Irregular presence of abnormal prion protein in appendix in variant Creutzfeldt-Jakob disease

We have investigated the presence of disease related prion protein (PrPSc) in appendix samples obtained at necropsy from four neuropathologically confirmed cases of vCJD. Creutzfeldt-Jakob disease (vCJD), PrPSc was detected in only one vCJD appendix, at a level lower than found in a diagnostic tonsil biopsy sample obtained from the same patient. The single PrPSc positive appendix, but not the other samples, also showed abnormal prion protein immunohistochemistry. The finding that appendix samples from three of four cases of vCJD are devoid of detectable PrPSc questions the utility of screening appendicectomy tissues to estimate the prevalence of pre-clinical vCJD infection within the UK population.

The appearance of a novel human prion disease, variant Creutzfeldt-Jakob disease (vCJD), in the United Kingdom from 1995 onwards, and the experimental confirmation that this is caused by the same prion strain as that causing BSE in cattle, has raised the possibility that a major epidemic of vCJD will occur in the United Kingdom and other countries as a result of dietary or other exposure to BSE prions. The pathogenesis of vCJD differs significantly from that of other forms of CJD. Disease associated prion protein (PrPSc) is readily detectable in lymphoreticular tissues in vCJD and not in classic CJD. High levels of PrPSc are uniformly found in the central nervous system and lymphoreticular system of vCJD patients. The highest levels of PrPSc seen outside the central nervous system in vCJD are in tonsil (about 10% of that found in brain) and tonsil biopsy is used for ante-mortem diagnosis of vCJD. To date, positive prion protein immunohistochemistry has been reported in only a single appendix sample, although, importantly, this was removed from the patient before the onset of overt features of vCJD. While the stage at which lymphoreticular infection occurs in vCJD is unknown, PrPSc accumulation is detectable in the lymphoreticular system in natural sheep scrapie and in experimental rodent models of scrapie at a very early stage of the incubation period, long before the clinical phase of the disease. Based upon these data it has been suggested that large scale screening of surgical tonsillectomy and appendicectomy tissues for PrPSc could provide early warning of a high level of vCJD prion infection and several such studies are in progress.

Recently we reported our concern after finding that PrPSc was undetectable in appendix samples obtained at necropsy from two neuropathologically confirmed vCJD cases. While we were not able to examine these samples using immunohistochemical methods, we have now had the opportunity to investigate appendixes from two further vCJD cases by both high sensitivity western blotting and immunohistochemistry.

Methods

Tissue samples

Tissues were collected at necropsy with consent of relatives from two patients with clinical presentations consistent with vCJD. Definite diagnoses of vCJD were confirmed by neuropathological examination and the demonstration of type 4 PrPSc in tonsil. Appendix samples from these vCJD cases, and appendixes from single neuropathologically confirmed cases of either sporadic CJD or inherited prion disease (144 base-pair insertion), were divided and prepared as either 10% homogenates in phosphate buffered saline (PBS) or fixed in 10% formal saline.

Immunohistochemistry

Tonsil tissue was fixed in 10% buffered formal saline and inactivations of prion infectivity was accomplished by incubation in 98% formic acid for one hour. After further washing for 24 hours in 10% buffered formal saline, tissue samples were processed and paraffin wax embedded. Sections were cut at a nominal thickness of 4 μm, treated with 98% formic acid for five minutes and then boiled in EDTA-TRIS-citrate buffer pH 7.8 for 20 minutes. Immunohistochemical staining was performed with anti-PrP monoclonal antibody 12F10 on a Ventana automated immunohistochemical staining machine using a basic dianminobenzidine detection system according to the manufacturers instructions (Ventana Medical Systems, Tucson, Arizona).

Detection of PrPSc

Sodium phosphotungstic acid precipitation of PrPSc from 0.5 ml 10% tissue homogenates and western blotting using high sensitivity enhanced chemiluminescence was performed as described previously.

Results

Recently we reported that appendix samples obtained at necropsy from two neuropathologically confirmed vCJD cases contained undetectable levels of PrPSc. We have now examined appendix samples from two further neuropathologically confirmed vCJD cases and have detected PrPSc in only one vCJD appendix (fig 1A). The level of PrPSc present in this appendix was compared directly with the level of PrPSc present in a diagnostic tonsil biopsy sample obtained from the same patient. After proteinase K treatment of equivalent aliquots (20 μl) of 10% appendix homogenate or 10% tonsill biopsy homogenate, we observed clear detection of PrPSc in biopsy tonsil homogenate, but not in appendix homogenates (fig 1B). Similarly, PrPSc was readily detectable in necropsy tonsil obtained from the vCJD patient with PrPSc negative appendix (fig 1C). The background single immuneactive band seen in appendix is also present in vCJD tonsil.

