CLINICOPATHOLOGICAL CONFERENCE

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Progressive cognitive decline and myoclonus in a young woman: clinicopathological conference at the Edinburgh Advanced Neurology Course, 2007

C A Heath, C Smith, R Davenport, G A Donnan

C A Heath
Specialist Registrar Neurology, Ninewells Hospital, Dundee, UK

C Smith
Senior Lecturer and Honorary Consultant Neuropathologist, University of Edinburgh, Edinburgh, UK

R Davenport
Consultant Neurologist, Western General Hospital, Edinburgh, UK

G A Donnan
National Stroke Research Institute, Department of Neurology, Austin Health, Professor of Neurology, University of Melbourne, Melbourne, Australia

Correspondence to:
Dr C Heath
Specialist Registrar Neurology, Ninewells Hospital, Dundee DD1 9SY, UK; Craigheath@nhs.net

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In April 2002, a 24-year-old right-handed shop assistant developed "dizzy turns". These were stereotyped and occurred several times a day. She described dysequilibrium, lasting 20–30 seconds, with speech arrest and altered awareness. Recovery from each attack was rapid, and in between attacks she was normal. Systemically she was well. Three months previously she had reported low mood, anxiety and headaches, which were considered to be the result of a recent bereavement and she had been treated conservatively. There was little in the way of significant background history of note with the exception of a single episode of abdominal pain of undetermined origin aged 6. She was taking no prescribed or illicit medication at presentation and there was no family history of neurological illness. There were no risk factors for HIV and she had never been outside the UK.

In July 2002, she developed brief episodes of right-sided facial twitching. Each attack lasted approximately 20 seconds and awareness was preserved throughout. These were different, from the initial "dizzy turns" and became very frequent, occurring many times a day. An EEG technician reported right-sided "facial distortion" with associated speech arrest during one such episode.

Neurological examination was normal, no diagnosis was made, and she was lost to follow-up.

In January 2003, she fell and fractured her distal fibula. Her family became concerned in April 2003 when she became increasingly forgetful and withdrawn. Soon afterwards she developed frequent, brief body "spasms". A further neurological review was sought, and she was seen in June 2003. This demonstrated a remarkable decline over only 11 months. She was awake and undistressed, but scored only 13/100 on the Addenbrooke's cognitive examination. Verbal response was limited to single words and she was unable to follow single stage commands. Vertical upgaze was reduced and smooth pursuit eye movements lost. Tone was increased in all four limbs and

