A DIFFICULT CASE

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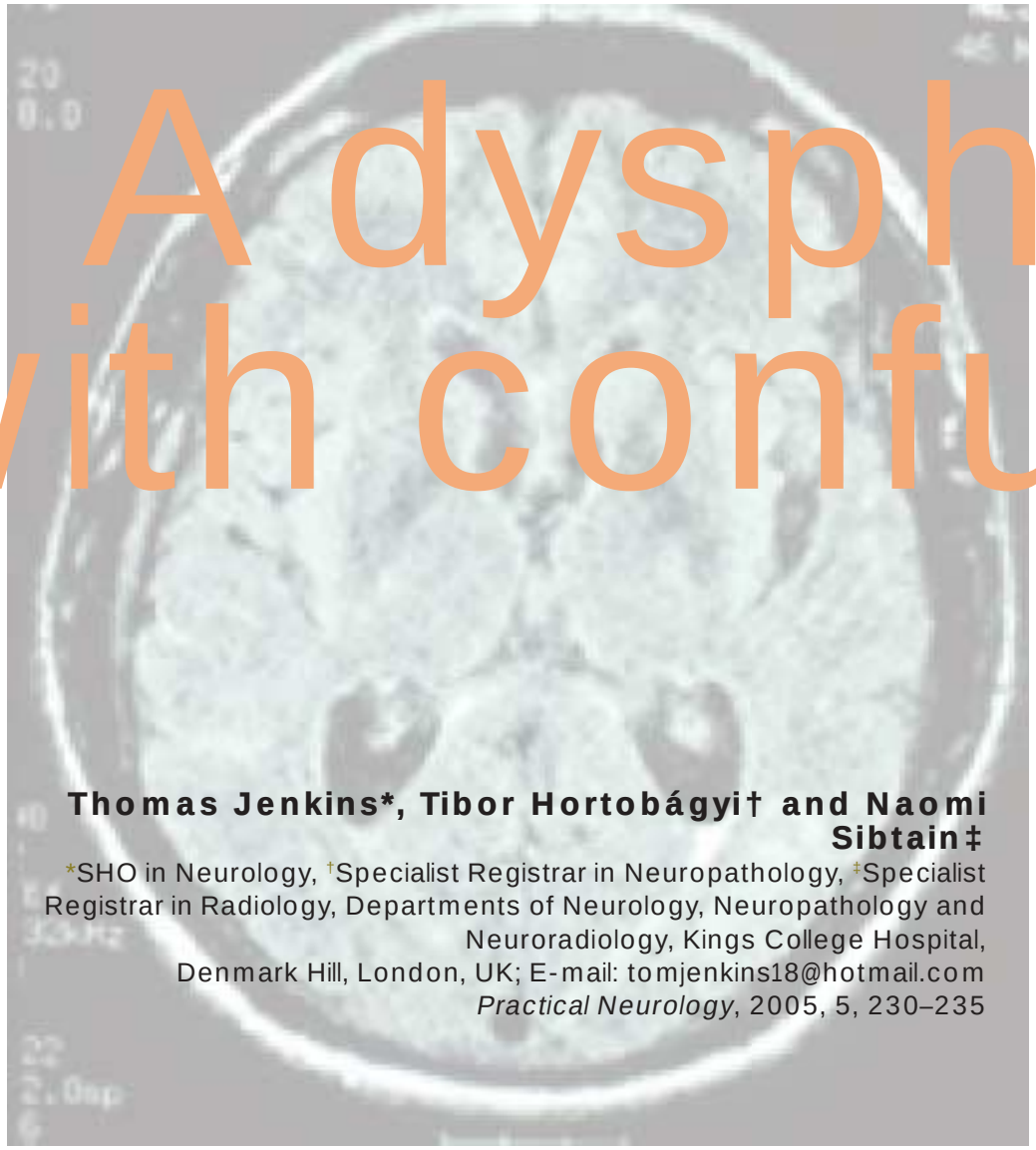

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THE STORY

A man in his forties was admitted with confusion, headache and diabetic ketoacidosis. He had a long history of type 1 diabetes mellitus and hypertension. His neighbours had found him pacing up and down, and not speaking. They said he had not been himself for the last few weeks. He had been complaining of headache. Over the previous 36 h he had developed word-finding difficulties. He was taking porcine insulin, aspirin and antihypertensive drugs. He did not smoke but he drank occasional alcohol.

