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CREUTZFELDT-JAKOB DISEASE - THE STORY SO FAR*

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The story began in the 1920s when Creutzfeldt and Jakob described independently an unusual fatal neurological disorder.[1,2] Considerable disagreement still exists over the precise nature of what was described in the earliest reports and recognition of Creutzfeldt-Jakob disease (CJD) as a distinct entity over subsequent years was slow, because of its rarity and the lack of specific diagnostic criteria.[3] It was realised subsequently that the neuropathological changes in the brain were diagnostic, but it was not until 1978 that a full evaluation was made of the significance of the characteristic spongiform change in the cerebral grey matter,[4] which gave rise to an alternative name - subacute spongiform encephalopathy.

The aetiology and pathogenesis of CJD remained obscure for many years; various suggestions, including metabolic and vascular defects, were put forward.[3] The disease was successfully transmitted to primates in 1968,[5] when it was also realised that CJD was related to other rare transmissible neurological disorders, including kuru,[6] which was transmitted from human to human via ritualistic practices associated with cannibalism in the Fore tribe in Papua, New Guinea; the Gerstmann-Straussler-Scheinker syndrome (GSS)[7] - a very rare hereditary form of progressive cerebellar ataxia first described in Austria in 1936; and scrapie,[8] an endemic disease of sheep and goats in the United Kingdom and other European counties which had been identified for at least 200 years.

Scrapie was first transmitted from sheep to sheep in 1936;[9] recognition of the neuropathological similarities between scrapie and kuru led to the successful attempt to transmit kuru in 1966.[10] The human spongiform encephalopathies were subsequently shown to occur as sporadic, familial and acquired disorders[11] (Table 1); the latter group included cases of iatrogenic disease,[12] the first of which was reported in 1974 following a corneal transplantation from a patient subsequently shown to have died from CJD.[13]

TABLE 1
Classification of human transmissible spongiform encephalopathies.

Idiopathic		Sporadic CJD
Acquired	Human source	Iatrogenic CJD Kuru
	Bovine source	New variant CJD
Genetic		Familial CJD GSS Fatal familial insomnia

The nature of the transmissible agents responsible for the spongiform encephalopathies remains unproven,[11] but it has been known for many years that these

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agents were remarkably small and resistant to most forms of physical and chemical means of inactivating conventional viruses and bacteria.[14,15] It had been suggested that the agents might be composed only of protein,[16] and this possibility has been developed by Prusiner into the prion hypothesis;[17] this states that the transmissible agent is composed entirely of a modified host cell surface glycoprotein, the prion protein (PrP), which accumulates in the brain in scrapie, CJD and related disorders.[18]

Advances in the understanding of the cell biology and molecular genetics of PrP have largely supported this hypothesis.[18] The human PrP gene is located on the short arm of chromosome 20; familial CJD, GSS and fatal familial insomnia are associated with point mutations or insertions in the gene.[19] These genetic forms of human spongiform encephalopathy are also experimentally transmissible, thereby supporting the prion hypothesis.[20] A naturally occurring polymorphism is present at codon 129 in the PrP gene, which influences disease susceptibilty[21,22] and affects the clinical and pathological phenotype in CJD.[23,24]

Sporadic CJD occurs in a worldwide distribution at an incidence of approximately one per million population per annum.[25] The aetiology of sporadic CJD remains unknown, despite several large-scale epidemiological studies.[25,26] Scrapie, the naturally occurring transmissible spongiform encephalopathy in sheep, has not been shown by these studies to be associated with CJD.[25,26] Surveillance studies have allowed the development of clinical diagnostic criteria which, in experienced hands, are of predictive value, although post-mortem neuropathological examination is required to confirm a clinical diagnosis of CJD.[27]

In the United Kingdom, most patients with sporadic CJD are aged 60-69, and present with a rapidly progressive dementia accompanied by ataxia, movement disorders including myoclonus, visual disturbances and ultimately akinetic mutism.[27,28] Around 60% of patients exhibit a characteristic electroencephalogram (EEG), with triphasic complexes occurring at 1Hz.[29] Presenting features vary widely, although rapidly progressive dementia and myoclonus are most characteristic. Most patients die in less than six months from diagnosis, although very occasionally patients survive for much longer.[25,27]

CJD SURVEILLANCE IN THE UNITED KINGDOM

Surveillance of Creutzfeldt-Jakob disease (CJD) was reinstituted in the United Kingdom in 1990, following the identification of a new disease in cattle, bovine spongiform encephalopathy (BSE), in 1986.[30] Epidemiological studies identified meat and bonemeal feed as the likely vehicle for infection, and this was banned for consumption by ruminants in 1988.[31] BSE occurred as an epidemic in the United Kingdom, with a peak incidence of around 1200 cases per week in 1992-1993.[32] In 1989 the human consumption of bovine offal (including brain, spinal cord and lymphoid tissues) was banned. However, the possibility remained that the population in the United Kingdom had been exposed to the BSE agent through the food-chain prior to that date.[32] BSE has been transmitted by the oral route to other species including antelopes in zoos and domestic and wild cats, raising the possibility that this disease (unlike scrapie in sheep) might transmit to humans.[33,34,35]

