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Bovine spongiform encephalopathy and Creutzfeldt-Jacob's disease
15 years later, where do we stand?

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Σπογγώδης εγκεφαλοπάθεια βοοειδών και νόσος Creutzfeldt-Jacob: Πού βρισκόμαστε 15 χρόνια αργότερα;

Περίληψη στο τέλος του άρθρου

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1. INTRODUCTION

Spongiform encephalopathies are progressive diseases caused by unconventional infectious agents. Stanley B. Prusiner and his colleagues suggested that the infectious agents are composed not of nucleic acid, but protein,[1] and that these "proteinaceous infectious particles" or "prions" are the disease causing agent.

The prion protein (PrP) found in infected brains resisted breakdown by the cellular enzymes called proteases (PrP^{res}).[2] Because most proteins are degraded rather easily, scientists were led to the concept that the "scrapie-causing PrP" is a variant of a normal protein. This variant protein is called "cellular protein", and the infectious version "scrapie PrP". Their difference lies not in the primary structure of the protein, but rather in its conformation, which confers the ability to withstand degradation. When abnormal PrPs enter the system, the body can convert their normal counterparts into abnormal forms. This leads to the formation of aggregates of abnormal PrP, especially in the neurons, resembling those found in the neurons of patients with Alzheimer's disease. It is still unclear whether the presence of such aggregates is the cause of disease, but the symptoms that follow are degeneration of physical and mental abilities, and ultimately death.

The multiplication of these proteins occurs when abnormal protein molecules convert normal molecules into scrapie PrP, simply by inducing them to change their conformation. It is not known exactly how the multiplication of scrapie PrP damages cells. In cell cultures the conversion of normal PrP to the scrapie form occurs inside the neurons. As the diseased cells die, creating holes in the brain, abnormal prions are released and attack other cells.

2. SPONGIFORM ENCEPHALOPATHY

2.1. Bovine spongiform encephalopathy

Bovine spongiform encephalopathy (BSE), otherwise known as "mad cow disease", was identified in 1986 in cattle in England. Current evidence suggests that the disease originated from supplementary feed containing meat and bone meal nutritional elements contaminated by a scrapie-like agent derived from sheep or cattle.[3] This was probably a result of the changes that occurred in the processing of sheep carcasses in the 1970's. This specific agent, however, exhibits properties different from those of any known scrapie. It is also widely maintained that the agent causing BSE is not present in the blood or most other tissues.

The UK was the country worst affected by BSE. The factors that are considered to play a role in this include the facts that the UK has the world's largest ratio of sheep to cattle, a high prevalence of scrapie in sheep and a high proportion of use of meat and bone meal in cattle feed.

In July 1988 the UK government banned the use of material derived from ruminants in cattle feed. The most infective parts of the animals are the brain and the spinal cord. In 1989, measures were enforced in England and Wales to ensure that BSE would not enter the human food chain, by banning the use of certain bovine parts from human consumption. In general, the selection of culling

policies depends on several factors, such as social and political factors, public health policies and ethical values. In 1992, the BSE epidemic showed a peak of approximately 36,500 cases in cattle, and just one year later this number increased alarmingly to 100,000 cases. In 1997, the number of cases rose to 160,000 and it is considered that it would have been much higher had cattle not been slaughtered before symptoms developed. In countries such as Australia and Brazil, where cattle were fed on grass pastures, cattle did not develop BSE. Ireland and France however, reported 1,300 and 900 cases, respectively.[4] However, the UK was the worst affected country, with a total of 183,500 cases reported.

Most affected animals acquire infection soon after birth and the incubation period was estimated to be 5 years. Given an incubation period of 5 years, an average age of infection of about 1 year, and a life expectancy at birth of 3 years, it is obvious that the animals acquiring infection do not survive long enough for the symptoms to appear. There is compelling evidence that the vast majority of BSE cases have resulted from contaminated feed.[2]

2.2. Creutzfeldt-Jacob's disease

The final most important event in the chronology of the BSE epidemic was the announcement, in 1996, of a suspected possible link between BSE in cattle and Creutzfeldt-Jacob's (CJD) disease in humans.[5] CJD occurs worldwide, even in areas where there is no scrapie, such as Australia, and it usually becomes evident as dementia.

