Refractory Non-Convulsive Status Epilepticus in Creutzfeldt – Jakob Disease

We describe a rare case of a previously fit patient who presented with a rapidly progressive dementia and gait ataxia. EEG showed features of non-convulsive status epilepticus that was not responsive to anti epileptic drugs. Post mortem brain biopsy confirmed sporadic Creutzfeld-Jakob disease (sCJD).

A diagnosis of sCJD should be considered in patients with rapidly progressive dementia with non-convulsive status epilepticus especially with positive CSF protein 14-3-3 markers.

Introduction

Sporadic Creutzfeldt-Jakob disease (sCJD) is an insidious prion disease commonly presenting with rapidly progressive dementia, motor dysfunction, myoclonus, and characteristic periodic complexes on electroencephalogram (EEG). Partial, complex partial and secondary generalised seizures may occur in sCJD but are relatively uncommon, and status epilepticus is a rarity and may cause diagnostic confusion. Non convulsive status epilepticus (NCSE) is characterised by continuous epileptiform patterns on EEG, alteration of consciousness including coma and the absence of convulsive motor activity. We present an unusual patient who was admitted with a rapidly progressive global cognitive impairment, fluctuating level of consciousness and EEG features of NCSE. Post mortem examination of the brain confirmed sCJD.

Case report

A 63-year-old previously well right-handed housewife was admitted with a 1-month history of progressive unsteadiness of gait and changes in personality and behaviour. She had become apathetic, withdrawn, disorientated in time and unconcerned about her appearance. She had been unable to cope with her housework and increasingly dependent on her husband. Her verbal output had been reduced with inappropriate answers and she had been unable to follow conversations. She had a past history of hypothyroidism and took regular thyroxine replacement.

Initial neurological examination revealed receptive dysphasia. She was disorientated in time and place. Cranial nerves were intact. There was a bilateral Gegenhalten increase in muscle tone and motor perseverations but no grasp reflex. All reflexes were moderately brisk with flexor plantar responses. There was no myoclonus. Her gait was ataxic but a detailed assessment of limb coordination was not possible.

Routine blood and urine investigations, thyroid function and anti-thyroid antibodies, extensive autoimmune profile, anti-neuronal antibodies, serum electrophoresis, Vitamin B12 and folate levels and chest X-ray were normal. CT scan of the brain and the CSF examination were normal. However, the EEG revealed widespread, almost continuous repetitive 1-1.5Hz triphasic sharp and slow waves at 100-150uV, with an anterior emphasis, intermixed with rhythmic 5-7Hz theta waves in the posterior and central regions (20-30uV) (Figure 1) which did not alter during periods of agitation or eye opening. There was a brief response to intra-venous lorazepam. The EEG changes were suggestive of non-convulsive status epilepticus (NCSE). MRI scan of the brain revealed areas of high signal in the caudate and lentiform nuclei with normal

Dr J Vaz graduated in India before moving to the UK and obtaining her MRCP diploma. She currently works as the Neurology Registrar at Jersey General Hospital in the Channel Islands. She has a special interest in epilepsy management.[1]

Dr K Sieradzan[1]
Dr N Kane[2]

[1] Department of Neurology, Frenchay Hospital, Bristol
[2] Department of Neuro Physiology, Frenchay Hospital, Bristol.

Corresponding author:
Dr J Vaz,
42 Westaway Court,
Savile Street,
St Helier, Jersey,
JE2 3XG, UK.