Cases of suspected CJD are referred to the CJD Surveillance Unit in Edinburgh from healthcare professionals (mainly neurologists and neuropathologists) throughout the United Kingdom. Detailed clinical and epidemiological data are obtained as part of a case control study, using parallel methodology to other comparable studies in several European countries.[36] Prion protein genotype is investigated when informed

consent is obtained, and the majority of suspected CJD cases (at least 70%) undergo autopsy. Cases are classified as sporadic, familial or iatrogenic CJD,[27] and since the surveillance project began there has been an increased detection of sporadic CJD in the United Kingdom, particularly in elderly individuals, as a consequence of increased case ascertainment.[28]

NEW VARIANT CJD

In 1996, the CJD Surveillance Unit published a series of ten patients with an apparently new variant of Creutzfeldt-Jakob disease.[37] These cases had a remarkably early age at onset (mean 26 years, range 16-39 years) with unusual clinical features. These were psychiatric symptoms including depression, behavioural and personality changes and sensory symptoms with paraesthesiae particularly in the lower limbs and face.[38,39] This was followed by ataxia, other movement disorders including myoclonus and chorea, and eventually dementia with akinetic mutism. The duration of the illness on average was around 14 months, in contrast to typical sporadic CJD which has an average duration of illness of around five months.[27] None of the patients had a characteristic EEG for sporadic CJD, and all were methionine homozygotes at codon 129 in the prion protein gene.[37]

Since then, 14 subsequent cases of new variant CJD have been confirmed in the United Kingdom and one case in France.[40] The clinical and genetic features of the illness in all these patients are relatively constant; the oldest patient so far became ill at the age of 48 years.[39] Surveillance data to date have identified no other specific risk factors for this disease, and in particular no common occupational or iatrogenic source of transmission has been identified.[39]

New variant CJD exhibits the characteristic neuropathological features of human transmissible spongiform encephalopathy, including spongiform change, neuronal loss, gliosis and amyloid plaque formation.[37] However, the features of the lesions in the brain are unique and are characterised by spongiform change occurring in an irregular distribution in the cerebral cortex, with the occipital cortex being most severely involved.[41] Within the cerebral cortex there are numerous amyloid plaques which typically occur as large fibrillary plaques surrounded by a rim of spongiform change within an otherwise intact neuropil.[37] These resemble the 'florid' plaques first described in transmissions of Icelandic scrapie to mice.[42] The 'florid' plaques are most numerous in the occipital cortex, but can be detected in all cortical regions. Immunocytochemistry for prion protein (PrP) shows dense staining of the amyloid plaques and in addition demonstrates multiple smaller plaques which are usually not detected on routine stains[10] (Figure 1). Spongiform change is most evident in the corpus striatum, particularly in the caudate nucleus, with PrP accumulation around neurones and axons (Figure 2). The thalamus is severely involved with marked neuronal loss and astrocytosis, particularly in the pulvinar. Cerebellar pathology is also widespread; spongiform change is observed in the molecular layer accompanied by variable loss of Purkinje cells. Granular neurones with cortical atrophy and marked astrocytosis are found. Amyloid plaques, including 'florid' plaques, are present in a widespread distribution in the cerebellum (Figure 3). These patterns of PrP accumulation are unlike those found in sporadic cases of CJD in any of the cases identified since 1990 in the CJD Surveillance Unit.[43]

Comparison of the pathology of new variant CJD with sporadic CJD shows striking differences, particularly in cases who are methionine homozygotes at codon 129 in the PrP gene.[24] In sporadic CJD, individuals with this genotype almost never show amyloid plaques in the brain, and have not been found to have 'florid' plaques in any brain

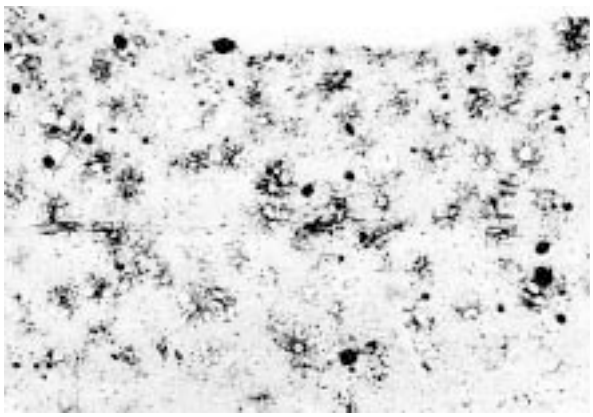

FIGURE 1
Immunocytochemistry for prion protein shows strong staining of the rounded amyloid plaques with multiple smaller plaques and diffuse deposits in the cerebral cortex in new variant CJD x 240.

