Creutzfeldt–Jakob disease (CJD) is a rare neurodegenerative illness which was first described in 1921 [1]. The disease is invariably fatal and is characterized by progressive multifocal neurological dysfunction and dementia leading to death in a few months. Most cases occur sporadically, with mean age of onset at around 65 years. A small number of cases are familial, related to mutation of the prion protein gene, and there have been rare iatrogenic cases.

In 1996, a new clinico-pathological variant was described, variant (v)CJD, which is caused by transmission of bovine spongiform encephalopathy from cattle to man [2]. This variant was hitherto thought to be confined to a younger age group, as the mean age at death was 29 years (range 14–53) [3]. However, the recent description of a case of vCJD confirmed at autopsy in a 74-year-old man raises the possibility that dementia in this age group may be caused by CJD, with implications for future surveillance [4].

Clinical features

Cases of sporadic (s)CJD can present with a variety of prodromal symptoms before any obvious neurological involvement. These include alteration of personality, insomnia, anorexia and depression. Because of multifocal involvement, neurological features depend on the areas of cerebral cortex most severely affected. Ataxia and cognitive impairment predominate, but pyramidal or extrapyramidal signs and myoclonic jerks are also common [5]. Rarer presentations include a stroke-like onset, occipital blindness and a pure cerebellar syndrome [6].

Whatever the presentation, the course is characterized by relentless deterioration involving multiple cerebral areas leading to death within a few months. The clinical features of sCJD in elderly patients are similar to those in younger age groups [7]. The rare cases of familial CJD have more atypical presentations depending on the mutation identified.

Cases of vCJD have a different clinical phenotype. The 112 cases described up until now have an extended disease duration (median 14 months compared with 4 months in sCJD) and involve a younger age group (median age at death 29 years). There can be marked psychiatric morbidity in the early stages. In addition to depression, patients frequently experience hallucinations, fleeting delusions and, occasionally, aggression. Another early feature is sensory disturbance, either paraesthesia or dysesthesia. Clear neurological signs and/or cognitive impairment may not become apparent until many months after onset and the clinical course is then rapid, with a mean duration from becoming ataxic to becoming bedbound of 6 months [8, 9].

The clinical phenotype in the older patient recently described with neuropathologically confirmed vCJD was consistent with previous descriptions, although the length of illness was a little less than the mean [4].

Although the definitive diagnosis rests on neuropathological evaluation, in vivo investigations can point towards a diagnosis. Bilateral pulvinar high signal on magnetic resonance imaging has been identified as a sensitive and specific sign in the first 36 cases of vCJD when compared with controls (Figure 1) [10]. A magnetic resonance image was not available in the single case to date in an older person. In sporadic cases, one retrospective study showed that 79% of scans demonstrated a high signal in the caudate nuclei and putamina on T2 and proton-density-weighted images, probably due to gliosis and spongiform change (Figure 2) [11]. Although not specific for CJD, such changes are more common in older sporadic cases, as the extrapyramidal grey matter nuclei show decreased signal intensity with normal ageing—perhaps because of iron deposition [12].

Cerebrospinal fluid in CJD typically contains no inflammatory cells, although the protein content can be slightly elevated [5]. One marker of acute cell death detectable in cerebrospinal fluid, the 14-3-3 protein, is a highly sensitive and specific marker for sCJD in suspected clinical cases [13]. False-positives are seen in more common clinical conditions such as recent stroke, Alzheimer’s disease or central nervous system infection, highlighting the importance of performing the test only in those cases with a high index of clinical suspicion [14]. The 14-3-3 assay is less helpful in the diagnosis of vCJD.

Electroencephalograms have been a component of the criteria since 1979, and the characteristic appearance of 0.5–2 Hz generalized bi- or triphasic complexes are seen in about 60–70% of sporadic cases [5]. These changes are not seen in vCJD.

One feature shared by magnetic resonance image scanning, cerebrospinal fluid 14-3-3 analysis and electroencephalography is their high specificity in suspected cases. When applied to a more general group of patients, this specificity will inevitably decrease.
Pathology

The characteristic pathological hallmarks are spongiform change, neuronal loss, and astrocytosis. In addition, amyloid plaques which stain positively on immunohistochemistry for prion protein (PrP\textsubscript{c}) are seen in the grey matter. These changes vary in severity and distribution from case to case [15]. In vCJD, the same key changes are present, but additional characteristic changes include ‘florid’ PrP plaques surrounded by a halo of spongiform change widespread throughout the cerebral and cerebellar cortex, as well as cluster plaques seen in all grey matter regions, particularly in the occipital cortex, basal ganglia and cerebellum [16].