Figure 1 (A–D) Western blots of tissue homogenates with anti-PrP monoclonal antibody 3F4. Western blots were analysed by high sensitivity ECL. The positions of molecular mass markers are indicated in kilodaltons (kDa). (A) Proteinase K (PK) digestion products from a sodium phosphotungstic acid pellet from 0.5 ml 10% normal human tonsil homogenate spiked with a control level of 10% vCJD brain homogenate (C) is compared with PK digestion products from sodium phosphotungstic acid pellets from 0.5 ml 10% appendix homogenates from vCJD (V), sporadic CJD (S) or inherited prion disease (I) cases. (B) PK digestion products from 20 μl 10% normal human tonsil spiked with a control level of 10% vCJD brain homogenate (C) is compared with PK digestion products from 0.5 ml 10% appendix homogenates from vCJD (V), sporadic CJD (S) or inherited prion disease (I) cases. (C) Proteinase K digestion products from 20 μl 10% normal human tonsil homogenate (NT) is compared with PK digestion products from 0.5 ml 10% necropsy tonsil homogenate from the vCJD case with PrPSc negative appendix. (D) The western blot shows PK digestion products from 10 μl 10% normal human brain homogenate obtained in the absence of spike (NB) or after spiking with either a control level of 10% vCJD brain homogenate (C) or 0.05, 0.1, 0.25, 0.5, or 1 μl of 10% brain homogenate from the vCJD case with PrPSc positive appendix. The control level of spike of 10% vCJD brain homogenate (C) shown in panels A, B, D is equivalent to 50 nl 10% brain homogenate from a vCJD case previously reported to have a maximal level of PrPSc in brain; we estimate that an equivalent level of PrPSc is present in about 0.75 μl 10% brain homogenate from the vCJD case with PrPSc positive appendix. (E) Photomicrograph of PrPSc positive appendix. Immunoreactivity for PrPSc in a lymphatic follicle of the appendix (anti-PrP monoclonal antibody 12F10). The immunostaining pattern is similar to that reported in tonsils in vCJD patients and suggests deposition mainly in dendritic cells.

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seen in normal tonsil and is attributable to weak cross reactivity of the secondary antibody with an immunoglobulin fragment. While this band is consistently observed after high sensitivity enhanced chemiluminescence of total lymphoreticular homogenate, it is not recovered after sodium phosphotungstic acid precipitation. We determined that the level of PrPSc present in the brain of the vCJD patient with PrPSc positive appendix patient is approximately 15-fold lower than the maximum level we have observed in vCJD brain (fig 1D). Based upon these findings we estimate that biopsy tonsil and appendix, contain levels of PrPSc of about 4% and about 0.5%, respectively, of that found in the brain of the same vCJD patient (see legend to fig 1).

Importantly, we were able to correlate the detection of PrPSc by western blotting in vCJD appendix with the detection of abnormal prion protein staining by immunohistochemistry. Abnormal prion protein deposits were clearly observed on sections from the PrPSc positive appendix patient (fig 1E), while prion protein immunoactivity was unremarkable on sections from the PrPSc negative vCJD appendix or on sections of appendix from the sporadic CJD or inherited prion disease cases (data not shown).

**Discussion**

Our findings, together with our previously reported inability to detect PrPSc in two other vCJD appendixes,1 indicate that appendix does not reliably report vCJD infection even at the end stage of the disease. This observation must be considered when estimating the possible prevalence of vCJD based upon the analysis of archival appendicectomy tissue.2 Although only a minority of appendixes in vCJD may contain detectable levels of PrPSc, surgical instruments used for appendicectomy should remain a cause of concern for potential iatrogenic transmission of vCJD prions.

**References**


**Table 1** Differences between HIV seropositive and HIV seronegative patients with tuberculous meningitis

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>HIV positive</th>
<th>HIV negative</th>
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<th>Stage 2</th>
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<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
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<tr>
<td>IL-10 (pg/ml)</td>
<td>24.6</td>
<td>0–127</td>
<td>17.3</td>
<td>0–296.3</td>
</tr>
</tbody>
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IFN, interferon; IL, interleukin; TNF, tumour necrosis factor.