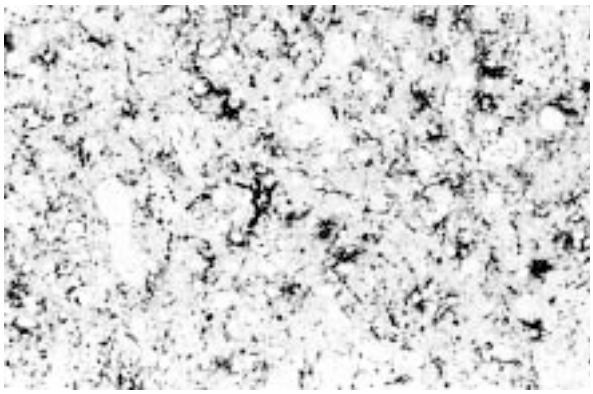

FIGURE 2
In the caudate nucleus, PrP accumulates around neurones (centre) and axons in new variant CJD, with few plaques present x 300.

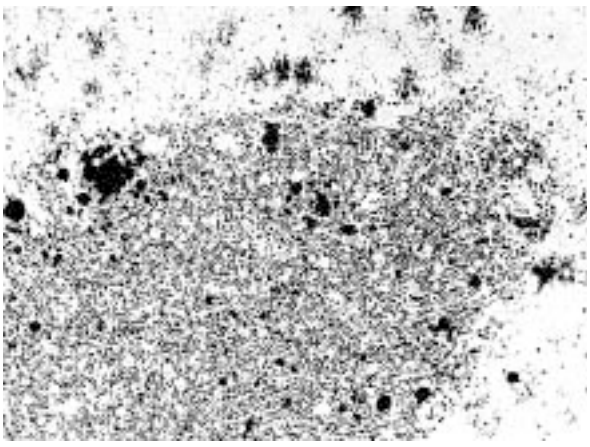

FIGURE 3
New variant CJD is characterised by massive PrP accumulation on immunocytochemistry in the cerebellum in the form of large dense-staining plaques in the granular and molecular layers x 180.

region.[44] Amyloid plaques are commoner in heterozygotes and valine homozygotes in sporadic CJD, and in certain types of familial CJD and iatrogenic CJD occurring in growth hormone recipients.[43,44]

Studies on lymphoid tissue in new variant CJD have revealed for the first time in humans the presence of disease-associated PrP in the tonsil.[45] This finding has raised the possibility of the use of a tonsillar biopsy as a diagnostic investigation for new variant CJD. Involvement of the lymphoid system in new variant CJD has also raised additional questions concerning disease pathogenesis, particularly the possibility of spread of the transmissible agent by circulating lymphoid cells. This in turn raises the possibility of disease transmission by blood transfusion or inoculation of blood products.[46] In sporadic CJD there is no evidence that blood transfusion is a risk factor,[47] but further studies are required to investigate the possibility of the infectivity of blood in new variant CJD.

THE RELATIONSHIP BETWEEN NEW VARIANT CJD AND BSE

The epidemiological features of new variant CJD suggested a causal link with BSE.[37] Additional supportive evidence for this link between new variant CJD and BSE came from an experimental transmission study of BSE in the macaque monkeys, which revealed clinical features similar to those in new variant CJD and a strikingly similar neuropathology, with florid plaques in the cerebral cortex.[48] Analysis of PrP by Western blotting in new variant CJD and BSE has shown a similar glycosylation pattern, which was also found in experimental transmissions of BSE to other species, and on transmission of both BSE and new variant CJD to transgenic mice which over-express the human PrP gene. This finding supports the hypothesis that BSE is the cause of new variant CJD.[49,50]

The most convincing scientific evidence for a causal link between these disorders has come from experimental strain-typing studies in mice. This approach has identified around 20 distinct strains of the agent in scrapie.[51] In BSE, however, only one strain has been identified; this strain has also been identified from species with BSE-related disorders in antelopes and cats, and following experimental infection with BSE in sheep, goats and pigs.[51] Preliminary results of strain-typing studies in the brains of infected mice of new variant CJD and sporadic CJD have shown that whereas BSE and new variant CJD have an identical incubation period and neuropathological lesion profiles, cases of both contemporary and historical sporadic CJD had entirely different incubation periods and neuropathology.[52] Thus the results of these investigations indicate that the BSE agent is the cause of new variant CJD in man ('human BSE').[53]

The link between BSE and new variant CJD has raised many important questions which remain unanswered at present. A dietary route of exposure to the BSE agent appears the most likely, but host susceptibility factors are poorly understood (other than methionine homozygosity at codon 129 in the prion protein gene). The infectious dose of the BSE agent required to produce new variant CJD in man is unknown and it is not certain whether cumulative low dose exposure can be pathogenic. The incubation period for new variant CJD in humans is also unknown, and cannot be estimated with certainty because of the effect of the 'species barrier' between cow and human which may prolong the incubation period. A lengthy incubation period for new variant CJD could indicate that the present cases are only the beginning of what might be a large epidemic, but at present it is not possible to predict with any certainty future numbers of cases.[54]

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