

Correlative clinical, neuroradiological and pathological findings in subacute sclerosing panencephalitis

A report of 5 cases

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Summary

Changes in the brain in subacute sclerosing panencephalitis (SSPE) as detected on computed axial tomography (CT) have so far been insufficiently assessed. An attempt was therefore made to correlate the clinical, neuroradiological and pathological findings in 5 consecutive, unselected cases, 4 of which were somewhat atypical. It is concluded that within the context of a degenerative neurological disorder of childhood, the CT findings in SSPE correlate well with clinical staging, and also illuminate certain aspects of the pathogenesis and dynamics of the disease process.

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A clinical diagnosis of subacute sclerosing panencephalitis (SSPE) is readily confirmed by the demonstration of a raised measles antibody titre in the cerebrospinal fluid (CSF).¹ Often, however, the clinical presentation is unusual, and SSPE may not even be considered. In these circumstances, children with neurological illness usually undergo computed tomography (CT), so that abnormalities of hemispheric grey or white matter may be apparent for some time before a diagnosis of SSPE is entertained and the CSF assay performed. The neuroradiological diagnosis of SSPE is thus frequently a retrospective one, and there have been conflicting reports in the recent literature on the interpretation and value of brain scanning in this condition.^{2,3}

In this article, we present 5 cases of somewhat atypical SSPE; an attempt is made to correlate the clinical staging of the disease with the CT findings and the lesions observed in brain biopsy samples.

Patients and methods

The study comprised 5 consecutive and unselected cases of SSPE seen at Tygerberg Hospital between 1977 and 1980 (Table I).

Scans in the orbitomeatal line were obtained with the EMI Mk

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I Scanner, with 13 mm slice thickness, and the routine use of contrast material (60% meglumine iohalamate). Brain biopsies were performed under general anaesthesia, the site depending to a certain extent on the scan findings. Material was cut in the fresh state for virological studies, and to allow glutaraldehyde fixation of the largest surface of clearly recognizable grey and white matter. After 1 hour in this fixative, smaller (3 x 3 mm) representative blocks of cortex and white matter were trimmed anatomically and returned to the glutaraldehyde, while the remainder of the tissue was transferred to formalin for routine processing. Both plastic and paraffin sections were cut at right angles to the surface of the brain. Stains included a haematoxylin and eosin (HE), luxol blue-cresyl violet (LB/CV), Holmes' silver-cresyl violet (Holmes/CV) and Lendrum's phloxine tartrazine-haemalum stain for inclusions. The plastic sections were subjected to routine processing for ultrastructural examination.

Results

CT findings (Table II)

Patients 2, 3 and 5, judged clinically to be in stage I or II of the disease, all showed neuroradiological evidence of small ventricles, interpreted as brain swelling — the 'mass effect'. Areas of low density were also apparent, mainly in the vicinity of the posterior horns and the posterior limbs of the internal capsule region (Fig. 1a). Atrophic changes were considered to be represented by ventricular dilatation, prominence of major fissures and cisterns, and more diffuse (lobar or hemispheric) decrease in white-matter density (Figs 1b, 2a, 2b). These alterations were observed in patient 1, placed in stage III initially, and in patients 3 and 4 after progression of the disease to stages III-IV.

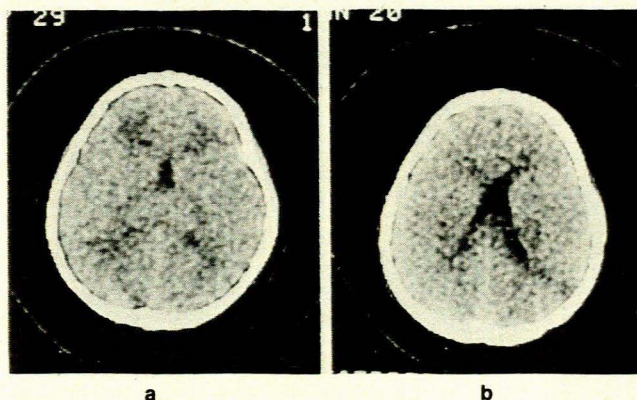


Fig. 1. Case 3: a — scan showing phase of brain swelling, with symmetrical low-density areas in white matter and 'tight' ventricles; b — probably phase of commencing brain atrophy, with white-matter low-density areas in relation to the anterior and posterior horns, as well as ventricular dilation.

