Creutzfeldt-Jakob disease

General information

Key concepts

● an invariably fatal encephalopathy characterized by rapidly progressive dementia, ataxia and myoclonus

● death usually occurs within 1 yr of onset of symptoms

● 3 forms: 1) transmissible (possibly via prions), 2) autosomal dominant inherited, 3) sporadic

● characteristic EEG finding: bilateral sharp wave (0.5–2 per second)

● pathology: status spongiosus without inflammatory response

Creutzfeldt-Jakob disease (CJD) is one of 4 known rare human diseases associated with transmissible spongiform encephalopathy agents, also called prions (proteinaceous infectious particles). Although sometimes also referred to as a “slow virus,” these agents contain no nucleic acids and are also resistant to processes that inactivate conventional viruses.

Prions do not provoke an immune response. The other human prion diseases are kuru, Gerstmann-Sträussler-Scheinker disease, and fatal familial insomnia. The protease-resistant protein associated with disease is designated PrPres or PrPSc, and is an isoform of a naturally occurring protease-sensitive protein designated PrPsen or PrPC. In the abnormal state, PrPsen, which is a predominantly alpha-helical structure, undergoes a post-translational conformation change to PrPres, which has large betasheets, and which accumulates in neural cells, disrupting function and leading to cell death and vacuolization. The famous choreographer George Balanchine died of CJD in 1983. CJD occurs in 3 forms: transmissible (possibly via prions), inherited (autosomal dominant) and sporadic

Epidemiology

Annual incidence of CJD: 0.5–1.5 per million population with little change over time and no geographic clustering (except in locations with large numbers of familial cases). Over 200 people die of CJD in the U.S. each year.

Acquired prion diseases

Natural route of infection is unknown and virulence appears low, with lack of significant dissemination by respiratory, enteric, or sexual contact. There is no increased incidence in spouses (only a single conjugal pair of cases has been verified), physicians, or laboratory workers. There is no evidence of transplacental transmission. The only known cases of horizontal transmission of CJD have occurred iatrogenically. Kuru has been transmitted via handling and ingestion of infected brains in ritualistic

funereal cannibalism practiced among the Fore (pronounced: “fore-ay”) linguistic group in the eastern highlands of Papua, New Guinea,14 a practice which was generally abandoned in the 1950s. Kuru is a subacute, uniformly fatal disease involving cerebellar degeneration (the word “kuru” means “to tremble” in the local language. Most noniatrogenically transmitted cases of CJD occur in patients > 50 yrs old, and is rare in age < 30. The incubation period can range from months to decades. The onset of symptoms following direct inoculation is usually faster (common range: 16–28 mos), but still may be much longer (up to 30 years with corneal transplant,16 and 4–21 yrs with hGH transmission). In experimental models of CJD, higher inoculation doses produce shorter incubation periods.

Inherited CJD

5–15% of cases of CJD occur in an autosomal dominant inheritance pattern with abnormalities in the amyloid gene18 on chromosome 20 with a penetrance of 0.56.

Since familial CJD is dominantly inherited, analysis for the PrP gene is not indicated unless there is a history of dementia in a firstdegree relative.

Sporadic CJD

In ≈ 90% of cases of CJD, no infectious or familial source can be identified, and these cases are considered sporadic. 80% occur in persons 50–70 yrs old.13 Sporadic cases show no abnormality in the PrP gene. There appears to be a genetic susceptibility in the sporadic and iatrogenically transmitted CJD cases, with the majority of these showing specific changes in the human prion protein.

Iatrogenic transmission of CJD

Several pathological studies using autopsied patients with iatrogenic Creutzfeldt-Jakob disease (CJD) showed that cerebral β-amyloidosis in addition to the CJD pathology could be transmitted among humans via medical procedures, such as human growth hormone derived from cadaver injection and cadaveric dura mater graft. In addition, although cerebral amyloid angiopathy (CAA), which is Aβ deposition in the cerebral vessels, related cerebral hemorrhage rarely develops in young people, several patients with CAA-related cerebral hemorrhage under the age of 55 with histories of neurosurgeries with and without dura mater graft in early childhood have been reported. These patients might show that Aβ pathology is often recognized as Aβ-CAA rather than parenchymal Aβ deposition in the transmission of cerebral β-amyloidosis in humans, and Hamaguchi et al. proposed an emerging concept, “acquired CAA”. Considering that there have been several patients with acquired CAA with an incubation period from neurosurgery and the onset of CAA-related cerebral hemorrhage of longer than 40 years, the number of cases is likely to increase in the future, and detailed epidemiological investigation is required. It is necessary to continue to elucidate the pathomechanisms of acquired CAA and urgently establish a method for preventing the transmission of cerebral β-amyloidosis among individuals [1)].