The most common forms of CJD are three:

- Sporadic CJD:[6] Unknown etiology, but the most common form
- Iatrogenic form:[7,8] Due to the attempt to treat another medical problem
- Familial form:[9] Due to a mutation in the PrP gene.

Most of the cases of CJD diagnosed belong to the sporadic form, which strikes individuals at around 60 years of age. In 1996, however, 10 cases of CJD in young people were reported. By 2009, 164 people had died of CJD in the UK, and 42 elsewhere.[10–12] It is believed by most scientists that the disease may be transmitted to human beings who eat the brain or spinal cord of infected carcasses.[13,14]

About 10–15% of the cases are inherited. A smaller number is iatrogenic, apparently transmitted by corneal transplantation, implantation of dural matter or electrodes in the brain, use of contaminated surgical instruments and injection of growth hormones (GH) derived from human pituitary, before the use of recombinant GH became available.

The typical symptoms of CJD are dementia, which is followed by loss of coordination, although sometimes the sequence is reversed.

The distribution of cases is:

– Sporadic CJD: 1 person per 1,000,000 worldwide
– Inherited CJD: Extended in 100 families
– Iatrogenic CJD: 100 cases identified but none since 1976 when sterilization procedures were adopted.[15]

CJD patients have a characteristic electroencephalographic (EEG) appearance. Death occurs 4–6 months after the observation of the symptoms.[10]

Because of the epidemic of BSE in cattle, surveillance of CJD in the UK was reinstituted in May 1990. Ten cases of young people with CJD that appeared to have differences from the known cases of sporadic CJD were examined. Death certificates, clinical details and information on potential risk factors were obtained using a standard questionnaire, and blood was taken for DNA analysis. Neuropathological examination was also carried out. The ages of the individuals infected ranged from 19 to 41 years. The clinical features included behavioral changes, which were observed quite early, pain in the feet during the illness, and ataxia. Early in the course of the disease, all the patients developed progressive dementia, some memory impairment and choreoathetosis. Late in the course of the disease myoclonus was diagnosed. None of those patients showed the EEG features usually associated with CJD. Information on the PrP genotype is available for 8 of the 10 cases, of which all were methionine homozygotes at codon 129 of the PrP gene (chromosome 20), and none of the known mutations associated with the inherited forms of CJD was identified. In a study of codon 129 in sporadic CJD cases in the UK between 1990 and 1993, 111 (83%) had methionine.[16] Neuropathological examination in all 10 cases showed spongiform-like changes in the brain and the presence of PrP plaques, confirming the diagnosis of CJD.[17] On cerebral biopsy in two cases and necropsy in the remaining 8 cases, spongiform changes, neuronal loss and astrocytosis were the most evident histopathological features.

Many plaques had a dense eosinophilic center and pale periphery and were usually surrounded by a zone of spongiform change. This unusual feature was not seen in any of the other sporadic CJD cases investigated. PrP deposition was observed in a pericellular distribution in the cerebral cortex and in the molecular layer of the

cerebellum, the pattern of which suggested deposition around small neurons. PrP proteins were also seen in the thalamus and in the basal ganglia.

None of these patients had a history of iatrogenic exposure to CJD through neurosurgery or administration of human GH, and none had had a blood transfusion. Four had no history of any operation, and four had undergone minor surgery. One had worked as butcher, but generally the activities and life style of all 10 individuals exclude any risk factor for transmission. Eight of the patients used to eat meat, but never the brain, while one person was strictly a vegetarian.

The features that appeared in these 10 cases showed differences from those previously seen, such as specific neuropathological profile not seen before (immunocytochemical analysis showed numerous amyloid plaques surrounded by vacuoles and PrP accumulation in a high concentration), the young age of the patients, extended (at least 6 months) and the unusual clinical course and the absence of EEG changes typical of CJD. These findings raise the possibility that the cases represent a new clinicopathological variant of CJD (vCJD).