Seven years previously he had had an episode of ataxia, dysarthria and polyarthropathy for 4 months. Brain magnetic resonance imaging (MRI) was normal but cerebrospinal fluid (CSF) examination showed a raised protein (155 mg/100 mL) and 86/cumm white cells (100% lymphocytes). He recovered without treatment.

EXAMINATION AND INVESTIGATIONS

His temperature was 39.2° C. He had a mixed expressive and receptive dysphasia, mild right facial weakness and background diabetic retinopathy. Everything else was normal.

Blood tests showed a glucose of 32.6 mmol/L, sodium 133 mmol/L, potassium 6.5 mmol/L, urea 14.1 mmol/L and creatinine 156 µmol/L. Liver function, calcium and C-reactive protein were all normal. Full blood count was normal except for a slightly increased white cell count 11 790/µL. (neutrophils 10 570/µL, lymphocytes 730/µL). Arterial blood gases showed a partially compensated metabolic acidosis with pH 7.22 and no hypoxia. Urinalysis showed ketones, protein and blood. Blood and urine cultures were sterile. Chest Xray was normal. He was treated with intravenous fluids, insulin and ceftriaxone.

Computerized tomography (CT) of the brain showed mild dilatation of the temporal horns of the lateral ventricles. The CSF opening pressure was 16.5 cm water with no xanthochromia, white cells or organisms, protein was 85 mg/100 mL and glucose 13.7 mmol/L (plasma 18.3 mmol/L). CSF viral serology and polymerase chain reaction for herpes simplex and zoster, Epstein–Barr, cytomegalovirus and enterovirus were negative. Oligoclonal bands of IgG were present in the CSF but not the serum.

CLINICAL COURSE AND FURTHER INVESTIGATIONS

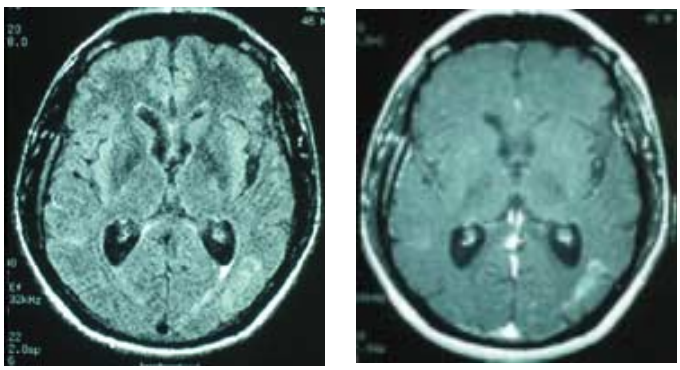
By day 2 of his admission, his fever and metabolic abnormalities had recovered and his facial weakness had improved, but his language difficulties and confusion persisted. At this stage some kind of vascular disorder in the brain or infective encephalitis were considered likely possibilities. Electroencephalography showed brief bursts of frontal slow waves on a background of normal alpha rhythm. Echocardiogram and carotid Doppler scans were normal. On day 3 he had a generalized tonic clonic seizure and was started on phenytoin.

During days 4–14 of his hospital admission he continued to have language and memory difficulties and remained confused. He had two more tonic-clonic seizures. His temperature spiked to 39.7° C. Serial blood and urine cultures were sterile. Repeat chest X-ray was normal. Blood serology was negative for human immunodeficiency virus, cytomegalovirus, toxoplasmosis, syphilis, Coxiella, Chlamydia, Mycoplasma, Borrelia, human T cell lymphotropic virus, hepatitis B and C and Brucella. Tumour markers were negative (prostate specific antigen, alpha fetoprotein and Ca 199). Serum angiotensin converting enzyme (ACE), lactate dehydrogenase and rheumatoid factor were normal. Antinuclear, anti neutrophil cytoplasmic, antineuronal, anti GAD and anti-voltage gated potassium channel antibodies were negative. Brain MRI showed a slight increase in FLAIR signal in the CSF overlying the left parietal cortex, which is non-specific and seen in early infarct, subarachnoid haemorrhage and meningitis. CT angiography to help exclude an ischaemic encephalopathy secondary to aneurysmal subarachnoid haemorrhage was normal. He received ceftriaxone for 10 days and aciclovir for 14 days.