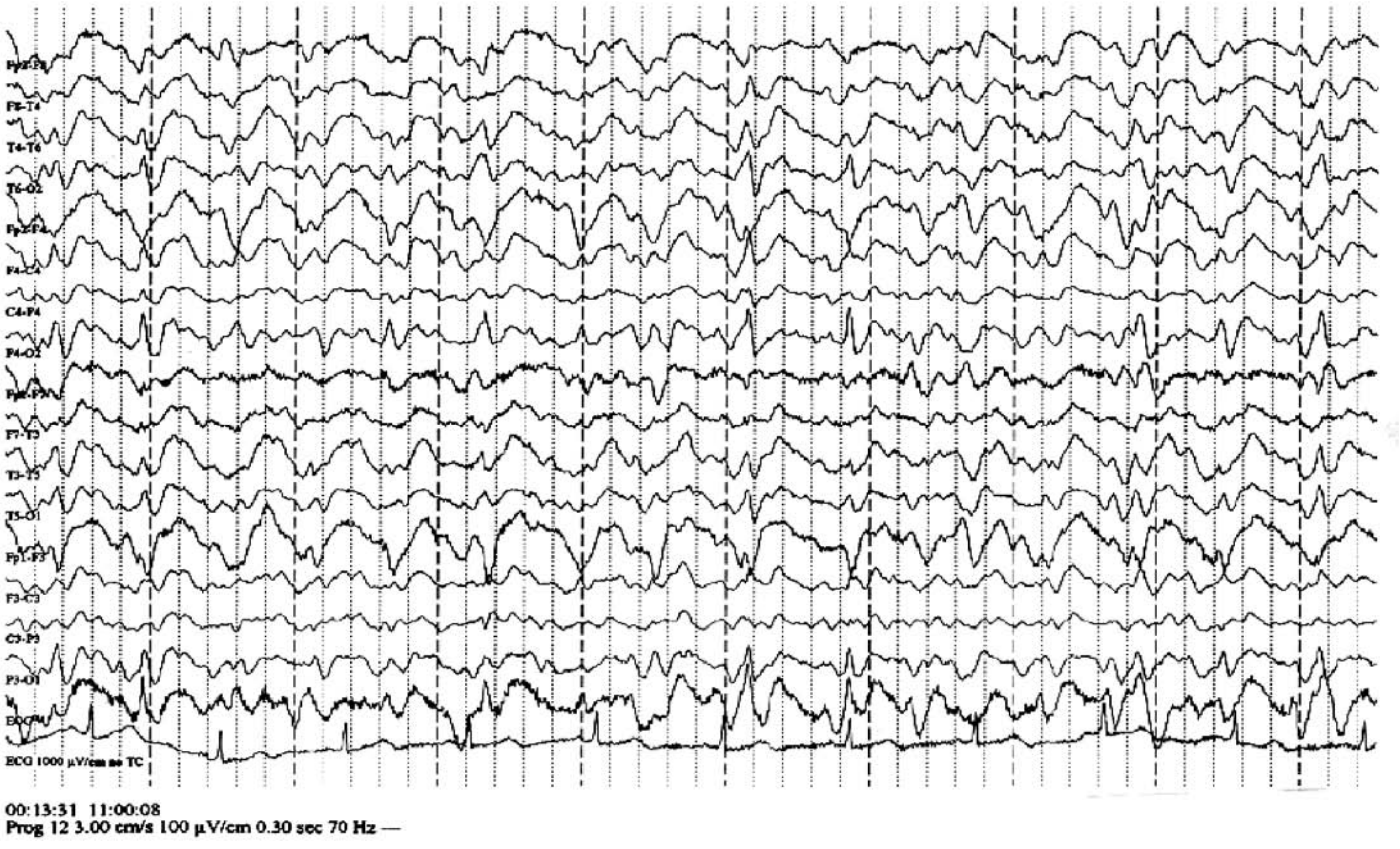

Figure 1: Almost continuous repetitive 1-1.5 Hz triphasic sharp, slow waves with an amplitude of 100-150uV that was widespread with an anterior emphasis intermixed with rhythmic 5-7 Hz theta waves in the posterior and central regions (20-30uV).

thalami. In view of these findings CSF was re-examined for CJD markers was and was found to be positive for protein 14-3-3.

The patient's level of consciousness fluctuated widely with Glasgow Coma Score (GCS) of 5-13. Repeated EEG's showed her to be in persistent NCSE that was resistant to treatment with phenytoin, sodium valproate, lorazepam and phenobarbitone.