**Cytokine profiles in HIV seropositive patients with tuberculous meningitis**

The immunological response in pulmonary and pleural tuberculosis has been extensively studied. However, the response in tuberculous meningitis has not been well documented.1 In pulmonary disease, exposure to tuberculous antigens results in a T cell and natural killer cell-mediated pathogenesis. Various cytokines, mainly of Th helpler type 1 (Th1) origin. Stimulated macrophages elaborate tumour necrosis factor (TNF) α, interleukin (IL) 12, and IL-1, promoting further recruitment and activation of T cells and B lymphocytes. TNF α correlates with disease severity and may contribute to tissue necrosis; however, TNFα has also contributed to survival in mouse studies.2 Transforming growth factor β (TG α cytokine) suppresses macrophage activation. IL 2 may be beneficial in promoting an immune response in HIV seropositive patients. Th1 and Th2 cytokine responses have been observed in HIV seropositive patients with tuberculous meningitis.3 Whether the response is similar in HIV seropositive patients with tuberculous meningitis is unknown.

We studied the cytokine response and its correlation with disease severity in HIV seropositive and HIV seronegative patients with tuberculous meningitis. Tuberculous meningitis was diagnosed on clinical and radiological grounds, after exclusion of viral, acute bacterial, and other causes of aseptic meningitis. Disease severity was assessed according to the Medical Research Council stages 1 to 3. HIV ELISA was done on all patients. CSF samples were subjected to microbiology, culture, protein and glucose analysis, cryptococcal antigen analysis, viral studies, and serological analysis for patients in stages 1 and 2. We studied the cytokine response and its correlation with disease severity in HIV seropositive and HIV seronegative patients with tuberculous meningitis.

The positive correlation between IFN-γ and TNF-α concentrations correlated poorly with CD4 counts, 0.47 for TNF-α, 0.22 for IFN-γ, and 0.04 for IL-10. Correlation coefficients between ADA (p = 0.4) and CD4 counts (p = 0.19) in CSF and cytokine concentrations (table 1).

Ten patients (37%) were classified as having grade 1 tuberculous meningitis; 2 (6%) had grade 2 and 1 (4%) grade 3, which for analysis was considered to be grade 2. Table 1 summarises the cytokine concentrations for patients in stages 1 and 2. Patients with stage 2 disease had significantly stronger Th1 responses. There was no difference in the IL 10 concentrations. The two patients with stage 2 disease who died had very high IFN-γ concentrations, both greater than 2048 pg/ml. IL-10 concentrations were moderately positively correlated with IFN-γ concentrations (r = 0.53). The correlation coefficients were 0.18 for IFN-γ, 0.33 for TNF-α, and 0.04 for IL-10. Correlation coefficients between ADA and cytokine concentrations were 0.34 for IFN-γ, 0.47 for TNF-α, and 0.22 for IL-10. Cytokine concentrations correlated poorly with CD4 counts in CSF. It is postulated that in HIV infection a predominant Th2 response accounts for extrapulmonary disease.1 This study does not favour a predominance of either Th1 or Th2 in the pathogenesis. It is possible that a Th0 response, which is a non-differentiated response seen early in immune activation, was seen in our patients, as they were examined untreated and relatively early in the disease. Other investigators have also documented this phenomenon.2 The positive correlation between IFN-γ and IL-10 suggests that these were produced concurrently. This may reflect a control mechanism regulating Th1 and Th2 responses.
Further studies to confirm our findings would be of value.

The significantly greater TNF α and IFN γ concentrations in the severe group of tuberculous meningitis is confirmed by other studies and suggests that disease severity results mainly from the immune response rather than the organism itself.

The lack of correlation between CD4 and cytokine concentrations may be explained by the fact that there are other sources of cytokines in the CSF, namely macrophages and natural killer cells. Concentrations of ADA, which are derived from lymphocytes, are consistent with other reports, where they were found to be correlated with cytokine concentrations.

There was no correlation between the IgG index and cytokine concentrations, suggesting that the blood brain barrier did not significantly influence concentrations. Unfortunately, corresponding serum concentrations were not available. This would have been valuable. This is the first study correlating CSF cytokine responses to severity of tuberculous meningitis and comparing HIV positive with HIV negative patients. Further studies should be done to confirm these findings, perhaps to define their relevance to complications and to explore the possibility of IL 2 treatment in HIV positive patients.

