

SHORT REPORT

New variant Creutzfeldt-Jakob disease: three case reports from Leicestershire

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Abstract

Since a report in 1996 of 10 cases of Creutzfeldt-Jakob disease (CJD) with onset in a younger than usual age, a pattern of the disease has emerged. This includes early neuropsychiatric features and sensory symptoms and neurological signs such as ataxia and involuntary movements later in the course of the disease. Three patients with varied clinical presentations and disease course seen at a single neurology unit are described. The first patient was characterised by cognitive and psychiatric symptoms together with neurological signs. The second patient presented with unusual behavioural disturbance and episodes of collapse. The third patient exhibited striking psychomotor retardation and had abnormal CSF and MRI findings. All patients succumbed in a state of akinetic mutism and myoclonus. All three patients had the methionine/methionine genotype at codon 129 of the PrP gene and in two of the three patients a tonsil biopsy was performed with positive results. These two patients also tested positive for the 14.3.3. protein in the CSF.

Whereas late features of the disease seem very similar in all cases, the initial presentation was variable and underlines the uncertainty of the range of the clinical phenotype. Successful diagnosis demands a high index of clinical suspicion.

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By March 1999 the number of deaths of new variant Creutzfeldt-Jakob Disease (new variant CJD) recorded by the national CJD Surveillance Unit in Edinburgh was 39.¹ Since the report by Will *et al*² in 1996 of 10 cases of CJD with onset at a younger than usual age, early neuropsychiatric features, and a new neuropathological profile a pattern of the new variant of the disease has emerged. This clinical pattern is associated so far in all cases with homozygosity for methionine at codon 129 of the PrP gene,³ and at least in some cases, with a characteristic appearance on MRI (Gillian Stewart, CJD Surveillance Unit, Edinburgh,

personal communication). These features help in distinguishing the new variant from the sporadic form of CJD. In our department three cases confirmed at postmortem were seen between the end of 1996 and 1998. The purpose of this paper is to detail presentation and progression of the disease in these three patients. We wish to highlight the fact that there remains a very wide variability of individual disease characteristics emphasising the uncertainty of the range of the clinical phenotype.

Case report 1

Pamela, a 23 year old woman, was referred by a local psychiatrist with a 4 month history of progressive gait disturbance, clumsy upper limb function with difficulties in writing, and slurred speech. In addition, she had complained of a non-specific and constant headache for the previous month. Her memory for recent events had deteriorated. A diagnosis of depression was made and she was admitted to a local psychiatric unit where treatment with fluoxetine was started. Her mood subsequently improved. She denied any visual, sphincter, or sensory symptoms. Her general health had been good and there was no history of neurological problems before the onset of this illness. She was taking the oral contraceptive pill. There was no family history of neurological disease.

On neurological examination she had a wide based ataxic gait. There was mild titubation of the head and cerebellar dysarthria. She had jerky ocular saccades. Choreiform movements of the head, arms, and legs were noted. There was ataxia of the limbs together with pyramidal tract signs. She had an infantile affect with apparent lack of insight. She had no knowledge of any current events, was unable to name the month, prime minister, or United States president, and failed at serial sevens. Detailed neuropsychological assessment demonstrated impairment of memory, verbal fluency, spatial judgement, and language, indicating a generalised cortical disease process.

The condition progressed slowly over the next 6 months. She then deteriorated more rapidly in both motor and cognitive function and about 1 year after presentation had become mute with marked spasticity of the lower limbs. Feeding via gastrostomy had been started after an admission with aspiration

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pneumonia. She had become doubly incontinent. Seventeen months after initial presentation she was completely bed bound, opening her eyes spontaneously and appearing to track visually; there was no verbal response although she was able to make her distress known by groaning. There were widespread generalised myoclonic jerks. Pamela finally died after a disease duration of 27 months.

Extensive investigations for common and uncommon causes of cerebellar syndromes with dementia were normal. Analysis of CSF yielded no cells or organisms, the protein was normal, and there were no oligoclonal bands. One EEG showed episodic ill defined higher amplitude slow wave discharges on a normal background, although a second EEG a few days later was normal. Brain MRI with T1 and T2 images was normal. Analysis of CSF for 14.3.3 protein was positive, genotyping showed the patient to be homozygous for methionine at codon 129 of the PrP gene. Tonsil biopsy showed marked immunoreactivity to PrP antibodies. The diagnosis was confirmed at postmortem.