Described only in cases of direct contact with infected organs, tissues, or surgical instruments. Has been reported with: corneal transplants, intracerebral EEG electrodes sterilized with 70% alcohol and formaldehyde vapor after use on a CJD patient, operations in neurosurgical ORs after procedures on CJD patients, in recipients of pituitary-derived human growth hormone (hGH) (most cases have occurred in France; there is no longer a risk of CJD with growth hormone in the U.S. since distribution of pituitary derived hGH was halted in 1985 and current hGH is obtained from recombinant DNA technology), and dural graft with cadaveric dura mater (Lyodura®) (most cases have occurred in Japan). Ethylene oxide, autoclaving, formalin, and ionizing radiation do not inactivate the CJD agent

Diagnosis

Creutzfeldt-Jakob Disease Diagnosis.

Differential diagnosis

Cerebrospinal fluid analysis to exclude infections such as tertiary syphilis or subacute sclerosing panencephalitis is recommended. Toxicity from bismuth, bromides, and lithium must be ruled-out. Myoclonus is usually more prominent early in toxic/metabolic disorders than in Creutzfeldt-Jakob disease, and seizures in CJD are usually late [2)]

Case series

Consecutive series of 230 patients with neuropathologically verified Creutzfeldt-Jakob disease (CJD), the disease was found to affect men and women with approximately equal frequency in a peak plateau between the ages of 55 and 75 years (mean, 61.5 years). Familial cases accounted for 4 to 8% of the total series. Nonspecific prodromal symptoms occurred in one third of the patients, and the neurological presentation, although usually a gradually evolving mental deterioration, was of rapid onset in 20% of patients and in 36% of patients consisted exclusively of neurological symptoms. The great majority of these symptoms were of cerebellar or visual origin. Extrapyramidal muscular rigidity, myoclonus, and characteristic periodic electroencephalographic (EEG) complexes were observed comparatively late in the illness, and some type of involuntary movement or periodic EEG activity was seen in over 95% of the patients. The median duration of illness was 4 months (mean, 7.6 months); 90% of patients died within a year of onset [3)].

1994

Four patients who received dural grafts of cadaveric origin in the course of posterior fossa procedures subsequently developed Creutzfeldt-Jakob disease (CJD). The interval from dural placement to clinical onset of CJD ranged from 16 months to nine years. Initial clinical presentation consisted of cerebellar symptoms, with dementia and myoclonus developing in later stages of the disease. EEGs showed diffuse slowing that evolved to a periodic activity pattern. CT and MRI were unremarkable in the early stages but pronounced cerebral and cerebellar atrophy with widened sulci and collections of fluid over the convexities were seen in the late stages of disease. The diagnosis was histologically proved by

brain biopsy in all four cases. Molecular genetic analysis showed that the four patients were homozygous for methionine at codon 129 of the PrP gene. From this experience, and from six previous descriptions of this occurrence in the literature, it is manifest that awareness of the means of iatrogenic transmission of CJD, and the adoption of preventive measures, constitute the only effective way to stop the spread of CJD among patients who have neurosurgery [4)]

Case reports

2017

Fujioka H, Soejima Y, Izumihara A, Yamashita K. [A Case of Creutzfeldt-Jakob Disease before Trepanation Presenting as a Chronic Subdural Hematoma]. No Shinkei Geka. 2017 Nov;45(11):1011-1014. doi: 10.11477/mf.1436203637. Japanese. PubMed PMID: 29172208 [5)].

1993

A 10-year-old boy underwent a posterior fossa craniectomy for removal of a grade 2 cerebellar astrocytoma. Dural closure was achieved by the placement of a dural graft. Eight years later the patient developed dementia and myoclonus. Electroencephalography demonstrated generalized slow activity that evolved into a pattern of periodic triphasic waves. Computed tomography scan and magnetic resonance imaging were unremarkable. Brain biopsy confirmed spongiform encephalopathy of the Creutzfeldt-Jakob type. In the light of previous reports of four similar occurrences, and of our own experience with two further cases of this disease, we believe that the cadaveric dura was the source of transmission of Creutzfeld-Jakob disease in our patient. The authors remark the importance of the awareness of this late complication of dural substitutes, both for the diagnosis of possible future cases and for taking preventive measures to stop the spread of the disease [6)]

1)
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6)
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