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References


Festination as the leading symptom of late onset idiopathic aqueductal stenosis

Late onset idiopathic aqueductal stenosis (IAS) may be manifest clinically either by headaches or by hydrocephalic symptoms such as gait disturbance, urinary urge, and cognitive impairment. Rarely, patients with IAS may also present with parkinsonism following repeated episodes of shunt failure. Although the gait disorder of IAS has not been fully characterised, it shares similar features with that of normal pressure hydrocephalus of the elderly. Here, we report on two patients who presented with festina- tion as the leading symptom of IAS.

Case histories

Case 1

A 59 year old man had a seven year history of gait disturbance. During the months before admission, he became more unsteady and he no longer walked with the assistance of a Zimmer frame. He fell frequently. For several months, no diagnosis was made and his gait disorder was considered possibly organic. After imaging showed pronounced triventricular hydrocephalus he referred for further evaluation and treatment. On admission, he also reported occasional nocturnal urinary incontinence. The most remarkable finding of his physical examination was his gait disorder. He was able to walk without falling only when holding on to a handrail or to the wall. When he walked freely, his stride length became successively shorter, his step height decreased, while his walking speed increased. He was unable to slow his walking speed or to stop abruptly. He then would bend his upper body forward and foot floor clearance became “magnetic gait” fairly well depicts its typical clinical features. The gait may also adopt a shuffling appearance resembling somewhat a parkinsonian gait disorder. It may be classified as being a middle level of the unified Parkinson disease rating scale according to its presentation and biomechanical evaluations. Clinical aspects of hydrocephalic gait vary widely depending on the progression of the underlying condition and on any accompanying parkinson disease. The hydrocephalic gait disorder may occur as early as 30–50% of patients with idiopathic normal pressure hydrocephalus. Festation, however, is seen only rarely in hydrocephalic patients but when it occurs it is generally associated with more severe hydrocephalus and a clinical picture of Parkinsonism. It is not fully understood how hydrocephalic disorders induce gait disturbance and parkinsonism. The underlying pathomechanisms may include mechanical distortion of fibres of the corticospinal tract and of dopaminergic pathways but also disturbed supraspinal control mechanisms of gait. Following the report of the occurrence of festination in the presented cases of IAS may have been related more specifically to distension of the third ventricle. The anatomical substrates of festination have not been elucidated but it is most likely related to functional disturbances of diencaphalic or brainstem locomotor centres. This assumption would also explain the reversibility of festination after third ventriculostomy and shunting. In summary, this is the first report of the occurrence of festination as the leading symptom of IAS. As shown, festination may be misinterpreted and be considered psychogenic in an elderly patient who otherwise is suffering only mild hydrocephalic symptoms.
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Myoclonic movement disorder associated with microdeletion of chromosome 22q11

With a prevalence of approximately 1 in 5,000, the interstitial chromosome 22q11 deletion within the DiGeorge syndrome critical region is the most common chromosome microdeletion syndrome. The better known clinical features of this disorder are cardiac abnormalities, short stature, palatal abnormalities or velopharyngeal insufficiency, renal abnormality, hypocalcemia, psychotic symptoms, learning difficulties, and developmental delay. There is wide variability in this clinical spectrum and many case reports drawing attention to new clinical features have been published. Alongside the larger studies of 22q11 cohorts these have proved useful in delineating this particular syndrome.

Case report

We present a family where the proband at 3 years of age exhibited the typical facial features of deletion of chromosome 22q11 (fig 1a) of low set posteriorly rotated ears, small mouth and mandible, short philtrum, and short palpebral fissures, as well as developmental delay. His height was on the fourth centile and he also had pectus carinatum. His mother (fig 1b) also had learning difficulties and delayed motor milestones as a child and subsequently developed an unusual movement disorder, which was first noted as a tremor at age 5 and was brought to medical attention in her teens. The movement disorder consisted of longstanding pronounced myoclonus of the head, trunk, and limbs, which is worsened by intention and exacerbated by startle. She had slow tongue movements. Eye movements were normal. Extensive neurological investigations were normal: caeruloplasmin, molecular testing for Huntington’s disease, myotonic dystrophy, mitochondrial mutations, muscle biopsy, electroencephalography, and magnetic resonance imaging of the brain. Echocardiography and renal ultrasound in both mother and son were also normal. Although standard cytogenetic testing showed a normal karyotype, fluorescence in situ hybridisation analysis with the probe for the DiGeorge syndrome critical region showed that both mother and son had a deletion in this region.

