doi:10.1093/brain/awp260 Brain 2009: 132; 2623–2626 | 2623

BRAIN
A JOURNAL OF NEUROLOGY

FROM THE ARCHIVES

Spastic pseudosclerosis (cortico-pallido-spinal degeneration), *by* Charles Davison (New York), *Brain* 1932: 55; 247–264 and Severe dementia associated with bilateral symmetrical degeneration of the thalamus, *by* K. Stern (From the National Hospital, Queen Square, London), *Brain* 1939: 62; 157–171.

Dr Davison has recently seen two cases in adults—running a rapid course characterized by mental symptoms, pyramidal and extrapyramidal signs, and muscle atrophy—that 'do not conform to any disorder recognized hitherto'. J.R. has a 3-year history of weakness in the left leg that does not change until 1 year before presentation, when his speech deteriorates and the upper limbs become involved. On admission he is bedridden, drooling, with spasmodic laughter and crying and severe dysarthria. Examination shows rigidity, dystonia in a 'striatal attitude', increased tendon reflexes and bilateral Babinski signs, as well as muscle atrophy with generalized 'fibrillary twitchings'. He is dishevelled, with impaired memory and responds only to simple commands. Bulbar function deteriorates thereafter and within a few months he is dead from aspiration pneumonia. At autopsy, the brain and spinal cord are obviously atrophic. Microscopic examination shows proliferated and occluded small vessels, some with calcification, in the cortex and basal ganglia. However, the most conspicuous histological findings are destruction of ganglion cells in the third, fifth and sixth layers of the cortex, with vacuolation; loss of the giant pyramidal Betz cells; 'enormous' proliferation of microglia and protoplasmic astrocytes in white and grey matter; marked neuronal loss and demyelination of surviving axons, in the rostral and middle portions of the globus pallidus, corpus Luysii and paraventricular nuclei; and degeneration both of the pyramidal tracts and anterior horn cells (Fig. 1). Taken together, these pathologies are not those of a primary inflammatory or vascular disorder; nor are the plaques and other pathological hallmarks of Alzheimer's disease present; and in the spinal cord, the appearances are typical of amyotrophic lateral sclerosis.

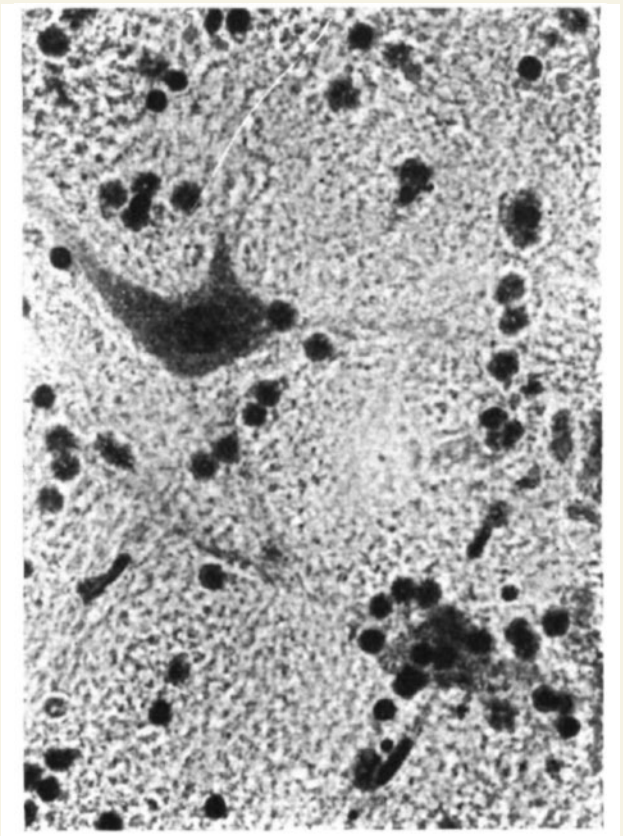

Figure 1 Case 1 (J.R.): two ganglion cells from the globus pallidus; one showing satellitosis and the other poor chromatin substance. Cresyl violet stain, ×700 (reproduced from Davison, 1932).