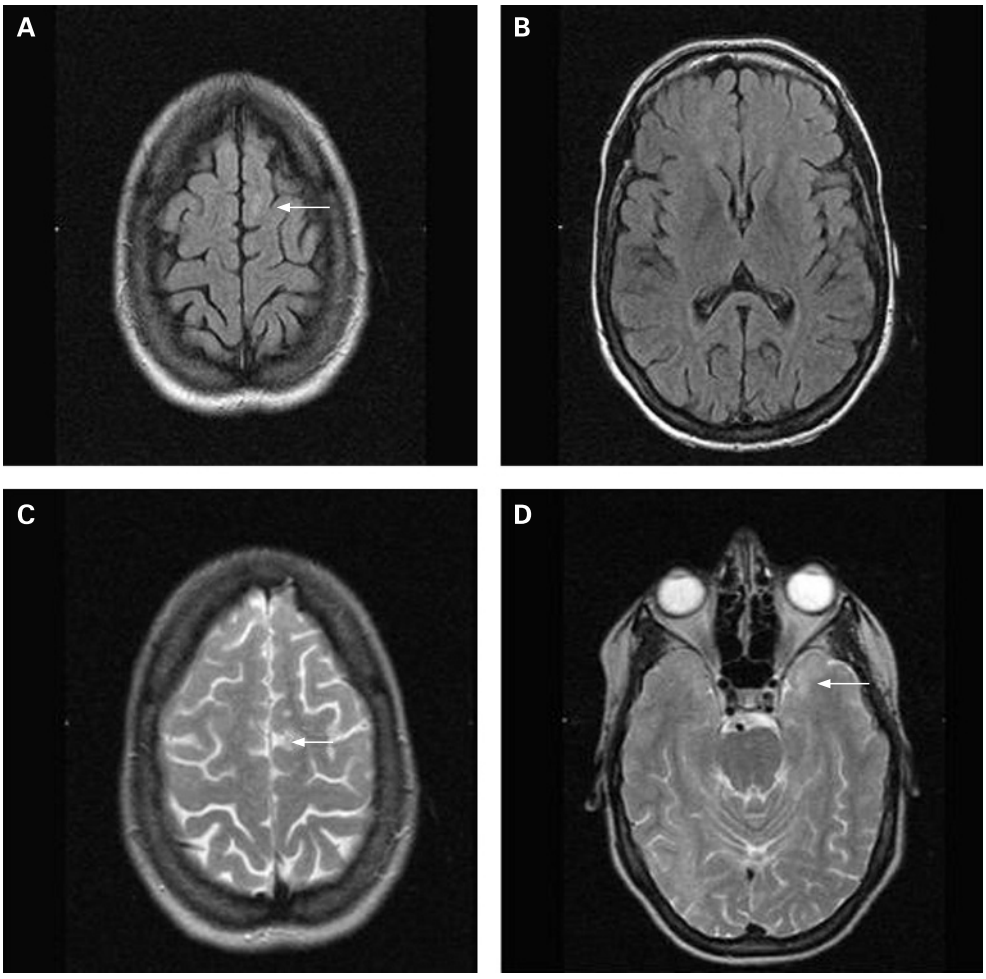

Figure 1
MR FLAIR sequences at the level of the cortex (A) demonstrating a tiny area of hyperintensity (arrow) and basal ganglia (B) considered normal. T2 weighted sequences at the level of the cortex (C) demonstrating more extensive areas of hyperintensity (arrow) and temporal lobes (D) demonstrating a small area of hyperintensity on the left (arrow).

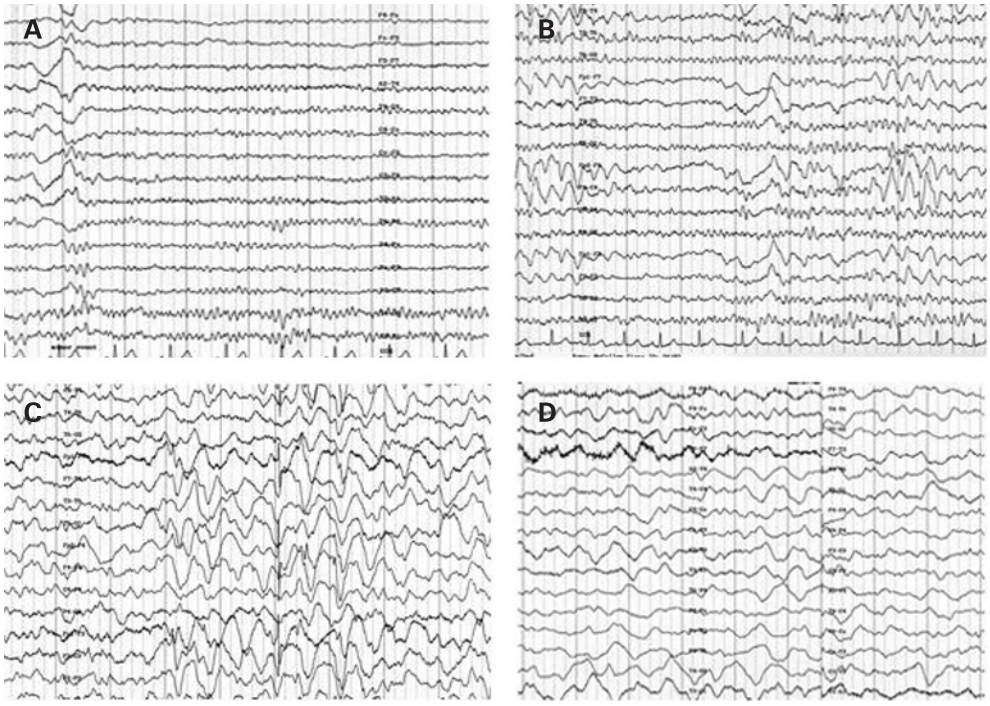

Figure 2
A summary montage of serial electroencephalograms (A) July 2002—preserved cortical rhythms. The patient had multiple attacks including distortion of the right side of her mouth during the EEG. (B) January 2003—cortical rhythms remain well preserved but there are frequent right anterior quadrant epileptiform discharges with secondary spread. (C) Early June 2003—diffuse high voltage slow activity with transient epileptiform discharges seen bifrontally. (D) Late June 2003—grossly abnormal background rhythms with superimposed fairly stereotyped repetitive complexes at 10–12 second intervals.

