Iatrogenic Creutzfeldt–Jakob disease presenting 24 years after human growth hormone administration

Introduction

Creutzfeldt–Jakob disease (CJD) is one of the transmissible spongiform encephalo-pathies also known as prion disease. Iatrogenic CJD (iCJD) is one of four forms of CJD, the others being sporadic, variant and genetic CJD. The first human growth hormone-related death from iCJD was in 1985.

Discussion

The first reported case of iCJD was in 1974 following a corneal transplant (Duffy et al, 1974). In this patient, CJD developed 18 months after transplantation of a graft that had been obtained from the cadaver of a patient with confirmed CJD.

ICJD is a rare condition. Between 1970 and 2004 there had only been 51 cases identified in the UK (National Creutzfeldt–Jakob Disease Surveillance Unit and London School of Hygiene and Tropical Medicine, 2003). Forty-three of these cases had been caused by human growth hormone (HGH) injection (National Creutzfeldt–Jakob Disease Surveillance Unit and London School of Hygiene and Tropical Medicine, 2003). Other iatrogenic routes of transmission have included corneal implants, dura mater implants, human gonadotrophin injection and from neurosurgical instruments (Will, 2003).

Growth hormone injections have been used for a number of years to treat children with short stature. Before 1985 growth hormone was extracted from the pituitary glands of cadavers. Large volumes of hormones were pooled from multiple cadavers and then divided into individual doses of HGH. Unfortunately some of the glands were later identified to be from at-risk cadavers and a few of the recipients later developed iCJD. Since 1985 recombinant growth hormone has been available.

One case has been identified of a patient who acquired iCJD after a diagnostic procedure using HGH (Croes et al, 2002). Human pituitary gonadotrophin was also used over approximately the same time period to treat women with infertility. Several women receiving this treatment have subsequently been confirmed as having iCJD (Cochius et al, 1990).

iCJD can be divided into peripheral and central transmitted routes of infection. In peripheral infection the route of the infected material is through the circulation and not directly into the brain. In the central route the infected material is exposed close to the CNS. The clinical pattern varies considerably depending upon whether the disease was centrally or peripherally transmitted.

The clinical symptoms following peripheral transmission occur following a longer incubation period between 2 and 25 years, with an average of 12 years. The patient in this case study had an incubation period of 24 years. This is based on latency from the mid-point of treatment, as the precise timing of infection is not known. Patients with iCJD have a tendency to present with a progressive cerebellar syndrome. They may also exhibit psychiatric symptoms.

In contrast those patients who acquire the disease centrally present after a shorter incubation time (between 1.5 and 10 years for dura mater implants). The illness progresses more rapidly and has less cerebellar signs and more cognitive involvement, with patients presenting with a rapidly progressive dementia and memory deficit. The mean age of death following the human growth hormone use was 30 years, with a range from 20–45 years (National Creutzfeldt–Jakob Disease Surveillance Unit and London School of Hygiene and Tropical Medicine, 2003).

There appears to be a genetic susceptibility to acquiring iCJD. The general population has a common protein polymorphism at codon 129 of the human prion protein (PrP) gene. At this position either a methionine or a valine is encoded. The majority of patients with iCJD were homozygous at this codon. Heterozygosity appears to be protective.

Magnetic resonance imaging (MRI) can be useful in CJD. In iCJD MRI can be normal or show moderate cerebral or cerebellar atrophy. In some cases MRI may show gray matter involvement similar to in classic CJD. In sporadic CJD (sCJD) MRI findings usually include symmetrical, hyperintensity of the caudate head and putamen, which has been described in 67–79% of cases. Other gray matter structures may be affected in sCJD, including the hippocampus, peri-aqueductal gray matter and thalamus (Sellars et al, 2002). In variant CJD the most important feature is bilateral thalamic high signal, in particular in the pulvinar. This is a highly specific feature.

The diagnosis of CJD is a difficult one to make. The diagnosis tends to be a clinical one supported by laboratory tests during life, however, the definitive diagnosis is made at post mortem. The diagnosis of iCJD is defined by the National CJD Surveillance Group as a progressive cerebellar syndrome in a pituitary hormone recipient or sCJD with a recognized exposure to risk, e.g. dura mater transplant (National Creutzfeldt–Jakob Disease Surveillance Unit, 2005). This reflects the different clinical presentation of the peripheral and the centrally acquired infection.