Within days of admission the patient became bed-bound with increasing rigidity of all limbs, hyperreflexia, incontinence and monosyllabic speech gradually progressing to akinetic mutism. Two weeks after admission, she deteriorated dramatically with a drop in GCS to 5 accompanied by decorticate posturing. Repeat EEG confirmed her to be in NCSE with less than 5 sec bursts of normal activity in spite of therapeutic serum phenytoin levels. She was aggressively managed in the ITU with anaesthetic doses of propofol (achieving burst suppression), but remained in NCSE. She developed a chest infection and septicaemia and died a month after admission.

A post mortem brain examination revealed spongiform change in the brain with neuronal loss in the cortex, deep grey nuclei and cerebellum with synaptic pattern of PrP immunopositivity in the cortex, grey nuclei and cerebellum confirming sCJD.

Discussion

In 1920-21 Hans Jakob[1] and Alfons Creutzfeld[2] first reported cases of a progressive dementing neurological disease which bears their name. This uncommon disease presents as a rapidly progressive dementia associated with a range of neurological signs, most commonly myoclonus of the limbs, cerebellar ataxia, and rigidity[3] with a reported incidence of 1 per million-population year.[4]

In the absence of neuropathology, the patients are classified as probable if they present with progressive dementia, typical EEG changes and at least two of the following: myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, akinetic mutism (Masters classification).[5]

Usual EEG changes in sporadic CJD include slowing down of background rhythms with periodic sharp wave complexes that may be lateralized or diffuse[6] and may or may not be synchronous with myoclonus.[7] Generalized or focal seizures have been know to occur in 10-15% patients with CJD in the course of the disease and are often resistant to anti epileptic drugs.[8] NCSE is characterised by continuous epileptiform patterns on EEG in a particular pattern (focal, general, or bi-hemispheric pattern), alteration of consciousness including coma and the absence of convulsive motor activity.[9]

The MRI findings in our patient were typical of patients with sCJD as reported by Finkenstaedt et al. in 1996[10] with increased signal in bilateral caudate and putamen regions. The 'pulvinar sign' characterised by signal intensity in the posterior thalamus commonly noted in variant CJD (vCJD) was not noted in our patient.[11]

Although the presence of protein 14-3-3 in the CSF indicates rapid brain destruction, its presence and persistence is more indicative of CJD as compared to other dementias or inflammatory processes in the brain.[12] Furthermore, the presence of the protein is more indicative of sCJD[13] although it may be raised in 50% of the patients with vCJD.[14]

Our patient was unusual in that, in addition to a rapidly progressive dementia and motor disturbances, she presented with features of NCSE, in the absence of a previous history of epilepsy. Indeed only a few cases have been reported with CJD presenting as NCSE.[15,16] Schwinn et al.[15] presented 4 patients diagnosed retrospectively with a mean age of 64 years presenting with acute and sub acute changes in their mental status and NCSE. All were aggressively treated with anti-convulsants and none showed clinical improvement (despite improvement in their EEGs) with death ensuing within 3 months.

Shapiro et al[17] has recently reported a 70-year-old patient with sCJD presenting with a one month history of deteriorating mental status, EEG revealed NCSE, which did not respond to standard anti-epileptic medication, and thus the patient was managed with a midazolam infusion in the ICU in a bid to control the NCSE. The clinical description is very similar to our patient.

Conclusion

This case demonstrates the diagnostic dilemma when presented with a patient with progressive alteration in mental status and altered level of consciousness with no convulsive motor movements. When the aetiology of NCSE cannot be established the diagnosis of CJD should be kept in mind. Serial EEGs, MRI scans and CSF evaluation for protein 14-3-3 can aid the clinical diagnosis and prognosis in these patients. Diagnosing CJD has significant consequences for the patient and potential risks for iatrogenic transmission need to be considered.

Acknowledgement

We would like to thank Dr Tim Moss Consultant Neuropathologist and Dr Samar Batnoumi, SpR in Neuropathology for conducting the neuropathological examination.