TABLE 1 Summary of investigations

Haematology:
Full blood count, serum folate, vitamin B12, plasma viscosity: normal
Biochemistry:
Urea, electrolytes, creatinine: normal
Random glucose: normal
Liver and thyroid function: normal
Serum immunoglobulins normal, no paraprotein band
Serum lactate: normal
Vitamin E: normal
Caeruloplasmin: normal
Serum ACE: normal
Very long chain fatty acids: normal
C-reactive protein: normal
Cerebrospinal fluid (CSF)
Acellular, no micro-organisms identified on gram stain, no growth on standard culture medium.
Protein: 0.95 g/l (normal 0.15–0.45)
Glucose: 3.6 mmol/l (normal 3.3–4.4)
Oligoclonal banding: bands detected in CSF and serum, some bands unique to CSF
CSF protein 14-3-3: negative
CSF s100: 0.22 ng/ml (normal)
Immunology:
Rheumatoid factor, antineutrophil cytoplasmic antibody, antinuclear antibody, thyroid antibodies, extractable nuclear antigens, anticardiolipin antibody: all negative
Complement studies: normal

was considered spastic in character, power was normal within the limits of her ability to comply with instructions. Deep tendon reflexes were symmetrically brisk and the plantar responses were both extensor. A general medical examination was normal.

Following this original and subsequent review a variety of investigations were undertaken and are summarised in table 1. Brain MRI was done on a number of occasions (August 2002, February 2003—not shown but considered normal—and in June 2003, fig 1). Finally, serial electroencephalograms were undertaken and a summary montage is illustrated in fig 2.

She deteriorated relentlessly, cortical visual loss was suspected, and she became bed bound and died in July 2003. A postmortem was performed.

PROFESSOR DONNAN'S DISCUSSION

When considering any clinicopathological conference (CPC) one must consider two important principles: first, the CPC is the domain of the rare—either rare presentations of common conditions or common presentations of rare conditions—and second, that treatable conditions are rarely presented.

As ever, the first question a neurologist should ask in this case is—where is the lesion? If one considers the presenting features it is conceivable that the episodes of speech arrest were partial seizures arising in the dominant hemisphere. Other possibilities at that time might include atypical migraine or, given the normal neurological examination and brain MR scan, a functional disorder. The first suggestion of sinister aetiology was in January 2003 when she fractured her distal fibula. Although the exact nature of the fall is unclear, a simple fall in this age group would be unusual and suggests perhaps the development of gait ataxia. A short while later the patient's family became increasingly concerned about her mood, memory and body "spasms". Following neurological review the decline was relentless, she became bed bound, cortically blind and died soon afterwards. In summary, this young woman's illness was characterised by a rapid decline following a fairly subtle onset some months earlier. The history and examination support the notion that a fairly widespread pathological process was responsible with evidence of cortical, subcortical, pyramidal, brainstem and cerebellar involvement.

We can now begin to consider what was responsible for this pathological process. Before thinking about the investigations, the differential diagnosis is exceptionally wide and includes neoplastic conditions, as well as infectious, toxic, metabolic and neurodegenerative causes. If due consideration is given to the second principle of the CPC (that is, treatable conditions are rarely considered), fungal, tuberculosis, central nervous system (CNS) Whipple's, listeria and deficiency syndromes are unlikely. A vascular aetiology is also unlikely, given the insidious onset, with the exception of primary angiitis of the CNS. Serious consideration should be given to a paraneoplastic syndrome (these are common in this context and probably account for approximately 30% of CPC cases) and other aggressive conditions such as variant (v)CJD, subacute sclerosing panencephalitis (SSPE)

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and aggressive demyelination. Other conditions which one might also consider include CADASIL (but too rapid and non-focal), MELAS (but too aggressive), granulomatous conditions (but should have had systemic manifestations), progressive multifocal leucoencephalopathy (PML) (but not immunosuppressed) and HIV.