Case report 2

A 17 year old mother was admitted after several collapses. Over the previous few weeks she had passed out with increasing frequency and on a few occasions the blackouts were preceded by vertigo and the sensation of an odd smell. Loss of consciousness lasted for a maximum of 1 minute and she became flaccid with no definite convulsive movements, tongue biting, or urinary incontinence. For 3 months before her admission she had been weepy, low in mood, quick tempered, and not sleeping well. As she had delivered a healthy child 6 months previously a provisional diagnosis of postnatal depression had been made. Antidepressant therapy with lofepramine was started and subsequently changed to paroxetine without significant benefit. The patient became increasingly agitated, shaky, and absent minded. Her mother also noted repeated twitching and rocking movements as well as some slurring of speech, particularly when tired. There were no visual, sphincter, or sensory symptoms. Her general health was good. She was dyslexic and a poor attender at school where there had been frequent bullying. There was no relevant neurological medical or family history and the regular use of recreational drugs was denied.

On neurological examination she was agitated and fidgety. Her gait looked clumsy. Cranial nerves were normal. She was hyperreflexic with flexor plantar responses. There were no frontal release signs. Coordination of the limbs was slow and clumsy without frank ataxia. She appeared childlike with no insight and poor concentration span. She could not give the current date or year and was unable to perform serial sevens.

The patient's condition steadily deteriorated. She became increasingly emotionally labile, aggressive at times, and tended to wander off the ward, making sedation with various combinations of neuroleptic drugs necessary. There were periods of prolonged

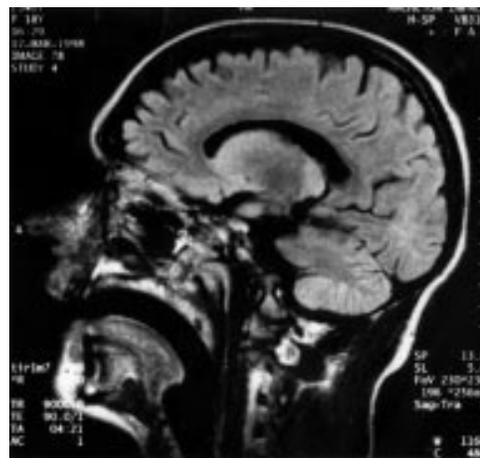


Figure 1 MRI, sagittal FLAIR sequence showing high signal from the posterior thalamus (patient 2).

wailing when the patient looked terrified. Only 1 month after admission she needed feeding and full care for almost all activities of daily living. She exhibited frequent attacks of arched posturing of back and neck with stiff limbs, stertorous breathing, and nasal flaring. These episodes would occur repeatedly while the patient remained unresponsive. There were also continuing vacant episodes lasting seconds and prolonged episodes of unresponsiveness without associated stereotyped movements. She was started on sodium valproate with no response. Three months after admission pyramidal signs were evident in both legs with an ataxic gait and frontal release signs. Five months later she rapidly deteriorated and became virtually mute. There were only occasional generalised myoclonic jerks but she had frequent bilateral myoclonus of the extraocular muscles. She finally died 17 months after initial symptom onset.

Extensive blood and urine tests were normal. Examination of the CSF disclosed acellular CSF with no organisms and normal protein, there were no oligoclonal bands. Repeated EEGs showed excess slowing with episodic higher amplitude slow waves but no overt epileptic activity or repetitive complexes. Brain MRI on two occasions at an interval of 4 months showed increased signal intensity from both posterior thalami on T2 and FLAIR images (fig 1). Analysis of CSF for 14.3.3 protein was negative, genotyping found the patient to be homozygous for methionine at codon 129 of the PrP gene. Tonsil biopsy was not performed but the clinical diagnosis was confirmed at postmortem.