On day 23 he deteriorated. He did not answer questions or obey commands. His speech was rambling and he sat with his arms outstretched in front of him. Neuropsychometry confirmed severe global cognitive deficits. A brain CT scan did not show anything new. CSF showed no cells, protein 104 mg/100 mL, glucose 4.7 mmol/L and no acid fast bacilli or cryptococcal antigen. Chest, abdomen and pelvis CT showed hepatomegaly and some small retroperitoneal lymph nodes. There was no reaction to a Heaf test. Brain SPECT scans showed non-specific perfusion defects, white cell scan showed right molar and right parietal hot spots but there was no clinical evidence of cerebral abscess, nor did any hotspot correlate with the MRI findings.

At times his behaviour became increasingly odd and paranoid. He laughed inappropriately and made flippant comments out of context. He stopped listening to his personal stereo because he was convinced it was interfering with his thoughts. He heard dogs barking under his bed and thought the other patients were plotting against him. MRI was repeated (Fig. 1). His symptoms fluctuated and on some days he was quite settled. Discussion took place whether to proceed to brain biopsy with its inherent risks in order to make a definitive diagnosis, to treat empirically with steroids, or to watch and wait to see if he improved spontaneously.

On day 72 the decision was made to do a right frontal brain and meningeal biopsy, because he had not shown sustained improvement and there were concerns about using steroids whilst the possibility of an infective aetiology remained. The frontal approach was chosen to minimize the risk of complications. The dura was unremarkable but the brain showed a granulomatous vasculitis with multinucleated giant cells in the deep cortical layers and inflammatory cells in and around vessel walls (Fig. 2). A Gallium 67 citrate scan subsequently



(a) (b)

Figure 1 (a) Brain MRI axial FLAIR image showing hyperintensity predominantly in the cortex and subcortical white matter of the left parietal lobe. (b) MRI axial T1 image post gadolinium showing nodular enhancement in the left parietal cortex.

