Creutzfeldt-Jakob disease, new variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy – An update

The recent report of a new variant of Creutzfeldt-Jakob disease (CJD) from the United Kingdom (1) among unusually young patients and with links to bovine spongiform encephalopathy (BSE) prompted this review of developments in this area. Transmissible spongiform encephalopathies (TSE) are rare forms of progressive neurodegenerative disorders that affect both humans and animals (2). Characteristic features include prolonged incubation periods, spongiform changes (microscopically visible vacuoles in the parenchyma of the brain) associated with neuronal loss and a failure to induce inflammatory response (3). Other neuropathological hallmarks include astrocytosis, and occasionally the presence of kuru plaques. TSEs include CJD, variant CJD, kuru, fatal familial insomnia and Gerstmann-Strausler-Scheinker syndrome in humans, and scrapie, mink encephalopathy, BSE, chronic wasting disease of elk, feline spongiform encephalopathy and spongiform encephalopathy of exotic ungulates in various animal species (1,4-8).

The prototype TSE in humans, CJD, has three distinct patterns. It may occur sporadically (approximately 90% of cases), through autosomal dominant inheritance (approximately 10% of cases) or through iatrogenic transmission of the infective agent (less than 1% of cases) (9,10). In iatrogenic cases, person-to-person transmission has been associated with corneal transplants, dura mater grafts, pericardial grafts, peripheral injections of pooled pituitary gland extract (growth hormone injection) and the use of contaminated neurosurgical instruments (11-17). CJD is a rapidly fatal dementing illness that occurs worldwide, with an estimated incidence of approximately one case per million persons in an equal male:female ratio. Although the ingestion of animal brains and a history of surgical procedures have been implicated as putative risk factors, a recent reappraisal of case control studies revealed only two risk factors including a family history of CJD and a history of psychotic illness (18-21).

Increasing evidence suggests that unconventional agents termed prion proteins (PrP), which are encoded by genes on chromosome 20, are considered of central importance in the etiology of CJD. The PrP is a fragment of a normal and ubiquitous protease-sensitive glycoprotein with a molecular weight of 33 to 35 kDa. The native protein is designated PrPC and the disease-related isofrom is designated PrPC (22). The latter disease-related isofrom PrPSC is distinguished from its normal isofrom by its insolubility and resistance to proteases. PrPSC is formed from the normal isofrom by a post-translational mechanism that involves a distinct conformational modification (23). Several lines of study support a model of PrPSC propagation that involves a direct interaction between the disease-related isofrom and the normal isofrom, acting to promote conversion of normal PrP to abnormal PrP. The pathological properties of these proteins lie in their three-dimensional configuration and ability to recruit and influence normal PrPs to undergo similar conformational changes. In the inherited forms of the disease, coding mutations in the PrP gene are thought to be responsible for the production of PrPSC. The two best studied forms of familial CJD are associated with a mutation at codon 200 of the PrP gene (24,25). Presentation of sporadic CJD is partially determined by polymorphism at codon 129 of the PrP gene.

The transmissibility of CJD has been verified with reports of iatrogenic transmission from a corneal transplant, electroencephalographic depth electrodes, neurosurgical instruments, cadaveric dura mater grafts and human pituitary hormone administration (11-17), as well as verified in laboratory studies (26-28). Intracerebral inoculation has been found to be the most efficient means of transmission, but oral ingestion and peripheral injection have also been documented as means of transmission (26-28). Tissues reported to be infective include the central nervous system, gut, lymphatic system and muscle. Although CJD transmission through blood has been documented in the laboratory, no cases of transfusion-related CJD have been confirmed in humans yet. Transmission studies have suggested there is a relative species barrier for different TSEs (29). However, events in the United Kingdom with respect to the occurrence of variant CJD (1) and reports of CJD in...
British cattle farmers (30-32) against a backdrop of a 20-year outbreak of BSE in the cattle population raise very significant concerns about BSE being transmitted to humans.

Recent studies have provided more direct evidence to support this epidemiological association. Feeding experiments in sheep have demonstrated transmissibility of BSE via the oral route substantiating the hypothesis that the use of contaminated beef and sheep by-products in feed given to cattle in the 1970s and 1980s contributed to the BSE outbreak (33). A study by Collinge and colleagues (23) provided the first scientific link between BSE and variant CJD. They found that the physicochemical ‘fingerprint’ of variant CJD prions transmitted to mice matched the disease-related isof orm of the PrP of BSE but differed from the disease-related isoform seen in patients with acquired or sporadic CJD (23). These latter findings and other experiments that are underway (23,34) will likely provide more evidence that BSE is the etiologic agent of variant CJD in humans.

REFERENCES


John M Conly MD FRCP C
Toronto, Ontario
Stephen D Shafran MD FRCP C
Edmonton, Alberta.