Having considered this wide differential diagnosis some thought should then be given to the various investigations. Routine serological investigations were unremarkable but cerebrospinal fluid (CSF) analysis provides some interesting and helpful clues; oligoclonal bands lead one to consider an inflammatory or "infectious" process (table 2), a consideration supported by a significant increase in the CSF protein. However, the acellular CSF makes a classical infectious aetiology unlikely. Bearing in mind the possibility of prion disease, CSF 14-3-3 was negative.

In summary, having given due consideration to the clinical features and now the laboratory tests, the main differential includes aggressive demyelination (seems too rapid and non-focal), vasculitis (but non-focal), SSPE (usually children, rare in developed countries) and vCJD (but CSF 14-3-3 negative and raised CSF protein which is also rare).

Turning now to the brain MR, this was surprisingly almost normal, especially given the relentless neurological decline—nonetheless this is in many respects quite helpful. Such relatively normal imaging makes the diagnosis of aggressive demyelination, primary angiitis of the CNS, gliomatosis cerebri, MELAS and PML very unlikely. Although a normal MRI is very unusual in vCJD the sensitivity is not 100%. Therefore, considering the laboratory tests and the MRI, a much narrower differential diagnosis would include just vCJD and SSPE.

The early EEG was dominated by slow rhythms with some epileptiform activity appearing in the third EEG (fig 2). The fourth EEG demonstrates frequent periodic complexes. The EEG can be helpful in sporadic CJD and SSPE with the development of periodic complexes, but is often less so in vCJD when the EEG is generally non-specifically abnormal.

Therefore, considering all the clinical and investigative aids, the likely diagnosis is either adult onset SSPE or vCJD (table 3). The clinical features of this case are consistent with SSPE including myoclonus, cognitive decline and seizures. According to the diagnostic criteria for adult onset SSPE (table 4) this case would be classified as "probable" on the basis of the clinical features and CSF analysis. Diagnostic criteria for vCJD have also been formulated

TABLE 2 Causes of cerebrospinal fluid oligoclonal bands

Multiple sclerosis
Acute disseminated encephalomyelitis
Central nervous system lupus
Neurosarcoidosis
Behçet's disease
Acute/chronic inflammatory demyelinating polyneuropathy
Human T lymphocytic virus
Cysticercosis
Subacute sclerosing panencephalitis
Neuroborreliosis
Trypanosomiasis
Neurosyphilis
Mumps

TABLE 3 Differentiating variant Creutzfeldt-Jakob disease (CJD) from adult onset subacute sclerosing panencephalitis (SSPE)

	Adult onset SSPE[3]	Variant CJD[20]
Mean age at onset (years)	21	28
Presenting clinical features		
Myoclonus	Common (>60%)	Unrecognised
Seizures	Uncommon (10%)	Unrecognised*
Sensory symptoms	Rare	Uncommon (35%)
Cognitive decline	Uncommon	Usually unrecognised at onset
Psychiatric features	Uncommon	Common (70%)
Investigations:		
Oligoclonal bands in CSF	Common	Rare (6%)
MRI brain—pulvinar hyperintensity	Unrecognised	Common† (95%)
EEG—periodic complexes	Common	Rare‡

*A single report of a case who developed localisation-related epilepsy 6 years prior to developing variant (v)CJD. Most authorities in prion disease consider this was a chance association.[21]
†The sensitivity of MRI critically depends on the sequence The figures provided are based on the acquisition of an axial FLAIR sequence.
‡From experience of UK surveillance, periodic complexes are unrecognised. However there are two case reports of patients monitored extensively during the terminal phase of illness when the EEG showed periodic complexes.[22, 23] EEG remains an important tool for differentiating vCJD from sporadic CJD outwith the terminal phase.