TABLE I. CLINICAL AND VIROLOGICAL DATA

Case	Presenting clinical features	Initial diagnosis	Measles anti-body titre	Clinical staging of SSPE	Duration of illness following diagnosis
1 W,F, 5 yrs, W. Cape	Involuntary jerking movements of left arm 4 wks before admission; 1 wk later developed generalized myoclonus and intellectual deterioration. Stuporous, with ataxic breathing; pyrexial; multifocal myoclonus and generalized spasticity; plantar reflexes extensor; fundi normal.	Encephalitis, probably SSPE	Serum 1:320 CSF 1:32	III	Death at 21 mo.
2 W,M, 5 yrs, SWA	Onset of aggressive behaviour 3 weeks before admission; over the next few weeks tendency to fall to one side, followed by seizures and vomiting. Disorientated; occasional myoclonic jerks of right leg; papilloedema; remainder of neurological examination negative.	Posterior fossa tumour/mass	Serum 1:5 120 CSF 1:640	II	Death at 6 mo.
3 C,F, 9 yrs, W. Cape	Sudden onset of constant grimacing movements and inability to walk. Conscious and orientated; choreiform movements of face and limbs. Over following month onset of coma-vigil state, generalized myoclonic jerks and hyperreflexia with Babinski responses; fundi normal.	Sydenham's chorea	Serum 1:5 120 CSF 1:1 250	II-III	Death at 14 mo.
4 C,M, 11 yrs, SWA	Admitted stuporous to a rural hospital in SWA. No clinical details other than 'fits' during the past year. Coma-vigil state, with decorticate posturing; generalized hyperreflexia with Babinski responses; no abnormal movements; fundi normal. Over following 2 wks developed Cheyne-Stokes respiration; all deep reflexes disappeared and muscle atrophy ensued.	Adrenoleucodystrophy	Serum 1:2 560 CSF 1:320	III-IV	Death at 4 mo.
5 W,M, 8 yrs, SWA	Onset of somnolence 1 wk before admission; for about 2 wks could only be roused for meals; 2 wks later became hyperactive, easily distracted, and at times unable to recognize parents. Disorientated, hyperactive, with inappropriate effect; probably dysphasic. Fundi normal and remainder of neurological examination negative.	Acute psychosis — behavioural disorder	Serum 1:10 240 CSF 1:1 280	I	Still living 1 yr later

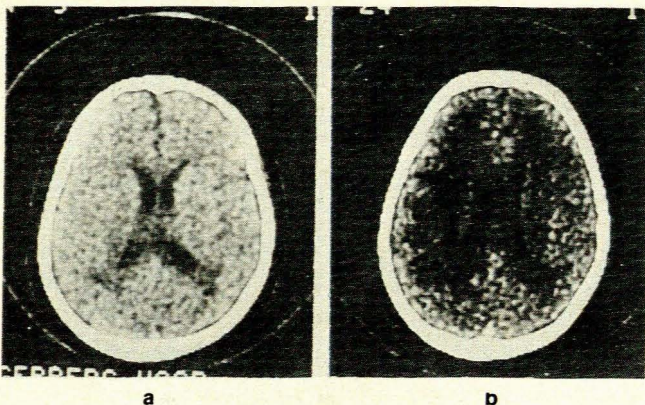


Fig. 2. Case 4: a — early phase of white-matter disease with marked low-density areas surrounding the posterior horns; b — progressive lesion with severe, somewhat asymmetrical myelin loss and ventricular dilatation (histological picture of sudanophilic leucodystrophy — see Fig. 4).

Pathological findings (Table II)

The presence of perivascular accumulations of chronic inflammatory cells suggested an encephalitic process in all cases except possibly patient 4, in whom the picture was one of a sudanophilic leucodystrophy (Figs 3a, 3b and 4). There were no detectable alterations in cortical lamination or neuronal structure; in particular, no inclusions could be found. Moderate-to-severe myelin loss with accompanying gliosis was seen in patients 1, 2 and 5. Inclusions were also sought using the electron microscope, but this was unsuccessful.

Discussion

First described by Dawson in 1933, SSPE is now generally regarded as a relatively slow infection of the central nervous system caused by a measles-like virus. The usual clinical picture is one of intellectual deterioration, myoclonic seizures, signs of