References

1. Jakob A. *Über eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Befunde (Spastische Pseudosklerose-Encephalomyelopathie mit disseminierten Degenerationsherden).* Zeitschrift für die gesamte Neurologie und Psychiatrie 1921; 64:147-228.
2. Creutzfeldt HG. *Über eine eigenartige herdförmige Erkrankung des Zentralnervensystems (vorläufige Mitteilung).* Z ges Neurol Psychiat 1920; 57:1-18
3. Brown P, Cathala F, Castaigne P, Gajdusek DC. *Creutzfeldt-Jakob disease: clinical analysis of a consecutive series of 230 neuro-pathologically verified cases.* Ann Neurol. 1986 Nov; 20(5): 597-602.
4. Hainfellner JA, Jellinger K, Diringer H, Guentchev M, Kleinert R, Pilz P, Maier H, Budka H. *Creutzfeldt-Jakob disease in Austria.* J Neurol Neurosurg Psychiatry 1996;61:139–42.
5. Masters CL, Harris JO, Gajdusek DC, Gibbs CJ Jr, Bernoulli C, Asher DM. *Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering.* Ann Neurol 1979;5:177–88.
6. Steinhoff BJ, Racker S, Herrendorf G, Poser S, Grosche S, Zerr I, Kretzschmar H, Weber T. *Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease.* Arch Neurol 1996;53:162–6.
7. Burger LJ, Rowan AJ, Goldensohn ES. *Creutzfeldt-Jakob disease. An electroencephalographic study.* Arch Neurol. 1972 May;26(5):428-33.
8. Cokgor, M. Rozear and J.C. *Morgenlander. Seizures and Creutzfeld–Jakob disease. A case report and series review.* North Carolina Medical Journal 1999;2:108-9.
9. Shneker BF, Fountain NB. *Assessment of acute morbidity and mortality in non convulsive status epilepticus.* Neurology. 2003;61:1066-73.
10. Finkenstaedt M, Szudra A, Zerr I, Poser S, Hise JH, Stoebner JM, Weber T. *MR imaging of Creutzfeldt-Jakob disease.* Radiology 1996;199:793-8.
11. Zeidler M, Sellar RJ, Collie DA, Knight R, Stewart G, Macleod MA, Ironside JW, Cousens S, Colchester AC, Hadley DM, Will RG, Colchester AF. *The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease.* Lancet 2000;355:1412-8.
12. Poser S, Mollenhauer B, Kraubeta A, Zerr I, Steinhoff BJ, Schroeter A, Finkenstaedt M, Schulz-Schaeffer WJ, Kretzschmar HA, Felgenhauer K. *How to improve the clinical diagnosis of Creutzfeldt-Jakob disease.* Brain. 1999Dec;122;2345-51.
13. Zerr I, Pocchiari M, Collins S, Brandel JP, de Pedro Cuesta J, Knight RS, Bernheimer H, Cardone F, Delasnerie-Laupretre N, Cuadrado Corrales N, Ladogana A, Bodemer M, Fletcher A, Awan T, Ruiz Bremon A, Budka H, Laplanche JL, Will RG, Poser S. *Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease.* Neurology 2000;55:811-15.
14. Green AJ, Thompson EJ, Stewart GE, Zeidler M, McKenzie JM, MacLeod MA, Ironside JW, Will RG, Knight RS. *Use of 14-3-3 and other brain-specific proteins in CSF in the diagnosis of variant Creutzfeldt-Jakob disease.* J Neurol Neurosurg Psychiatry 2001;70:744-8.
15. Schwinn PJ, Krumholz and Seiden LG. *Jakob-Creutzfeldt disease presenting as non-convulsive status epilepticus.* Epilepsia 2001;42 Suppl 7:146-7.
16. Fernandez-Torre JL, Solar DM, Astudillo A, Cereceda R, Acebes A, Calatayud MT. *Creutzfeldt-Jakob disease and non-convulsive status epilepticus: a clinical and electroencephalographic follow-up study.* Clin Neurophysiol. 2004Feb;115(2): 316-9.
17. Shapiro JM, Shujaat A, Wang J, Chen X. *Creutzfeld –Jacob disease presenting as refractory non convulsive status epilepticus.* J Intensive Care Med. 2004;19:345-8.