

SHORT REPORT

Creutzfeldt-Jakob disease in a recipient of human pituitary-derived gonadotrophin: a second case

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Abstract

A 44 year old female presented with a progressive cerebellar disturbance approximately 13 years after receiving human pituitary derived gonadotrophin injections as a treatment for infertility. The patient died approximately nine months later. Creutzfeldt-Jakob disease was confirmed at necropsy. This is the second reported case of Creutzfeldt-Jakob disease in a recipient of human derived gonadotrophin.

(*J Neurol Neurosurg Psychiatry* 1992;55:1094-1095)

Case report

A 44 year old Australian female presented with a 10 week history of gradually progressive unsteadiness of gait preceded by several months of profound fatigue and lethargy. The few weeks before her admission to hospital she had also noticed a degree of mental apathy as well as visual disturbances including intermittent diplopia and transient episodes of oscillopsia. Her writing had become increasingly illegible and she noticed mild clumsiness of her hands with other simple daily tasks. Her past history included anorexia nervosa, secondary amenorrhoea, and infertility for which she received human pituitary derived FSH injections between September 1976 and May 1978. She subsequently had two normal pregnancies.

On examination the patient was alert and there was no disturbance of intellectual function. Ocular movements were full, but there was intermittent jerky horizontal nystagmus on lateral gaze in both directions. In the limbs there were occasional myoclonic jerks and twitches, especially in the legs but also intermittently in the fingers. There was no weakness, the reflexes were intact and symmetrical and the plantar responses were flexor. There was mild finger-nose and heel-shin ataxia, and her gait was slightly ataxic and at times lurching in character. The general physical examination was normal.

Initial investigations including routine haematological and biochemical screens were normal. CSF examination was also normal. MRI brain scan and chest radiograph were normal and EEG demonstrated only a mild generalised non-specific episodic disturbance.

Over the next few months the patient became increasingly debilitated with profound

lethargy and generalised weakness, eventually becoming bedridden. Despite her dramatic physical deterioration there was only mild intellectual impairment, notably short-term memory loss. In the final stages of her illness increasing drowsiness prevented a more detailed assessment of mental function. She died finally, approximately nine months after the onset of her original symptoms.

Neuropathology

The brain weighed 1154 grams. It showed no remarkable features to naked eye examination apart from mild generalised cerebral atrophy. Multiple sections of cerebral cortex, white matter, basal ganglia, thalamus, brain stem and cerebellum were examined. These revealed characteristic changes of Creutzfeldt-Jakob disease: spongiform change, astrocytosis and neuron loss. The severity of the changes was variable depending on the site examined. Severe changes were especially noted in the cerebellar vermis where both Purkinje cells and granule cells were depleted and Bergmann gliosis and prominent spongiform change were evident in the molecular layer (fig 1).

Elsewhere in the cerebellar cortex the granule cells were more depleted than the Purkinje cells and there was widespread spongiform change. The dentate nuclei were relatively preserved as were most brainstem nuclei. In the deep grey matter of the cerebrum, the putamen and head of the caudate nucleus were severely affected and the thalamus and hypothalamus mildly to moderately affected. Spongiform change of mild to moderate severity was distributed particularly throughout the frontal, temporal and parieto-occipital cortex (fig 2). Prion protein antibody reactions were not carried out.

Discussion

Although Creutzfeldt-Jakob (CJD) disease has been well documented in recipients of human growth hormone, to our knowledge, this case is only the second reported case of Creutzfeldt-Jakob disease occurring in a recipient of human pituitary-derived gonadotrophin, specifically follicle stimulating hormone.

The first case¹ has many similarities with our reported case. Both patients experienced what has now become recognised as a reasonably predictable course of the illness in pituitary hormone treated patients with a predominant cerebellar disturbance, little intellectual

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Received 6 November 1991
and in revised form
21 February 1992.
Accepted 2 March 1992

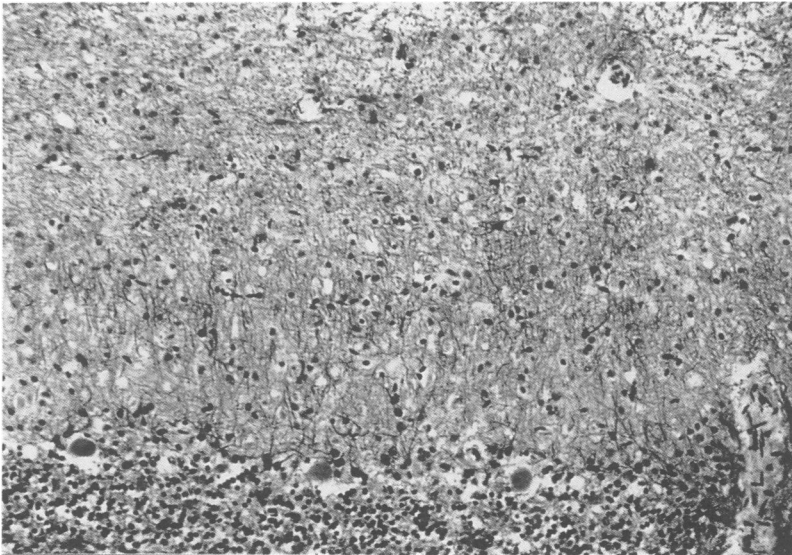


Figure 1 Bergmann gliosis and prominent spongiform change in the molecular layer of the cerebellum ($\times 100$). PTAH stain.