E.G. dies the day after admission 'in a stuporous state'. The story is of progressive difficulty with walking and intellectual failure over the previous year. No diagnosis has been established at two other institutions. Examination is necessarily rudimentary and confined to establishing that she has generalized pyramidal and extrapyramidal signs including a Parkinsonian facies, dementia and catatonia—but no muscle atrophy. Macroscopically, there is cortical atrophy, in particular of the temporal lobe but also involving other areas. Microscopic examination of the nervous system shows abnormalities that are similar to those observed in J.R., but differ in several respects (Fig. 2). Histologically, apart from calcified vessels and atherosclerosis, the changes seen are swelling and loss of ganglion cells in layers five and six; reduced numbers of Betz cells; no apparent alteration in microglia or the presence of 'Giant' glia, although protoplasmic astrocytes are increased; extensive demyelination in the basal ganglia with loss of ganglion cells especially in the globus pallidus; and the spinal cord showing demyelination, axonal transections, gliosis and

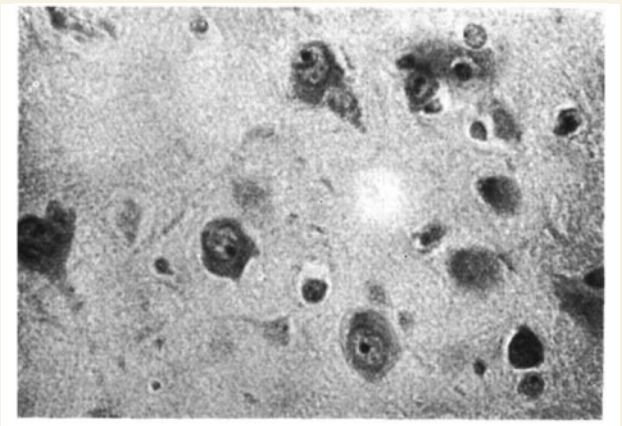

Figure 2 Case 2 (E.G.): swelling of the ganglion cells from the frontal convolution, eccentric nuclei and poor Nissl substance. Cresyl violet stain, ×700 (reproduced from Davison, 1932).

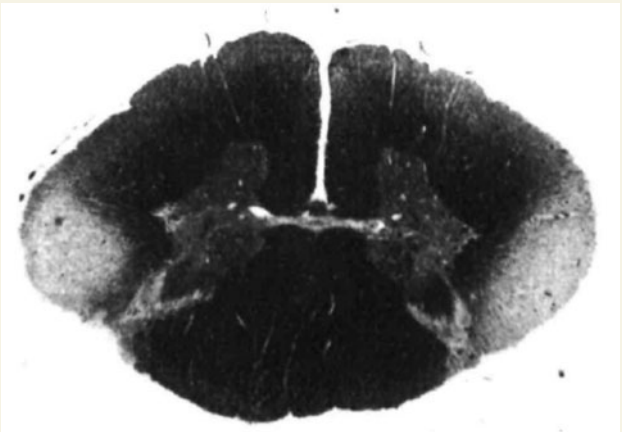

Figure 3 Case 2 (E.G.): transverse section of the spinal cord showing demyelination of the lateral pyramidal tracts. Myelin sheath stain (Weil modification) (reproduced from Davison, 1932).

swollen anterior horn cells that are much reduced in number—together, the appearances again suggesting amyotrophic lateral sclerosis (Fig. 3).

Although multiple sclerosis, Wilson's disease and amyotrophic lateral sclerosis with mental symptoms are considered, no diagnosis has been made in life. But Dr Davison immediately identifies the similarity of his cases to those described by Creutzfeld in 1920 and by Jakob in 1920 and 1921, which Jakob has designated as 'spastic pseudo-sclerosis'. The clinical features of Jakob's cases were early mental and physical symptoms with a subsequent progressive yet fluctuating course manifesting diffuse pyramidal, 'thalamo-striatal' (movement disorder) and cerebellar deficits, and ending with severe cognitive impairments 'which reminded one of Korsakoff's syndrome', coma and death after an interval of several weeks to 1 year. Pathologically, they had shown diffuse cortical lesions and involvement of the striatum, thalamus, bulbar nuclei and anterior horn cells with microscopic evidence for 'ganglion cell degeneration, fatty degeneration, swelling, neuronophagia . . . outfall of ganglion cells . . . small areas of devastation (''Verödungscherde'') . . . proliferation of protoplasmic glia . . . [and] . . . as a result of the lesions of the giant pyramidal cells of Betz in the precentral gyrus . . . a slight descending degeneration of the pyramidal tracts of the spinal cord'. There are similarities to a case described by Alzheimer in 1916, although without such marked changes in the cortex; a case of von Economo and Schilder from 1920 is clearly also of the same type but here with even more marked striatal changes; and Davison lists six further examples of what he now describes collectively as 'the Creutzfeld-Jakob group of spastic pseudo-sclerosis'. His cases belong in that same category even though he notes certain minor clinical, and some more problematic histological, discrepancies including relative sparing of the thalamus and less neuronophagia and glial abnormalities. Of the other possibilities, the condition recently described by Hallervorden and Spatz has some pathological resemblance but is clinically quite distinct; and the features do not match those of Wilson's disease, the pseudo-sclerosis of Westphal–Strümpell, chronic encephalitis or amyotrophic lateral sclerosis with mental symptoms. Jakob, too, had considered the diagnoses of multiple sclerosis, general paralysis, Alzheimer's disease, dementia praecox (schizophrenia) and pseudo-sclerosis of Westphal–Strümpell in his original descriptions, but no one of these seemed right; and, prior to the autopsy, he had even wondered if everything might be due to a functional disorder. Taking all these cases together, Dr Davison considers that 'for the present it is advisable to adopt Jakob's title ''spastic pseudo-sclerosis'' '.