TABLE 4 Diagnostic criteria for subacute sclerosing panencephalitis[19]

Clinical	Progressive, subacute mental deterioration with typical signs like myoclonus
EEG	Periodic, stereotyped, high voltage discharges
CSF	Raised gammaglobulins or oligoclonal bands
Measles antibodies	Raised titre in serum (>1:256)
Brain biopsy	Suggestive of panencephalitis

Definite case: positive biopsy +3/4 other criteria.
Probable case: 3/5 criteria (in the original definition there was no comment on biopsy, only that 3/5 criteria are required).

TABLE 5 Current World Health Organization diagnostic criteria for variant Creutzfeldt–Jakob disease

1 A: Progressive neuropsychiatric disorder
B. Duration of illness >6 months
C. Routine investigations do not suggest an alternative diagnosis
D. No history of iatrogenic exposure
E. No evidence of familial forms of transmissible spongiform encephalopathies
II A. Early psychiatric features*
B. Persistent painful sensory symptoms†
C. Ataxia
D. Myoclonus or chorea or dystonia
III A. EEG does not show typical appearance of sporadic CJD
B. MR brain scan shows bilateral symmetrical pulvinar high signal
IV A. Positive tonsil biopsy

*Includes depression, anxiety, apathy, withdrawal and delusions, the recognition of which should be within 4 months of onset.
†Includes frank pain and dysaesthesia.
Definite case: 1A and neuropathological confirmation of vCJD.
Probable: 1 and 4/5 of II and IIIA and IIIB or 1 and IVA.
Possible: 1 and 4/5 of II and IIIA.

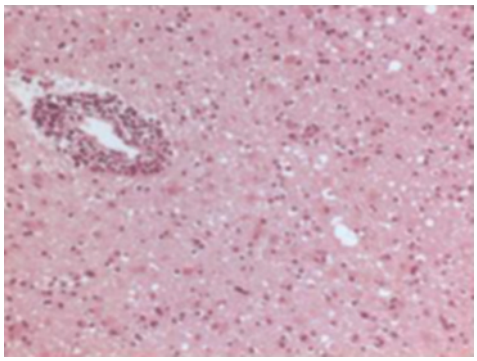

Figure 3
Haematoxylin and eosin stain (×20 magnification) demonstrating perivascular cuffing, gliosis and lymphocytic infiltration of the brain parenchyma (typical of encephalitis).

and are superficially similar to those of adult-onset SSPE (table 5). The case in question would be classified as "possible" according to the current World Health Organization (WHO) diagnostic criteria. Choosing a final diagnosis between these two diagnoses is almost impossible. Adult SSPE is more common in developing countries where widespread measles immunisation is not available. Given the evidence, adult onset SSPE seems a little more likely and if we were in any other city in the world this would be my final diagnosis. However, we are in Edinburgh, the location of the National CJD Surveillance Unit, and so this to me makes vCJD more likely.

Professor Donnan's final diagnosis

Variant CJD.

PATHOLOGY: DR COLIN SMITH

The fresh brain weighed 1240 g. Macroscopic examination revealed a rubbery texture to the cerebrum, but no focal lesions were seen. Microscopic examination, however, demonstrated extensive loss of cortical neurons with reactive gliosis extending throughout both the grey matter, and underlying white matter, particularly involving temporal and frontal regions, and extending into the thalami. In addition, there was perivascular lymphocytic cuffing both within the brain parenchyma and overlying leptomeninges in these regions (fig 3). No viral inclusions were convincingly demonstrated within any of the cells. These appearances are most consistent with SSPE. Brain tissue was then sent to the Enteric, Respiratory and Neurological Virus Laboratory, Health Protection Agency Colindale, London. They detected measles RNA in brain samples, D7 genotype, which confirmed the diagnosis of SSPE and indicated that infection was due to a strain which may have circulated in the UK in the 1970s and 1980s. Similar measles strains have been detected in other UK SSPE cases.[1]

Pathological diagnosis

Subacute sclerosing panencephalitis.

DISCUSSION

Member of the audience: Is it surprising that the CSF was acellular?

Dr Colin Smith: I am not that surprised because SSPE is not a particularly florid

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inflammatory condition and may cause only small focal perivascular lesions.

Member of the audience: Are the early symptoms relevant?

Professor Geoffrey Donnan: SSPE can result in a diverse range of symptoms, and despite their subtlety the early features may well have been relevant.