Discussion

In the European collaborative study presenting data on 558 patients with deletions within the DiGeorge syndrome critical region of chromosome 22q11 neurocognitive features were available for 548 patients and 8% had neurocognitive abnormalities. Three per cent had structural brain abnormalities such as cerebro atrophy, cerebellar hypoplasia, cerebral vascular abnormality, septum pellicudum cyst, hydrocephalus, hypoplasia of the corpus callosum, and enlarged ventricles. Eleven patients had asymmetrical crying faces, three had seventh cranial nerve palsies, and two had facial asymmetry. Seizure information was available for 290 patients of whom 21% had seizures, and in 42 of these were hypocalcaemic in origin. Nine per cent of children were reported to have either behavioural or psychiatric problems and 18% of adults had a psychiatric disorder.

There has been no previous association with a similar neurological disorder and microdeletion 22q11, although a parkinsonian-like movement disorder has been reported. In that case extrapyramidal symptoms (muscle rigidity, oral-buccal movements, and tremors of the tongue and upper extremities) predated the onset of psychotic symptoms at 15 years of age. As the mother of our proband first exhibited signs of a movement disorder at age 5 it will be interesting to see how he develops. Despite extensive neurological testing for the cause of the myoclonus in the mother, no cause was found. Three mutated genes for myoclonus-dystonia have been described in the literature, the most recent in 2001, and are not available as a diagnostic service. However, the phenotype we describe is different from that described in these cases: alcohol sensitive jerks, dystonia, usually torticollis or writer’s cramp, and often showing prominent psychiatric abnormalities. 22q11 microdeletion syndrome is a variable disorder and even within families signs can be very different. It is possible that many patients with physical and psychiatric abnormalities have an unrecognised genetic disorder. Increased awareness and access to testing may show a widening of the phenotypic spectrum of these disorders. We believe myoclonic movement disorder may be a previously unreported clinical feature of the chromosome 22q11 deletion.

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References
Phenobarbitone induced gingival hyperplasia

Among the long term adverse effects of anticonvulsants, gum hyperplasia is cosmetically disturbing and can give rise to complications such as bleeding and gingivitis. Long term use and high doses of phenytoin sodium (diphenylhydantoin) have been implicated in the occurrence of gingival hyperplasia. Serum phenytoin level in these patients are high. Rarely other drugs such as primidone, sodium valproate, nifedipine, and cyclosporin have also been implicated. Treatment consists of stopping the offending agent and providing corrective surgery. Phenobarbitone (phenobarbital) has not yet been reported to cause gum hyperplasia. We describe a patient who developed this complication in association with the long term use of phenobarbitone.

Case report

A 26 year old man had been suffering from hot water reflex epilepsy and primary generalised tonic-clonic seizures since he was 12 years of age. The seizures were poorly controlled because of his inability to avoid taking hot baths, inadequate dosage of anticonvulsants, and poor compliance. Since 1987, he had been taking phenobarbitone, 60 to 90 mg/day. In 1988, phenytoin (100 mg twice daily) was added for six months but was stopped because there was no benefit. In 1989, carbamazepine (200 mg twice daily) was added but was discontinued by the patient in 1996 onwards he had been receiving only phenobarbitone 120 mg/day. He was referred to us for progressive gum hyperplasia with bleeding from the gums, both spontaneously and with tooth brushing, since 1996. There was no history suggesting any haematological malignancy, and he was not on any other drug treatment.

On examination, he had gingival hyperplasia involving both the upper and the lower jaws (fig 1). There was occasional bleeding from the hyperplastic gum tissue. General physical examination did not reveal any pallor, hepatosplenomegaly, or lymphadenopathy and neurological evaluation was unremarkable. Haematological investigations, including haemoglobin, white blood count, erythrocyte sedimentation rate, and peripheral smear, were all normal. Blood glucose, renal and liver function tests, serum electrolytes, and urine analysis were normal. Scalp electroencephalography and cranial computed tomography were normal. Serum concentrations of phenobarbitone, phenytoin, and carbamazepine were measured. Phenobarbitone was within the therapeutic range (11.2 µg/ml) while the other two drugs were not detectable.