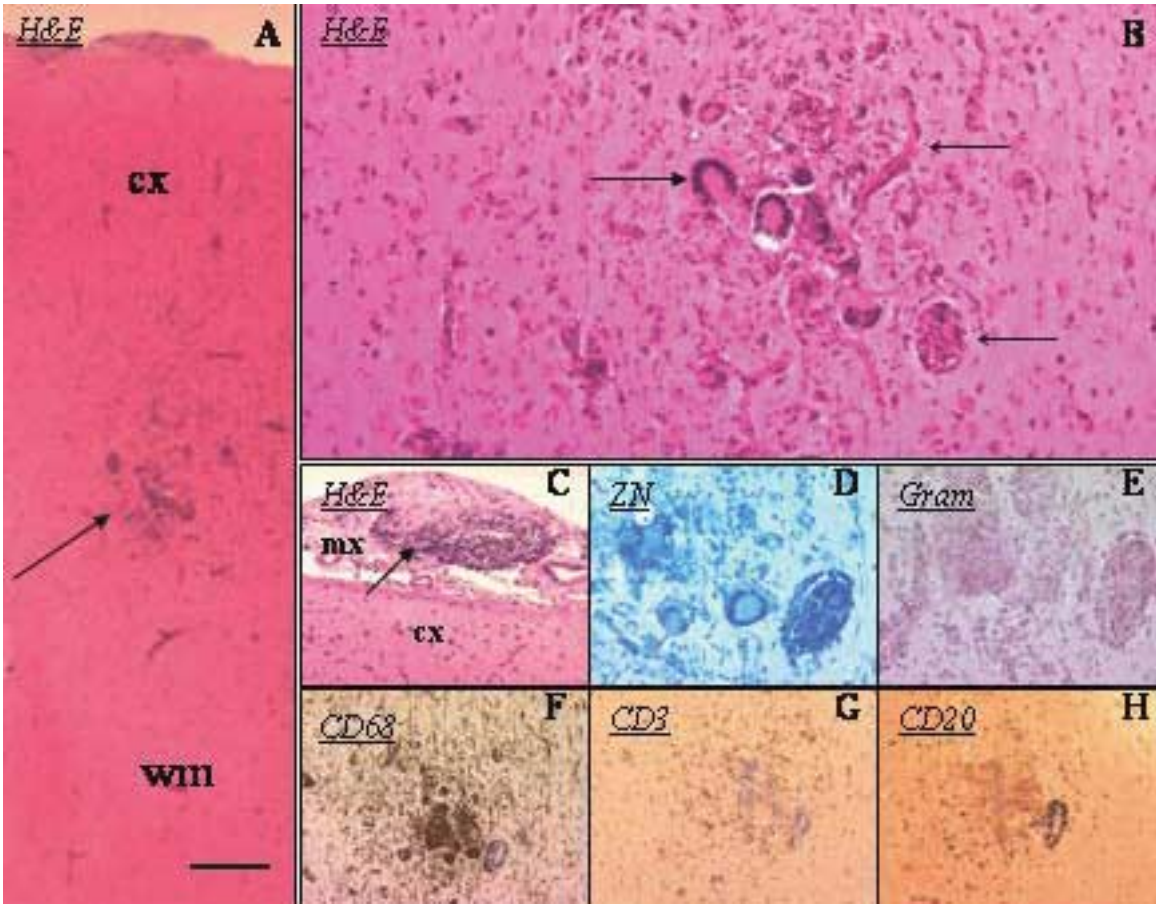


Figure 2 Right frontal brain biopsy showed a focus of non-necrotic granulomatous inflammation which affected the middle layer of the cortex. (A) The granulomatous lesion (arrow) in the deep cortex with prominent blood vessels, inflammation and multinucleated giant cells. (haematoxylin and eosin (H&E), original magnification × 20; scale bar: 50 μm) cx = cortex, wm = white matter, mx = leptomeninges. (B) Close up showing multinucleated giant cells (arrow pointing right) and blood vessels (arrows pointing left) with mononuclear inflammatory cells infiltrating and surrounding the vessel wall. (H&E, original magnification × 200). (C) Focal fibrotic thickening of the leptomeninges with collection of lymphocytes (arrow). (H&E, original magnification × 200). (D) Ziehl-Nielsen stain for acid fast bacilli was negative (original magnification × 200). (E) Gram stain was negative (original magnification × 200). (F–H) Immunohistochemistry highlighted inflammatory cells within the lesion (immunoperoxidase, original magnifications × 50). (F) Anti-CD68 showed microglial cells and macrophages; (G) Anti-CD3 showed T-lymphocytes; (H) Anti-CD20 showed B-lymphocytes.

The cerebral biopsy clinched the diagnosis of neurosarcoidosis, which was supported by the raised CSF cell count and protein, hepatomegaly, retroperitoneal lymphadenopathy, positive gallium scan and negative Heaf test despite a history of previous BCG vaccination.

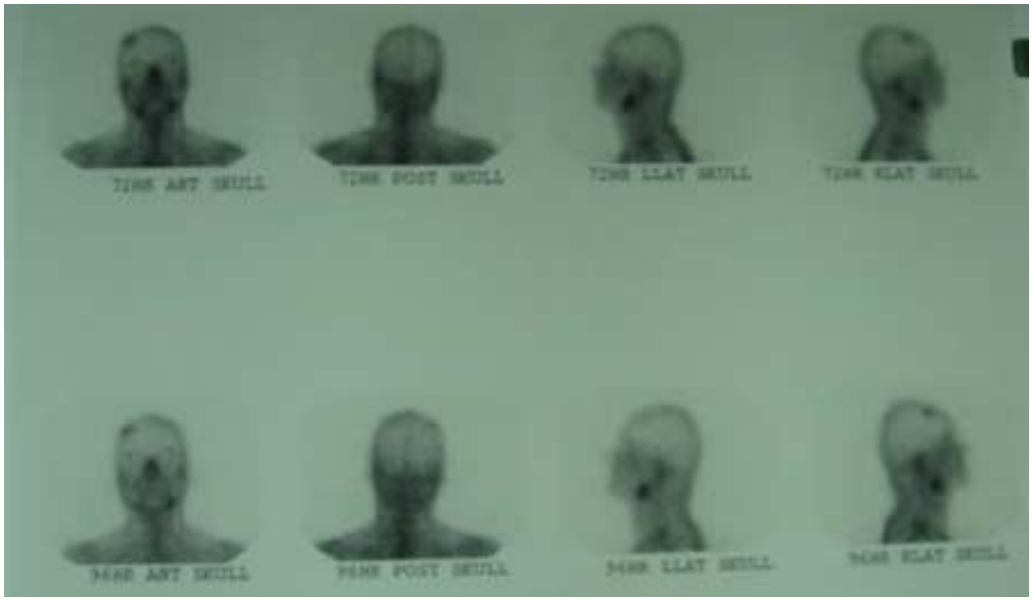


Figure 3 Gallium 67 citrate scan showing increased radionucleotide tracer uptake in the salivary and lacrimal glands typical of active sarcoidosis.

showed increased uptake in the lacrimal and salivary glands supporting the diagnosis of sarcoidosis (Fig. 3).