COMMENT

SSPE is a very rare but serious late complication of measles virus infection. It is caused by a persistent mutant measles virus long after the acute infection. In developed countries SSPE occurs in 4–11 cases per 100 000 cases of measles (there were only 756 cases of confirmed measles in the UK in 2006)[2] but it still remains an important public health issue in parts of the developing world with limited measles immunisation policies and consequently far more cases of measles.

Most reported cases of SSPE occur in children, with only around 100 cases of adult onset SSPE in the literature. The early clinical features are dominated by myoclonus (60%), behavioural changes (13%), seizures (8%) and cognitive decline (5%).[3] As the disease progresses, ataxia, ocular and visual manifestations (including papilloedema, retinitis, chorioretinitis, optic disc pallor, homonymous visual field deficits, and cortical blindness), pyramidal signs and dyskinesia are frequently recognised.[4] Although the clinical and investigative features of SSPE are similar to vCJD there are some important differences which may help aid diagnosis (table 3).

Given its rarity in adults there are no systematic studies evaluating the different diagnostic aids. Despite this, smaller studies have provided some interesting and potentially helpful observations. Routine investigations are often normal with no evidence of a widespread systemic response, although measles antibody titres may be raised in both the CSF and serum. The basic CSF constituents are, more often than not, within the normal range, although less commonly a mild pleocytosis or raised protein is recognised. The most remarkable feature of the CSF is the presence of a marked increase of IgG directed against the measles virus.[5] Further investigations using iso-electric focussing demonstrate the presence of oligoclonal bands.[i] Other investigative aids used to facilitate diagnosis include brain MRI and the electroencephalogram.

A normal or relatively normal MRI is well recognised, despite the relentless neurological decline, but cortical, subcortical and white matter abnormalities have been reported.[6] Contrast enhancement is not normally apparent although it has on occasion been recognised.[7] In the advanced stages of the illness generalised atrophy is common.

The EEG may be normal, non-specific or typical. The typical EEG pattern consists of periodic generalised, bilaterally synchronous and symmetrical high amplitude slow waves. These periodic complexes repeat at fairly regular 4–10 second intervals and appear to be related to the myoclonus.[4] Atypical patterns are also recognised.[8]

The clinical course is characterised by a relentless decline in most cases but long-term remission is recognised in around 5% (occasionally for more than 20 years).[9, 10] A variety of antiviral and immunodulating drugs have been evaluated in the treatment of SSPE including amantidine,[11] corticosteroids,[12] interferon,[13] intravenous immunoglobulin,[14] isoprinosine[15] and ribavarin.[16] As yet there is no conclusive evidence to support their use.

During the last decade or so there has been widespread media attention surrounding the MMR (measles, mumps and rubella) vaccine. This has mainly involved a supposed link with autism and colitis, a tentative association now considered by most to be unlikely.[17] Given such concerns, an overall evaluation of vaccine safety was undertaken by the WHO, which concluded that there is no causative association between the measles vaccine and the development of SSPE, indeed since the introduction of immunisation programmes the incidence of measles and SSPE have both fallen significantly.[18] In view of the importance of measles and its long-term sequelae, the WHO have set a goal of the global eradication of measles by 2005–2010.

[i] The presence of antigen-specific oligoclonal bands against the measles virus was detected in this case, which allowed a clinical diagnosis to be achieved in life. Had this information been available during the CPC it would have been rather too straightforward!

ACKNOWLEDGEMENTS

The CPC provides both established neurologists and trainees the opportunity to learn

from the experience of others. It often illustrates rare conditions which one may not routinely be exposed to in everyday clinical practice. Presenting such cases requires cooperation from a number of individuals. We would like to thank the next of kin for allowing this case to be presented in the setting of the CPC. We would also like to thank Dr Kathie White, Ninewells Hospital, Dundee, the clinician responsible for the patient's care, and Professor James Ironside (Edinburgh) for his assistance in obtaining consent. Finally, we would like to thank Drs Li Jin and DW Brown at the Enteric, Respiratory, and Neurological Virus Laboratory, Central Public Health Laboratory, Communicable Disease Surveillance Centre, Colindale, London, for their expertise in identifying and genotyping the measles RNA.

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