Case report 3

This 35 year old man was referred by his general practitioner with a 3 month history of increasing forgetfulness. He would get lost on local journeys and could not manage his computer games any longer. Over the same period his personality had changed and he became extremely emotional at times. The symptoms were rapidly progressive and by the time of admission he was unable even to tie up his shoe laces. His brother and work colleagues also

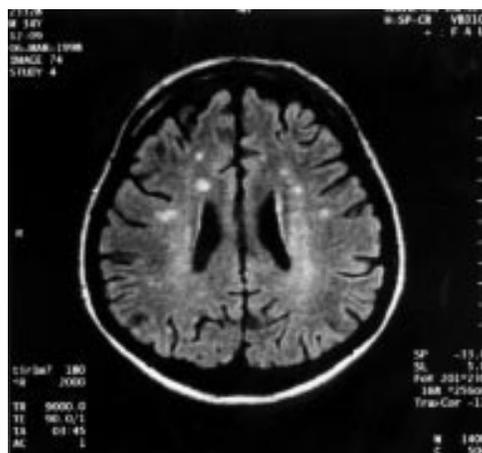


Figure 2 MRI, axial FLAIR sequence showing multiple areas of high signal in the white matter of both cerebral hemispheres (patient 3).

noticed that his gait had become odd and stiff with a tendency to drag his feet. There had been no preceding illness and no visual, sphincter, or sensory symptoms. His general health was good. There was no medical or family history of relevance to his presentation. He was not taking any regular medication.

On neurological examination he was withdrawn, irritable, and tremulous. He walked with a slow and deliberate gait. Cranial nerves were unremarkable. He had brisk reflexes and strong withdrawal on eliciting the plantar responses. There was no ataxia and there were no involuntary movements. The most striking feature was marked psychomotor retardation. He showed very little insight and scored 21 out of 30 on mini mental state examination later dropping to 16 out of 30. He could only recall current events in a very sketchy fashion. Neuropsychological assessment confirmed impaired level of cognitive functioning in all areas.

His condition remained largely unchanged until about 6 months after presentation when his gait became progressively unsteady and he withdrew more and more from spontaneous activities. There was little verbal communication and he now needed assistance in all activi-

ties of daily living. Two months later he was bed bound and mute with marked leg spasticity and needed feeding via gastrostomy. He continued to track visually rather than following noise but there was no communication. During the last month of life infrequent generalised myoclonic jerks were found. He eventually died 1 year after the onset of symptoms.

Numerous blood and urine tests to look for neurodegenerative diseases were normal. Examination of the CSF showed no cells or organisms but an increased protein ranging between 1.3 and 2.9 g/l on several occasions; oligoclonal bands were not detected. EEGs consistently showed generalised slowing without repetitive complexes. Three successive MRIs of the brain showed high signal intensity from both posterior thalami and, in addition multiple areas of high signal in the white matter of both cerebral hemispheres on T2 and FLAIR sequences. There was no enhancement with gadolinium (fig 2). Analysis of CSF for 14.3.3 protein was positive and the patient was homozygous at codon 129. Tonsil biopsy showed immunoreactivity to PrP antibodies. The diagnosis was confirmed at postmortem.

Discussion

Our three patients exhibited various clinical features which are summarised in the table together with the relevant investigations.

Pamela presented with an advanced syndrome of neuropsychiatric symptoms, cerebellar dysfunction, and headaches despite only 4 months of ill health. Further disease progression was in keeping with the findings made in the previously published cases.⁴ She was, however, the only one of our patients to have a largely unremarkable EEG and a normal MRI. A normal initial MRI which later became abnormal has been well documented in at least two cases previously described.⁴

The second patient presented in an unusual way. In addition to symptoms of depression together with behavioural abnormalities she experienced increasingly frequent blackouts which may have well been seizures despite the lack of supportive EEG evidence. Throughout

Summary of symptoms, signs, and investigations

| | Patient 1 | Patient 2 | Patient 3 |
|------------------------------|--|--|---|
| Age | 23 | 17 | 35 |
| Duration of illness (months) | 27 | 17 | 12 |
| Presenting symptoms | Unsteadiness Depression Headache Poor memory | Collapse Depression Behavioural change | Poor memory Personality change |
| Early signs | Cerebellar syndrome Choreiform movements Pyramidal signs Dementia | Agitation Dementia | Psychomotor retardation Dementia |
| Late signs | Akinetic mutism Spasticity Frequent generalised myoclonic jerks | Akinetic mutism Ocular myoclonus | Akinetic mutism Spasticity Infrequent myoclonic jerks |
| EEG | Normal | Non-specifically abnormal | Non-specifically abnormal |
| CSF | Acellular | Acellular | Acellular |
| Protein | Normal | Normal | Very high |
| Oligoclonal bands | Negative | Negative | Negative |
| 14.3.3 Protein | Positive | Negative | Positive |
| Genotype at codon 129 | Homozygous | Homozygous | Homozygous |
| Tonsil biopsy | Positive | Not done | Positive |
| MRI | Normal | High signal posterior thalamus bilaterally | High signal posterior thalamus bilaterally and patchy high signal change within the white matter of both cerebral hemispheres |

the first 5 months of her illness she continued to have attacks suspicious of seizures. To our knowledge this has so far not been described in any of the other cases. Her depressive symptoms fit well into the range of psychiatric presentations of new variant CJD.⁵ Her extreme emotional lability with agitation and aggression as well as periods of prolonged wailing and opisthotonus made her management rather difficult on a busy neurology ward.

