demarcated low attenuation lesions involving the deep cerebral white matter but sparing the subependymal regions has been described. There are reports in the literature of cases of "Alexander's disease" occurring in adults. These have received critical appraisal and the subject was extensively reviewed by Herndon et al. These authors classified the diseases characterised histologically by diffuse Rosenthal fibre formation into three groups:— (a) classical infantile onset Alexander's disease, (b) four cases (Refs 17, 18, 19 and patient no 3 of their own...
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