Discussion

This patient with longstanding epilepsy probably had phenobarbitone induced gingival hyperplasia. He had used phenytoin in 1988 for only six months without developing this symptom, and it only appeared later in 1996 when he was on phenobarbitone alone. After that time it ran a progressive course. Primidone, the metabolites of which contain phenylethylmalonamide and phenobarbitone, has also been reported to be a rare cause of gingival hyperplasia. However, it is difficult to state which of the two components contributes to the hyperplasia. Phenytoin sodium is known to be the most common cause of gingival hyperplasia. A minor degree of hyperplasia occurs quite commonly and this generally causes only cosmetic problems, especially for women. However, when phenytoin is used for prolonged periods in high dosage a severe degree of gingival overgrowth occurs. In such cases the hyperplastic gingiva bleed with minimal trauma or spontaneously, and may sometimes become secondarily infected.

The mechanism of anticonvulsant induced gingival hyperplasia is not known. It is believed that these drugs cause tissue collagen proliferation but the reason for this is unknown. It has been speculated that a high phenytoin concentration in the pituitary and adrenal glands may be related to hirsutism and gingival hyperplasia. However, there is no evidence that high concentrations of phenytoin in these tissues produce changes in their secretion rate, or indeed that these alterations cause hirsutism and gingival hyperplasia.

Antiepileptic drug levels are generally high in cases of gingival hyperplasia. However, in our case the phenobarbitone level was within normal therapeutic limits, while phenytoin and carbamazepine were undetectable. Buchmann et al reported nine cases of phenytoin induced moderate to severe gingival hyperplasia who underwent corrective gingivectomy. It was found that in eight of these cases the tissue diphenylhydantoin levels were higher than the plasma levels.

Treatment consists of stopping the offending drug and providing supplements of folic acid and ascorbic acid. If regression does not occur, reconstructive surgery of the hyperplastic gingival tissue is advised. Our patient has been switched to sodium valproate, and reconstructive cosmetic surgery is planned.

In conclusion, we report a case of phenobarbitone induced gingival hyperplasia because of its rarity. The mechanism of this side effect remains unclear. Accurate drug history, thorough investigations, and punctilious reporting of such cases may help us gain a better understanding of the condition.

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References


Hashimoto’s encephalopathy mimicking Creutzfeldt-Jakob disease: brain biopsy findings

A previous report in this journal described seven cases of Hashimoto’s encephalopathy (HE) clinically resembling Creutzfeldt-Jakob disease (CJD). Brain biopsies in such cases are rare and have suggested “vasculitis.” We contribute a report of rapidly progressive dementia in a patient undergoing brain biopsy before the diagnosis of HE was established, showing features suggesting early spongiform change but with inflammation.

A 57 year old woman was taken to a local hospital following a generalised seizure. She was discharged that night after negative cranial computed tomography and cerebrospinal fluid (CSF) analysis. Within a few days she was noted by family members to be acting strangely and hallucinating. Her doctor found her to be somnolent and rigid without focal neurological findings. Magnetic resonance imaging of the brain showed a questionable increase in gadolinium contrast uptake in a 7 mm area of the left medial frontal cortex. An electroencephalogram (EEG) showed bihemispheric slowing without epileptiform activity. Despite an extensive inpatient evaluation (including biochemical, haematological, endocrine, infectious, autoimmune, and toxic analyses), no cause for the encephalopathy could be found. The patient was then referred to our institution for brain biopsy and further care.