Our third patient presented with the previously well described combination of a dementing process and personality change. His marked psychomotor retardation stands in striking contrast to our two other patients. The most unusual features of this case, however, were the markedly raised CSF protein and prominent multifocal white matter changes in addition to posterior thalamic high signal on MRI. This patient together with our second patient and the two other previously published cases with thalamic high signal on MRI⁴ did not differ clinically from the remaining patients in any specific way.

Dysaesthesia and paraesthesia are presently regarded as a rather characteristic feature at presentation of the new variant disease affecting about half of the patients.^{4,5} None of our patients complained of sensory symptoms before severe dementia and mutism supervened. By contrast, they did exhibit most other previously described features including involuntary movements, pyramidal signs, cerebellar signs, and akinetic mutism. We did not encounter any delusions or hallucinations which have been described in many of the previously published 33 cases.⁵ All other psychiatric features including emotional lability, anxiety, apathy, forgetfulness, aggression, and depression were present.

The late features of the new variant disease were very similar in all three patients, with akinetic mutism and a variable degree of spasticity and myoclonus. This uniformity stands in striking contrast to the very variable symptoms and signs our patients exhibited at the onset of the disease.

Despite clear cognitive and neurological signs, our first patient's EEG was normal. This situation has been noted several times before⁴ and therefore, renders EEG unhelpful in excluding new variant CJD.

Two of our three patients showed high signal intensity from the posterior thalami on MRI. These changes seem to have increasing importance in the diagnosis of new variant CJD and seem very specific (Gillian Stewart, CJD Surveillance Unit, Edinburgh, personal communication). Our third patient also showed prominent multifocal white matter abnormalities in both cerebral hemispheres. Histologically there were no features particularly unusual for new variant CJD; in addition the white matter showed focal astrocytosis but no evidence of PrP accumulation. The meaning of this patient's changes in white matter on MRI is uncertain.

All three patients seen by us had the methionine/methionine genotype at codon 129 in line with the observations so far made by the CJD Surveillance Unit in all 39 definite and probable cases (Gillian Stewart, CJD Surveillance Unit, Edinburgh, personal communication).³ The results of testing for the presence of 14.3.3. protein in the CSF showed two patients to be positive and one negative. The published data on this test in new variant CJD is extremely limited. The important lesson from our and other cases is that the 14.3.3. protein may be negative.⁴ Its clinical usefulness is not yet clear^{3,6} and is currently under evaluation.

Biopsy of the tonsils or lymphoreticular tissue from the lingual tonsillar remnants⁷ remains a contentious issue. Accepting the limitations of this procedure with respect to its validity we have found it extremely helpful in the management of the two patients in whom it was performed. In both patients tonsil biopsy was performed early during the course of their illness. Firstly, this avoided the more invasive procedures such as brain biopsy with all its risks and limitations. Secondly, it allowed the relatives to come to terms with the diagnosis and to put into context the intense local and national publicity associated with it.

We think that in the current situation all diagnostic tests currently available should be applied for a patient with a reasonable clinical profile. This includes brain MRI, EEG, codon 129 of the PrP gene, CSF 14.3.3. protein, and finally tonsil biopsy; MRI, EEG, and CSF 14.3.3. protein may, however, be normal or negative as discussed earlier on.

In conclusion, although there may be an apparent classic phenotype of new variant CJD, presentation of individual cases can be varied and indicates a much wider clinical disease range than found to date. A high index of clinical suspicion is necessary to avoid missing this condition. Tonsil biopsy should be encouraged in the appropriate clinical circumstances together with all other currently available tests.

We thank Gillian Stewart from the CJD Surveillance Unit in Edinburgh for the latest information with respect to clinical presentation and investigation of cases unknown to us. Also we have to point out that consent for publication of data of our first patient was granted by her parents under the condition of referring to their daughter as Pamela and not anonymously as "this or that case".

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