CJD neuropathology is characterized by the accumulation of an abnormal isoform (PrP\textsubscript{Sc}) of a host-encoded glycoprotein, known as the prion protein (PrP\textsubscript{c}). PrP subtype analysis has shown the accumulation of a distinct type of PrP\textsubscript{Sc} in vCJD, similar to that found in bovine spongiform encephalopathy transmission studies [17].

The gene for human PrP is located on the short arm of chromosome 20. The methionine/valine polymorphism at codon 129 may confer susceptibility to the disease [8]. All vCJD cases and 79% of sporadic cases have displayed homozygosity for methionine (the MM genotype), compared with 37% of the normal population [18]. However, in sporadic CJD, the frequencies of codon 129 genotypes vary between age groups, with a relative excess of methionine homozygosity in the older age group.

In addition, the polymorphism may influence the disease phenotype and/or incubation period [19]. It may be that the MM genotype confers susceptibility to CJD or that the MM phenotype is more ‘typical’ and hence clinically detectable. The same may be true of vCJD, where all cases to date, including that in the 74-year-old man, have had the MM genotype. Again, alternative genotypes may present differently or have a longer incubation period. (Phenotype–genotype studies in kuru showed that heterozygous cases may have a longer incubation period [20]).

Epidemiological trends

The annual incidence of sCJD in the UK is estimated to be between 0.5 and 1 case per million, with similar rates reported in many countries [21]. Surveillance suggests a random distribution throughout the UK, with no evidence of clustering [22]. The mean age at death has shown a temporal increase, and is currently 65 years [3].

Until recently, it was thought that there was a fall-off in incidence in older age groups, particularly among those aged >75 years. However, this decline has become less marked with time, and age-specific trends over the period 1970–99 have shown that the greatest relative increase has been in those aged ≥70 years (Figure 3) [3].

Figure 1. Axial FLAIR magnetic resonance image of patient with variant Creutzfeldt–Jakob disease showing characteristic hyperintensity in pulvinar of thalamus.

Figure 2. Axial proton-density-weighted image showing high signal in putamen and caudate head characteristic of sporadic Creutzfeldt–Jakob disease (indicated by arrows). Note the area of high signal in left occipital cortex. This is an early feature of the disease.
The number of deaths identified in this age group was about 1 per year in England and Wales in the early 1970s and is now about 20 per year. Improved case ascertainment in elderly people may explain this trend. In contrast, vCJD has been confined to a younger age group, with a mean age at onset of 27, the upper age range being 54 years until the recently detected case in a 74-year-old man.

The aetiology of sCJD remains obscure. A meta-analysis of case–control studies carried out in 1996 found an increased risk of CJD in patients with a history of psychotic illness and a non-significant risk associated with a family history of other neurodegenerative illnesses [23]. Despite concerns, there is no suggestion to date of any association with blood transfusion. The random temporospatial distribution of sCJD suggests that it may be sparked by a spontaneous mutation of the PrP gene or by a spontaneous alteration of the PrP structure.

The evidence linking vCJD to bovine spongiform encephalopathy is now stronger as a result of transmission studies which have demonstrated that the agent causing bovine spongiform encephalopathy has very similar characteristics to that causing vCJD [24].

Discussion

There is a concern that sporadic or variant cases may be missed. In one study of the clinical and pathological causes of dementia, nine cases of CJD were found at autopsy in a series of 675 demented subjects. However, among the subset of patients from geriatric and psychiatric hospitals, only one case was detected in 445 autopsies. The remaining eight cases came from a large general hospital with an affiliated neurological unit and resulted from 230 autopsies on subjects whose dementia had no obvious aetiology [25].

Another review of pathological features in 1000 cases of dementia from the Runwell Hospital brain archive found 19 cases of CJD, only 11 of which had been identified before death. Six of the eight remaining patients who had were identified as having CJD on pathological examination only had presented atypically with longer duration and a history of gradual progressive mental deterioration before terminally giving rise to more rapid mental and physical decay [26]. The archive may not be representative of the current situation, as the great majority of samples date from the 1960s and 1970s.

Most cases of CJD in elderly subjects are sporadic, but it is possible that more variant cases may arise in the older population. The mean age at presentation of vCJD may rise because of a cohort effect and because phenotypes with longer incubation periods may occur. Clinical features correlate to varying degrees with neuropathological findings in dementia. Agreement rates of 85% have been reported for Alzheimer’s disease, but the values for multi-infarct dementia and other causes are lower [25]. For this reason, it is important that post-mortem examinations are considered in cases of unusual neurodegenerative or dementing illnesses.

In cases where there are suspicious clinical features (e.g. myoclonus or rapid progression), investigations such as electroencephalography and magnetic resonance image scanning may help in the diagnosis of CJD. However, neuropathological examination remains central to a definite diagnosis, and the identification of cases of sporadic or variant CJD in the older age groups may depend on a heightened awareness of the clinical features in suspect cases.

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