Samples of left frontal cortex showed light microscopic evidence of rare vacuoles abutting neurons, suggesting early spongiform
recently been added to the clinical criteria for and 99%, respectively) for the diagnosis of have a high sensitivity and specificity (96% is a CNS protein detected in spinal fluid was sent to be tested for the 14–3–3 protein, which reference range < 450 mg/l). A sample was and prominent frontal release signs. CSF akinetic, and mute, with startle myoclonus our patient's other clinical features of rapid cognitive dissolution, myoclonus, extrapyramidal rigidity, and aki- netic mutism suggest the diagnosis of prion disease. Although presentation with a seizure is unusual in CJD, our patient’s other clinical features of rapid cognitive dissolution, myoclonus, and extrapyramidal rigidity were highly suggestive of her cognitive change (fig 1). Gilford fibrillary acid protein staining showed moderate gliosis. A few perivascular lymphoid cells and macrophages were present, with microglia scattered throughout the parenchyma; there was no evidence of true vasculitis (inflammation and fibrinoid necrosis of arterial vessels) or of microglial nodules. Because prion disease could not be excluded histologically and because the clinical suspicion of CJD re- mained high, a tissue block was sent to the National Prion Disease Reference Laboratory (NPDRL). Subsequently the patient’s condition deterio- rated. She became wheelchair bound, akinetic, and mute, with startle myoclonus and prominent frontal release signs. CSF analysis showed increased protein (890 mg/dl, reference range < 450 mg/dl)). A sample was sent to be tested for the 14–3–3 protein, which is a CNS protein detected in spinal fluid (named after the chemical formula for one of its seven distinct isoforms and two phosphorylated forms) and has been shown recently to have a high specificity and sensitivity (96% and 99%, respectively) for the diagnosis of CJD. This is in contrast to what was found that the EEG has recently been added to the clinical criteria for the “probable” sporadic form of the prion disease. Magnetic resonance imaging re- peated with gadolinium and diffusion weighted sequences showed only postictal changes. Repeat EEG showed continued bi- hemispheric slowing with the addition of triphasic waves. The patient had a family his- tory of hypothyroidism but at the time of admission was euthyroid (thyroid stimulating hormone 2.89 mU/l, reference range 0.5–5 mU/l; thyroxine 65.79 pmol/l, reference range 64.1–149 pmol/l; triiodothyronine 1.346 pmol/l, reference range 1.078–2.464 pmol/l)). Nevertheless, in the absence of a clear cut cause and in view of prior reports of the clinical overlap between CJD and HE, we measured thyroid peroxidase antibodies, which were increased (79 IU/ml, reference range 0–20 IU/ml). An ultrasound of the thy- roid showed several hypoechoic areas, fine needle biopsies of which were non-diagnostic. The fact that many euthyroid middle aged women can be shown to have mildly increased thyroid peroxidase antibodies inevitably gave rise to speculation that the finding was incidental. However, in the absence of another obvious cause for the rapidly evolving demen- tia, and giving due weight to the findings in previous studies that the majority of reported cases were euthyroid, we began steroid treatment for a presumptive diagnosis of HE.2 Within 24 hours the patient had visible neurological improvement and within one week she was mobile and conversant, with reversal of most of her cognitive and motor deficits. Shortly thereafter, the NPDRL re- ported that the tissue did not show evidence of abnormal prion protein. The CSF did not contain the 14–3–3 protein. The patient was discharged on a slow taper of steroids. Six weeks later she was seen in the outpatient clinic and was considered fully recovered by her husband and her doctors. Rapidly progressive encephalopathy with myoclonus, extrapyramidal rigidity, and akin- netic mutism suggest the diagnosis of prion disease such as CJD. However, the differential diagnosis is wide and includes infections of the CNS, toxins, vitamin B12 deficiency, hypo- thyroidism, autoimmune or idiopathic cer- ebrovasculitis, paraneoplastic encephalitis, epileptic pseudodementia, and other rapidly progressive dementias, especially familial forms of Alzheimer disease. HE, a disorder of presumed autoimmune origin in which pa- tients present with altered levels of conscious- ness, seizures, and other extrapyramidal and extrapyramidal signs, the EEG, and a disorder of presumed autoimmune origin in which pa- tients present with altered levels of conscious- ness, seizures, and other extrapyramidal and extrapyramidal signs, the EEG, and the EEG, and the history of prior antithyroid treatments, the clinical picture was highly suggestive of a prion disease.3 The initial laboratory evaluation, the lack of convincing imaging findings, and the EEG were also con- sistent with early prion disease.4 In fact, according to the National Prion Disease Reference Labora- tory, the clinical and EEG features of this case alone already indicated a diagnosis of “prob- able” CJD.5 Furthermore, the presence of vacuoles on the brain biopsy was very sug- gestive of the spongiform change (due to swelling of neuritic processes) in early CJD, a diagnostic possibility additionally evoked by the moderate gliosis.6 Although the absence of pathognomonic amyloidotic (“kuru”) plaques on a limited biopsy does not exclude a diagnosis of “definite” CJD in a suspected patient, we felt that the features of the case justified immunoassay for prion protein in the tissue and CSF. The presence of perivascular mononuclear cells, though sparse, is not typical for CJD, and may, in the end, be the greatest supportive evidence of encephalitis as the true cause of the symptoms. The changes are reminiscent of those illustrated by Nolte et al., although we strongly disagree with their term “vascularitic”, instead preferring to reserve that term for true necrotising arteritis, which implies a differ- ent pathogenesis. Unlike their patient in whom the inflammation was confined to basal leptomeninges in the setting of prior subarachnoid haemorrhage, ours involves parenchymal vessels, with permeation of the cortex by microglia, suggesting a more cred- ible substrate for the seizures and cognitive deficits. In conclusion, we recommend that patients who, according to World Health Organization criteria, have clinical and EEG features of probable CJD2 be considered for empirical treatment with steroids for HE, pending labo- ratory results for antithyroid antibodies as well as for 14–3–3 protein. Furthermore, we present additional evidence that HE is an encephalitic process, likely autoimmune given the dramatic response to anti-inflammatory treatment. C P Doherty, M Schlossmacher, N Torres, E Bromfield, M A Samuels Department of Neurology, Partners Neurology, Brigham and Women’s Hospital, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA R Folkert Department of Pathology (Neuropathology) Competing interests: none declared Correspondence to: Dr C P Doherty; cpdoherty@partners.org References 1 Seipelit M, Zerr I, Nau R, et al. Hashimoto’s encephalitis as a differential diagnosis of Creutzfeldt-Jakob disease. 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Long term tolerability of high dose ergolone derived dopamine agonist therapy for the treatment of Parkinson’s disease During the past decade new direct acting dopamine agonists (DA) have become widely deployed for the treatment of the early stages of Parkinson’s disease (PD), because ran- domised controlled trials (RCT) have demon- strated that their use is associated with a reduced incidence of motor fluctuations and dyskinesias compared to levodopa therapy.7,8 Curiously these studies have also shown that the effect of levodopa on motor function or activities of daily living (measured by Unified Parkinson’s Disease Rating Scale (UPDRS) parts II and III) was superior to that obtained by the DAs, irrespective of whether the latter were administered as monotherapy or with open label levodopa supple- mentation.9,10 Our understanding of the reasons behind why the DAs were consistently less effective than levodopa on the UPDRS has been particu- larly as these RCTs were performed double blind. Two plausible explanations are: (1) the UPDRS does not capture the whole picture; for example, the DAs and levodopa may have differential effects on mood; or (2) the doses (therapeutic levels) deployed in these studies were set so that the DAs were slightly suboptimal compared to levodopa, but this difference was not apparent to the blinded clinicians assessing the trial patients.
The latter notion encouraged us to examine the dose of the DAs used to treat PD in routine clinical practice. Thus we systematically reviewed the database of all the PD patients under our care in order to identify those receiving DA therapy (cabergoline, pergolide, pramipexole, or ropinirole) above their maximum recommended therapeutic daily dose (respectively 6 mg, 5 mg, 4.5 mg, and 24 mg per day).