He was treated with oral prednisolone 60 mg daily and oral cyclophosphamide 150 mg daily with rapid improvement in his psychotic and behavioural problems, and his memory, although cognitive deficits persisted on review 5 months later.

THE DIAGNOSIS OF NEUROSARCOIDOSIS

We believe that the cerebral biopsy clinched the diagnosis of neurosarcoidosis, which was supported by the raised CSF cell count and protein, hepatomegaly, retroperitoneal lymphadenopathy, positive gallium scan and negative Heaf test despite a history of previous BCG vaccination. Curiously a parotid biopsy, taken after treatment was started, was negative. The frequency of various abnormal test results in neurosarcoidosis is shown in Table 1.

Isolated neurosarcoidosis without evident systemic involvement is rare. It may present as a cranial neuropathy, aseptic meningitis, mass lesions, encephalopathy, vasculopathy, seizures, psychiatric manifestations, hydrocephalus, hypothalamic-pituitary axis disorders, myelopathy, peripheral neuropathy and myopathy (Modi *et al.* 2004). The most common sites of presentation are the facial nerve (Lower *et al.* 1998), then the optic nerve and chiasm (Zajicek 1999). The speed of onset is variable but is usually subacute to chronic. Any early communicating hydrocephalus is due to ventriculitis and

Table 1 The percentage of patients with abnormal test results in a recent series of 68 patients with clinically probable or definite neurosarcoidosis (Zajicek *et al.* 1999)

Test	% positive results
Kveim (no longer widely available)	85
CSF – raised protein or cells	81
Gallium 67 scan – increased uptake in salivary and lacrimal glands, chest, spleen	45
Brain MRI	
Multiple white matter lesions	43
Meningeal enhancement	38
CSF	
Oligoclonal bands unique to CSF	37
ACE raised	33
Chest Xray (usually bilateral hilar lymphadenopathy, also interstitial changes)	31
MRI: optic nerve enhancement	28
Serum ACE raised	24
CSF: oligoclonal bands in serum and CSF	19

LEARNING POINTS

- Encephalopathy may be the presenting feature of neurosarcoidosis.
- Brain biopsy may be the only way of identifying treatable neuroinflammatory disease.
- There are no randomised controlled trials of treatments for neurosarcoidosis.
- Treatment with oral steroids and cyclophosphamide was followed by improvement in our patient.

arachnoiditis (Willigers & Koehler 1993). Sarcoidosis is also a cause of pyrexia of unknown origin. Anergy to the Heaf test in the presence of previous immunity is characteristic. There is no simple and specific diagnostic test. A positive biopsy finding of non-caseating granulomas in the context of typical clinical features, blood tests and imaging is required, but other causes of granulomatous inflammation in the brain must be excluded (Table 2).

Table 2 Major causes of granulomatous lesions in the brain (with or without vasculitis)

Non-infectious (mainly immune mediated)
Neurosarcoidosis
Wegener's granulomatosis
Polyarteritis nodosa
Churg–Strauss syndrome
Primary angiitis of the central nervous system
Lymphomatoid granulomatosis
Infectious: bacterial
Mycobacterium tuberculosis
Other mycobacteria
Treponema pallidum
Infectious: fungal
Aspergillus
Cryptococcus
Coccidiomyces
Candida
Zygomycetes (especially in diabetics)
Histoplasma
Infectious: protozoa and metazoa
Amoeba
Cistercus
Schistosoma
Toxoplasma
Infectious: viral
HIV
Varicella zoster

TREATMENT AND PROGNOSIS

Treatment is derived from clinical experience with pulmonary sarcoidosis, there are no randomised controlled trials in neurosarcoidosis. Steroids are the mainstay, with other immunosuppressants. In refractory cases cranial irradiation may be used. Surgery has a role in hydrocephalus and expanding mass lesions causing raised intracranial pressure. But, despite treatment, a recent case series found that 71% of 47 patients followed up for 18 months deteriorated (Zajicek 1999).

ACKNOWLEDGEMENTS

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