TABLE II. CT AND PATHOLOGICAL FINDINGS

Case	CT appearances	Morphological changes
1	Generalized widening of major sulci with multiple areas of non-enhancing low density, worse in left occipital region.	Cortical vessels show dense perivascular lymphocytic infiltrate; cortex and white matter diffusely infiltrated by plasma cells. No inclusions.
2	Mild, diffuse, symmetrical low-density areas in white matter; small ventricles, with obliteration of anterior and posterior horns (phase of brain swelling) (as in Fig. 1a)	Perivascular lymphocytic infiltrates, confined to grey matter; neuronophagia, numerous infiltrating plasma cells; marked myelin pallor and gliosis in white matter, with microglial clusters. No inclusions.
3	<i>1st scan:</i> mild diffuse white-matter low density, with small ventricles (Fig. 1a) <i>2nd scan after 6 mo.:</i> widened lateral sulci, ventricular dilatation and periventricular low density, especially posterior horns (Fig. 1b)	Very mild lymphocytic cuffing of occasional cortical vessels (Fig. 3a); sparse plasma cell infiltrate of white matter parenchyma, with some astrocytic hypertrophy. No inclusions (biopsy at time of 1st scan).
4	<i>1st scan:</i> mild ventricular dilatation, with marked circumscribed low densities around posterior horns (Fig. 2a) <i>2nd scan after 1 mo.:</i> ventricles more dilated; diffuse white matter, low density, worse on left (Fig. 2b) (phase of brain atrophy)	Picture of orthochromatic leucodystrophy: severe myelin breakdown; some plasma cells visible in perivascular spaces (Fig. 4). Cerebral cortex normal; no inclusions.
5	Mild, diffuse low-density of hemispheric white matter, combined with very small ventricles.	Normal cerebral cortex, white matter shows dense perivascular lymphocytic infiltrate with adjacent gliosis (Fig. 3b); no inclusions.

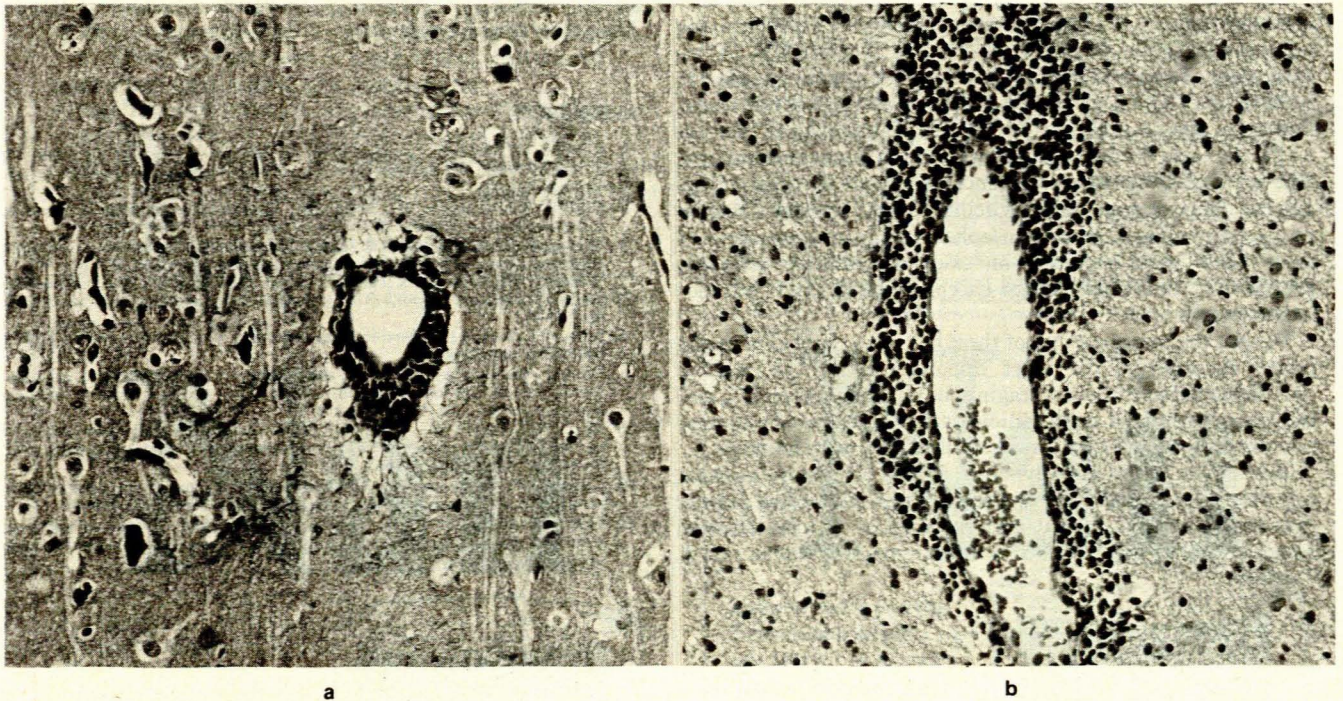


Fig. 3. Range of inflammatory infiltrate: a (case 3) — mild cortical vessel cuffing; b (case 5) — marked lymphocytic and plasma cell infiltration of white-matter perivascular space, with associated myelin loss and astrogliosis.

pyramidal and extrapyramidal involvement, and eventually death in a vegetative state. The course is typically one of months, but both this and the clinical features are liable to considerable variation.⁴

The progression of SSPE may be divided into four stages.⁵ Onset of the disease is heralded by intellectual impairment and behavioural disturbance, the former usually manifested as a rapid deterioration in school performance. Stage 2 is characterized by abnormal movements, particularly myoclonus, together with long-tract signs. In stage 3, the motor disturbances

worsen with hypertonia predominating, myoclonus increases and then decreases, and a coma-vigil state supervenes. The survivors, spastic and demented, constitute stage 4. Although, in our own cases, clinical staging of the disease correlated well with the symptoms and signs once the diagnosis had been established (Table I), it has to be emphasized that only in case 1 was SSPE entertained as the initial diagnosis.