Ataxia is an important sign in patients seen in an endocrine clinic who may have previously had exposure to human pituitary hormones. It should be remembered that because of the long incubation period of this condition it is likely that there will be more cases identified over the next few years. **BJHM**

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Case Report

A 39-year-old, right-handed female presented to the neurology outpatient clinic with a 6-month history of progressive unsteadiness. Before this she had been walking normally, but over the previous 6 months she had had recurrent falls and was now only able to walk with the aid of support. Her husband had also noticed that for the past few months she had jerky upper limb movements in her sleep and on waking from sleep, suggestive of myoclonic jerks. She was also having episodes of forgetfulness, e.g. forgetting to turn off light. She did not have any personality change or hallucinations, nor did she have any visual disturbance or difficulty with speech or swallow.

Her past medical history consisted of craniopharyngioma from the age of 6 years, which had been treated conservatively. From 12 –18 years of age she had been receiving human growth hormone injections for short stature.

Mini mental state examination was 28/30. The cranial nerves were all normal as was the motor system. She exhibited impaired coordination in all four limbs and walked with an ataxic gait. There was no obvious myoclonus on examination. Investigations revealed normal full blood count, renal and liver function tests. A magnetic resonance imaging (MRI) scan of her brain including fluid-attenuated inversion recovery (FLAIR) images showed increased signal in the caudate nuclei, and on diffusion images the caudate nuclei were hyperintense. There was increased signal adjacent to the aqueduct on T1 weighted imaging. Formal neuropsychological testing showed a mild to moderately severe impairment of short-term memory. These findings of a cerebellar syndrome in a patient with a past history of human growth hormone injection and supporting MRI findings were consistent with a diagnosis of iatrogenic Creutzfeldt–Jakob disease.

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Animal welfare, human health

'When I think that those guinea pigs won't suffer any more, I just feel so happy!' Thus spoke a deluded member of the human race this August celebrating the 'victory' of forcing the closure of a guinea pig farm by intimidation. The guinea pigs were intended for research. The intimidation included the digging up of the remains of a dead member of the family who owned the farm – and these people think that animal experimentation is disgusting.

Logical debate is impossible with animal activists. It may well be that there are still too many animal experiments, and that some are unnecessary (whatever that means). This is a view that can be supported by evidence and argued about. In fact, most anti-vivisectionists take this view. But most anti-vivisectionists don't put paint stripper on scientists' cars or dig up dead people. The activists are as dangerous as any other terrorists, and should be dealt with as such. They and unfortunately their more benign fellow travellers promulgate views that are just wrong, and the media seem only too happy to publish them. This is highly irresponsible. The BBC allowed someone to say that animals were so different from humans that nothing useful had ever been learned from animals. This statement is akin to claiming the Earth is flat or to Holocaust denial. The BBC would never allow anyone to say such things without proper discussion, if not dismissal or ridicule, and nor should they be allowed to ignore penicillin, blood transfusion, tuberculosis, asthma, meningitis vaccines, transplantation, and insulin – all introduced, cured, or developed using essential animal experiments (Parry, 2005). Before insulin was available, children who developed diabetes quickly died. The activists are saying that the lives of diabetics are worth less than a guinea pig, and they wouldn't care if they died.

Another ploy is using single examples as general proof. The *Guardian* published a letter about penicillin killing guinea pigs, which is true but irrelevant. To be fair, the *Guardian* published a rebuttal letter (guinea pigs die of fatal enterocolitis). Fortunately, mice, the species first tested, do not. Even if guinea pigs had been the first species tested and had died (the letter writer implying that penicillin would have been abandoned), it would not have been long before someone tested mice.

Then there are the drugs, tested on animals, which have harmed humans: thalidomide was the classic; now, the activists say look at Seroxat and Vioxx. But so what? Sometimes we get it wrong. But more often we get it right.

Then there is the computer simulation, cell culture argument. But it would be a brave, or foolish, person who would accept a drug tested only in this way; the mammalian body is more complex than the simple sum of its parts. The recent technique of micro-dosing is promising, but even if its promise holds there will still be need for animal work.

The irony is that most of the animals used in research are incredibly well looked after: they have to be, otherwise the experiments would be of little value. Why don't the activists pay more attention to the foul practices of intensive farming? Or are cows, pigs and chickens less appealing than guinea pigs? Humans would lose nothing for the loss of factory farming, unlike the loss from animal research. Which, although not often mentioned, is used to improve animal health as well. **BJHM**

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