2.3. Possible link

Scientists were interested to know whether the vCJD has any link with the BSE. It is already known that sporadic CJD has no relationship with BSE. Although the small number of cases in this report cannot be regarded as proof, the observation of a potentially new form of CJD in the UK was consistent with such a link. The common neuropathological picture may indicate infection by a common strain of the causative agent. Exposure of the human population to the BSE agent was more probable at the end of the 1980's, before the ban on the use of bovine offal. If the present cases are due to exposure to the BSE agent, it is not clear why this previously unrecognized variant of the disease is found only in people below 45 years of age. The absence of this variant in older people could be due to age-related exposure to the agent (although this is not supported experimentally) and misdiagnosis of this variant of the disease in older age groups in whom dementia is more common.

The thought that the new vCJD is due to exposure to BSE is perhaps the most plausible interpretation of the scientific findings, but no definitive evidence is available. The fact that these cases were found at this time and not earlier could be due to recent increase of awareness of BSE and the diagnosis of CJD. Others argue that this explanation represents just an extreme, since the fact that deaths occurred in young patients would have been spotted with time. It is of note that no vCJD cases have been identified in other countries in the European surveillance system. This variant may be unique to the UK, which raises the possibility of it being linked with BSE, since the UK had the highest prevalence of BSE by far, compared to other countries.

The most likely explanation at present for the occurrence of 10 cases (now 12 confirmed cases) of an apparently new variant of the rare but lethal CJD in humans was exposure to the etiological agent of BSE before regulations were introduced to eliminate cattle with clinical signs and prevent specified offal from all cattle entering the human food chain.

CJD is currently diagnosed only by the elimination of other treatable forms of dementia, such as encephalitis or chronic meningitis, by a spinal tap, which identifies the more common causes of dementia, and EEG to detect the brains electrical pattern. Computerized tomography (CT) can rule out other possible causes such as a brain tumor, and magnetic resonance imaging (MRI) scans reveal brain degeneration patterns. Brain biopsy is still the best way to confirm a diagnosis of CJD. A much easier and safer test for patients with clinical symptoms of the disease is the NINDS test, which detects a protein marker that indicates neuronal degeneration in the cerebrospinal fluid (CSF).

3. CONCLUSION

In 2008 there was one new diagnosis of vCJD in a patient who died the same year, bringing the total number of cases reported in the UK to 167, of whom 164 have died.[10] The median time from onset to diagnosis is 328 days, and from onset to death is 413 days. The overall median age at death is 28 years, with a range of from 14 to 74 years. However, the peak of the epidemic is estimated to have occurred in mid 2000. While it is still possible that new forms of vCJD develop, the prediction for vCJD diagnosis is less than 1 case for 2009,[16] making this disease almost a public scare of the past.

ΠΕΡΙΛΗΨΗ

Σπογγώδης εγκεφαλοπάθεια βοοειδών και νόσος Creutzfeldt-Jacob: Πού βρισκόμαστε 15 χρόνια αργότερα;

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Δεκαπέντε χρόνια μετά από την παρουσίαση της σπογγώδους εγκεφαλοπάθειας των βοοειδών (BSE), γνωστής ως νόσος των τρελών αγελάδων, εξετάζεται η σχέση της με την ανθρώπινη νόσο Creutzfeldt-Jacob. Η BSE οφείλεται στην πρωτεΐνη prion που βρίσκεται σε μολυσμένους εγκεφάλους. Αυτή η πρωτεΐνη είναι διπλωμένη με τέτοιον τρόπο ώστε να είναι ανθεκτική στη διάσπαση από τις πρωτεάσες και μπορεί να προκαλέσει τη μετατροπή φυσιολογικών πρωτεϊνών σε ανώμαλες. Το 1996 βρέθηκε η σχέση μεταξύ της BSE και της CJD, αλλά παρά τα πρώτα κρούσματα της CJD, οι προγνώσεις διαγνώσεών της για το 2009 είναι κάτω από μία, χωρίς αυτό να αποκλείει την περίπτωση νέας εκδοχής της CJD.

Λέξεις ευρετηρίου: Βοοειδή, Επιδημιολογία, Νόσος Creutzfeldt-Jacob, Πρωτεΐνη prion, Σπογγώδης εγκεφαλοπάθεια

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