Seven years later, Dr (Karl) Stern wants to describe a case 'for which no analogy could be found in the literature . . . [and which] appears to throw more light on the question of disturbance of thalamic functions, and to contribute to the morbid anatomy of the thalamus'. After feeling 'run-down', the patient (not identified) develops polyuria and polydipsia, becomes drowsy, progressively mute and unable to read or write, amnesic and confused. On examination, his appearance is of stuporose bewilderment with echopraxia and echolalia, constant fidgeting and irrelevant pointing; but no objective physical abnormalities other than loss of pupillary reactions to light and convergence. The course in hospital is characterized initially by primitive pouting, sucking and grasp responses with poor attention and fatuous behaviour, subsequently fading into coma and death in <1 year from onset. The consultant in charge, Dr FMR Walshe, initially diagnoses general paresis but the serology is normal; other possibilities are Alzheimer's or Pick's disease but eventually the working diagnosis in life is frontal tumour. This is not found at autopsy which reveals conspicuous lipoid neuronal degeneration and gliosis, involving 'all kinds of glia cells . . . fibrous astrocytes and monster glia', throughout the white and grey matter of the cerebrum and, more markedly, in the sharply defined parts of the thalamus some nuclei of which have completely disappeared (Fig. 4).

Neither inflammatory nor vascular aetiologies seem likely and there is nothing to suggest Pick's or Alzheimer's disease. The widespread but patchy cortical involvement raises the issue of whether the extensive thalamic changes might have arisen