In the other 4 patients the diversity of symptoms and signs led to the diagnoses shown in Table I, and for which the CT scans were requested. In view of the likelihood of a disease process

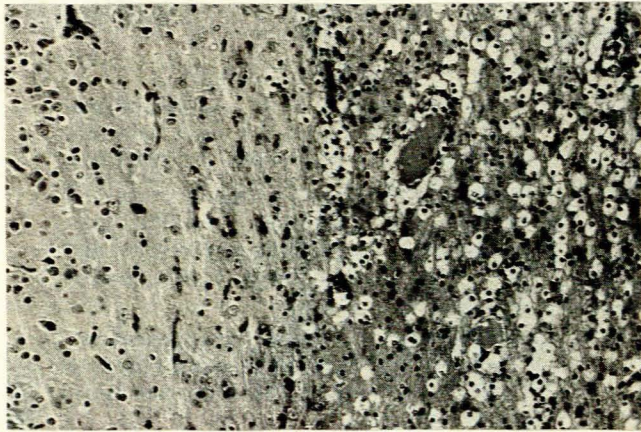


Fig. 4. Case 4: sharply circumscribed lesion with normal cortex (left) and active demyelination (right). Cells with haloes are lipophages. Picture is that of a sudanophilic leucodystrophy (scan Fig. 2b).

other than SSPE being considered in future cases, it becomes apparent that there is a need to determine whether the CT findings may be usefully correlated with the clinical staging and pathology of SSPE. The extent and topography of the pathological process have been positively correlated with clinical and neurophysiological findings in an excellent and detailed paper by Ohya *et al.*,⁶ in which the march of the disease from occipital to frontal lobes and from cerebrum to brainstem and cord was also confirmed. To the best of our knowledge, in only one other paper³ has a single case of SSPE been studied from the point of view of clinical, CT and pathological correlation. In this case, areas of reduced density in white matter corresponded to inflammatory and demyelinating lesions. The aim of our study, therefore, was to evaluate the role of CT-scanning in cases of SSPE of variable (and sometimes unusual) symptomatology. The 'mass effect', to which reference has already been made (Fig. 1a), has the same appearance, whether of viral, post-traumatic or post-ictal aetiology,⁷ while non-enhancing, patchy, low-density areas have been reported in cases of multiple sclerosis, progressive multifocal leuco-encephalopathy and adreno-leucodystrophy.⁸

Despite the nonspecificity of these lesions, a number of useful points do emerge, the most important being the positive correlation between clinical staging and changes seen on CT, and the apparently valid neuroradiological impression of a disease process progressing from brain swelling to brain shrinkage.

Bearing in mind the dynamic nature of these findings, together with the high local incidence of this disease,⁹ we believe that the combined clinical and radiological features become rather typical of SSPE. It is also worth remarking that in case 2,

CT was a rapid non-invasive means of excluding a posterior fossa mass, and in case 5 the organic basis for psychiatric disturbance was confirmed. In combination with brain biopsy, CT has also illustrated two correlative pathological features of great interest: one is that small ventricles ('mass effect') and demyelinating foci may coexist, leading one to conclude that whatever the basis for brain swelling is, it is not within these low-density areas. The second point relates to the selection of the biopsy sample, since this was always determined by the accessibility of low-density areas in the right hemisphere, and the assumption that such lesions would be most informative. In not one case could inclusions be found, in spite of the presence of typical perivascular infiltrates normally associated with encephalitis.

In case 4 the absence of inclusions, combined with a florid sudanophilic leuco-encephalopathy, was actually misleading and it is therefore suggested that brain biopsy samples should be taken from a site which appears unaffected on radiography.

From a combined study of these 5 cases, we conclude that within the context of a progressive cerebral disorder of childhood, the demonstration of posteriorly situated, non-enhancing low-density areas of white matter strongly suggests the possibility of SSPE. The presence of a 'mass effect' with these lesions, or their persistence and eventual association with ventricular dilatation, may be positively correlated with the clinical stage of the disease.

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