We identified 18 patients fulfilling these criteria. All were either on cabergoline (n = 11) or pergolide (n = 7), which are ergoline derived dopamine agonists. This represents about 23% and 27% of PD patients in our data sheets. Indeed it is clear from these data sheets that cabergoline delays the onset of motor complications: results of a double-blind levodopa controlled trial. Eur J Neurol 1999;6(suppl 5):S17–23.

Consequently, we speculate that the ergoline derived dopamine agonists (cabergoline and pergolide) may not have been deployed to their full therapeutic potential, either in the major RCTs comparing DAs with levodopa or in current clinical practice. However, we do not know whether this capacity is confined to the ergoline derived DAs. As the direct acting DAs are now considered to be first line therapy for younger people with Parkinson's disease, we would be very interested to hear of other neurologists' experiences of using these drugs for prolonged periods above their recommended doses. There is a case for further studies involving high dose dopamine agonist treatment for people with PD.

Finally, it should be noted that serosal inflammation is a rare, probably idiosyncratic, potentially reversible complication of ergoline derived dopamine agonist administration, which typically develops about two years after introducing this class of drug. However, we have not encountered this problem in our practice.

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Competing interests: PN was reimbursed by Pharmacia for attending the XIV International Congress on Parkinson's disease (Finland, 2001). The authors also conducted two double blind trials comparing the antitremor effects of pergolide with pramipexole, to which Pharmacia freely supplied the masked medications.

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Festination as the leading symptom of late onset idiopathic aqueductal stenosis

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