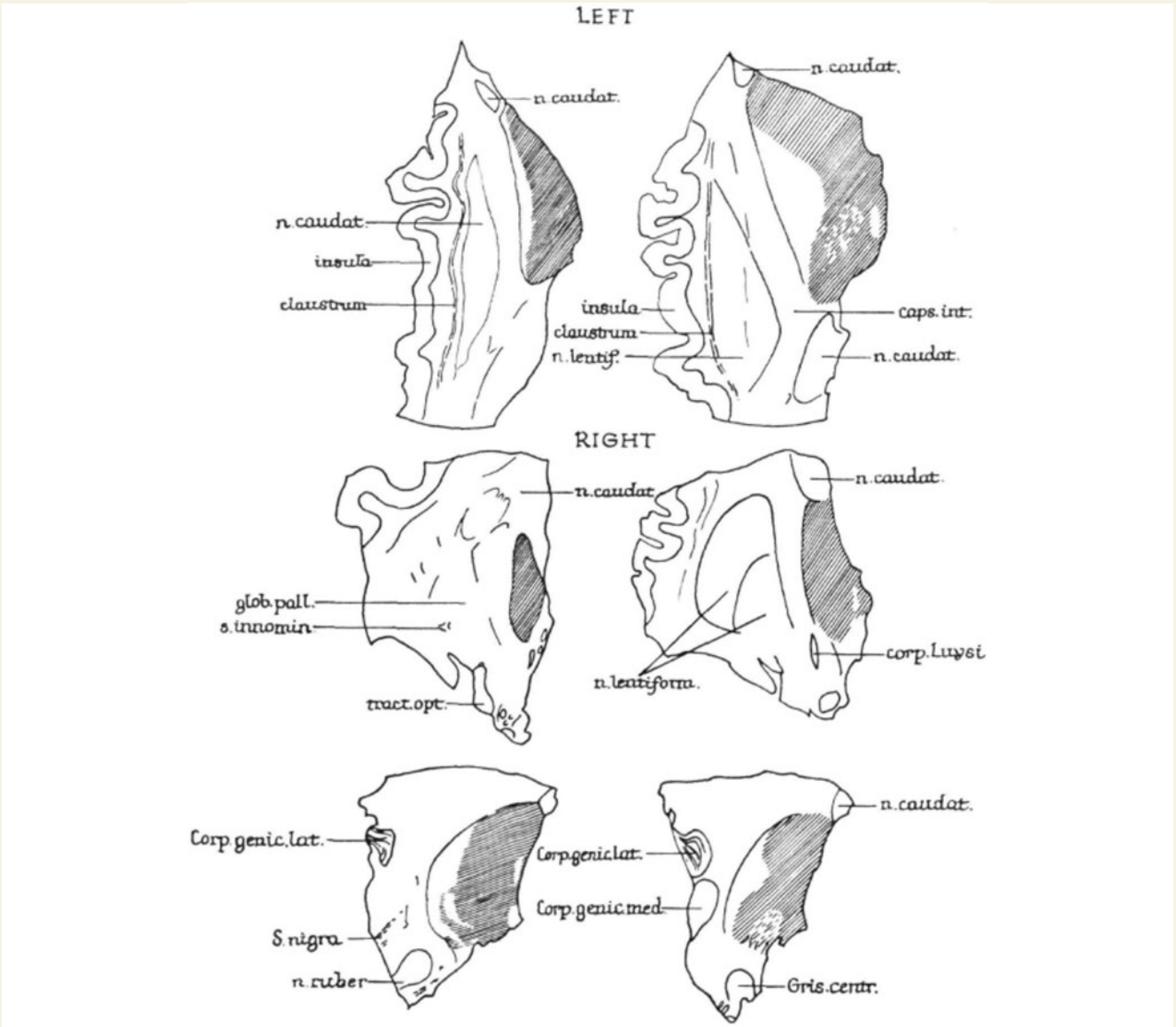

Figure 4 Representative sections from basal ganglia of both sides in camera lucida drawings. The left basal ganglia were cut in horizontal sections (upper two pictures). The degenerated areas are shaded (reproduced from Stern, 1939).

secondarily through degeneration of cortical connections. But Dr Stern concludes: 'from these facts it appears, by the exclusion of all other possibilities, that this is a genuine case of a system degeneration in the thalamus' manifesting the typical features of any other neurodegenerative disorder. These are symmetry, loss of neurons but with minimal 'fatty degeneration' and sparing of discrete developmental entities or systems, notably the phylogenetically ancient ventral nucleus and geniculate bodies, and the midline nuclei. The concept that the most recent structures suffer first in neurodegenerative disease plays on the concept of 'abiotrophy' proposed by Edinger. Lastly, Dr Stern considers whether his case might be similar to the widespread disease of the basal ganglia and cortex now known as 'Jakob-Creutzfeld's' disease; but he rejects this explanation through the absence of thalamic gliosis, and involvement of the lenticular nucleus and globus pallidus, pyramidal and extrapyramidal systems and motorneurons. 'It is obvious that the present case cannot possibly be classified even as an atypical form of ''Jakob-Creutzfeld's'' or any other known disease'.

Having declared his thalamo-centric interpretation of the pathology, Karl Stern is equally confident in arguing that the cortical changes cannot account for the degree of dementia displayed in life. Rather, only the thalamic involvement can explain the cognitive failure (and the hypersomnolence). Here, Dr Stern draws on his own previous work attributing mental deterioration to thalamic glioma, especially when medial structures are involved bilaterally; and explained mechanistically on the basis that large swathes of the frontal cortex have become disconnected from afferent thalamic impulses. On the iridoplegia, Dr Stern can only make the contribution that this must be due to involvement of structures around the third ventricle immediately rostral to the superior colliculi; and that such pupillary abnormalities obviously

may occur in situations other than damage to the peripheral neurons that subserve the light and convergence reflexes. Although Dr Stern summarizes his case as 'a peculiar system disease which has not hitherto been described' modern commentators, tracing the historical record of cases now considered to be examples of a prion disorder, include this report of thalamic disease from the department of neuropathology at Queen Square (see, for example, Cali *et al*., *Brain* 2006; 129: 2266–77)—a pathological sub-type that is further emphasized in the papers by Raffaele Lodi and colleagues (page 2680) and Isak Prohovnik and others (page 2669) in the present issue.

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