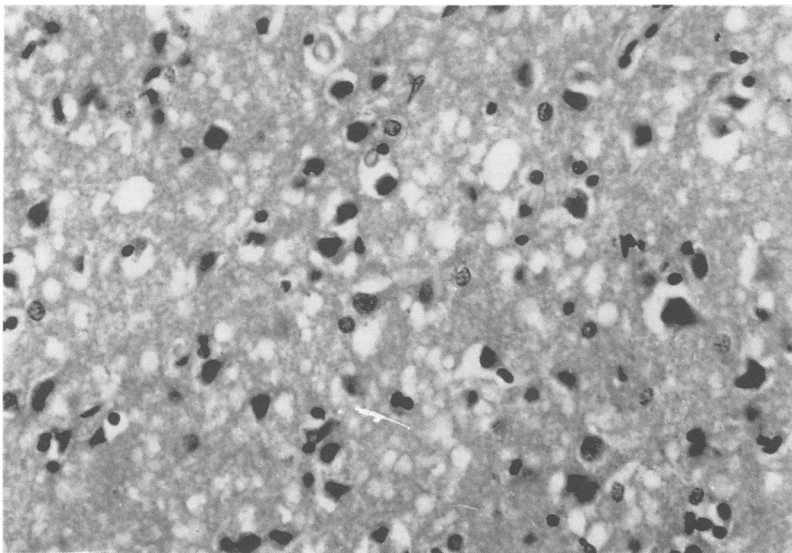


Figure 2 Spongiform change in the temporal cortex ($\times 200$). Haematoxylin and eosin stain.

impairment until the late stages of the disease and no periodic EEG activity. These features are rather unusual for sporadic CJD in which cerebellar function is not profoundly disturbed, particularly at presentation, and in which mental deterioration is usually much more severe.² Even the ataxic form of sporadic CJD, the so-called Brownell-Oppenheimer variant, is usually characterised by progressive dementia.³

The estimated incubation period of 12 to 14 years in this patient is also typical of the iatrogenic pituitary hormone-related cases of CJD in which minimum incubation periods of

between 4 and 19 years, with a median value of 14 years, have been reported.⁴ As opposed to direct intracerebral inoculation of the infective agent, which results in an infection rate of greater than 90% in most primate species, the subcutaneous or intramuscular administration of the CJD agent results in less predictable disease transmission, and when it does occur is associated with long incubation times.⁵ This unpredictability of transmission, in addition to the presumably low concentration of the infective agent contaminating the hormone injection, may explain the apparently low rate of infection in both the growth hormone and gonadotrophin recipient population. Recently, it has been proposed that genetic susceptibility to previous infection might also be a factor in determining iatrogenic CJD.⁶

In the American cases of growth hormone-related CJD, the possibility of a common source of infection through a single contaminated batch of hormone has been raised.⁷ In this respect it may be more than coincidental that both these FSH-treated patients received their treatments in Australia where several hundred infertile women had a course of human pituitary-derived gonadotrophin injections from the 1960s to the early 1980s. During the course of this patient's fertility treatment she received injections from five different batches of pituitary derived gonadotrophin supplied through Commonwealth Serum Laboratories. It has not yet been established, however, that these two patients received any injections from a common batch.

Regardless of whether such a link can be established between these two patients, this case serves to highlight the clinical characteristics of iatrogenic CJD, and to once again emphasise the ongoing need for vigilance of those patients who received not only cadaveric growth hormone but also gonadotrophin therapy before 1985.

- 1 Cochius JJ, Burns RJ, Blumbergs PC, Mack K, Alderman CP. Creutzfeldt-Jakob disease in a recipient of human pituitary-derived gonadotrophin. *Aust NZ J Med* 1990;20:592-3.
- 2 Brown P, Cathala F, Castaigne P, Gajdusek, DC. Creutzfeldt-Jakob disease: Clinical analysis of a consecutive series of 230 neuropathologically verified cases. *Ann Neurol* 1986;20:597-602.
- 3 Brownell B, Oppenheimer DR. An ataxic form of subacute presenile poliomyelopathy. (Creutzfeldt-Jakob disease). *J Neurol Neurosurg Psychiatry* 1965;28:350-61.
- 4 Brown P. Human growth hormone therapy and Creutzfeldt-Jakob disease: a drama in three acts. *Pediatrics* 1988;81:85-92.
- 5 Brown P. The clinical neurology and epidemiology of Creutzfeldt-Jakob disease, with special reference to iatrogenic cases. *Novel injections agents and the central nervous system*. Ciba Found Symp 135. Chichester UK: John Wiley & Sons, 1988:3-23.
- 6 Collinge J, Palmer MS, Dryden AJ. Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. *Lancet* 1991;337:1441-2.
- 7 Brown P. The decline and fall of Creutzfeldt-Jakob disease associated with human growth hormone therapy. *Neurology* 1988;38:1135-7.