Human Growth Hormone–Related Iatrogenic Creutzfeldt-Jakob Disease With Abnormal Imaging

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Background: Although more than 160 cases of iatrogenic Creutzfeldt-Jakob disease (iCJD) from human growth hormone (hGH) treatment have been documented, to our knowledge abnormal cerebellar findings on magnetic resonance imaging (MRI) have not been reported.

Objective: To report a case of hGH-related iCJD with abnormal cerebellar MRI findings on fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted MRI (DWI).

Design: Case report.

Setting: Outpatient neurology clinic at a university medical center.

Patient: A 33-year-old man who had subacute gait ataxia and blurred vision.

Results: Beginning 19 years prior, this patient had received cadaveric pituitary-derived hGH treatment for at least 5 years. Magnetic resonance imaging revealed FLAIR and DWI abnormalities, particularly in the cerebellum. He died 7 months after disease onset of autopsy-confirmed iCJD. Pathological changes corresponded largely to MRI findings.

Conclusions: To our knowledge, this is the first case of hGH-related iCJD with FLAIR and DWI abnormalities within the cerebellum. As symptoms referable to the cerebellum occur early in iCJD, it suggests that these MRI sequences may allow earlier diagnosis of this form of prion disease.

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FROM THE LATE 1950S UNTIL 1985, approximately 30 000 individuals, mostly children, were treated with human growth hormone (hGH) derived from cadaveric human pituitary tissue. The occurrence of autopsy-confirmed Creutzfeldt-Jakob disease (CJD) in 3 young adults in 1985,1-3 all of whom had been treated with hGH, suggested iatrogenic transmission of CJD. Since then, more than 160 cases of iatrogenic CJD (iCJD) from hGH treatment have been reported worldwide.4 We report the case of a former hGH recipient who was initially seen with a rapidly progressive pancerebellar syndrome due to hGH-related iCJD in whom brain magnetic resonance imaging (MRI) showed cerebellar diffusion abnormalities.

REPORT OF A CASE

A 33-year-old man was initially seen in 2003 with a 6-week history of a progressively unsteady gait. Balance was particularly poor when climbing stairs. Four weeks prior to presentation he noticed mild blurred vision while watching television or reading. He had a history of a childhood “pituitary problem” for which he had received cadaveric human pituitary-derived hGH treatment for at least 3 years starting in 1974. On neurologic examination, he had mild bilateral horizontal end-gaze nystagmus, symmetric past-pointing on confrontational testing, and dysmetria on finger-nose-finger and heel-knee-shin examinations. Gait was mildly wide-based, and he was unable to tandem walk. Findings from the remainder of his neurologic examination were normal. Computed tomography of the head without enhanced contrast medium and results of routine laboratory tests were normal. Lumbar puncture yielded clear, colorless cerebrospinal fluid with normal opening pressure; the following levels were noted in the cerebrospinal fluid: protein, 48 mg/dL; glucose, 64 mg/dL (3.6 mmol/L); red blood cell count, 23 × 10⁶/L; white blood cell count, 2 × 10⁶/L. The IgG index and cytologic findings were normal.

At the 3-week follow-up visit, his balance had worsened; he required handrail support while walking. Truncal and limb ataxia were more pronounced, affecting the left side slightly more than the right side. Speech was mildly slurred and he reported having double vision. He continued to report no cognitive symptoms. No myoclonus was observed. The Centers for Disease Control and Prevention, Atlanta, Ga, which has been tracking all US patients at risk for hGH-related CJD, confirmed he was a recipient of potentially contaminated hGH.

Brain MRI (Figure) revealed increased signal involving the superior cerebellar ver...
mis on both fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted MRI (DWI). The cortex of the paramedian frontal lobes demonstrated a more subtle increase in signal bilaterally on DWI with suggestion of an increase in FLAIR signal within the bilateral cingulate gyri and insula. Mildly increased DWI signal was also observed in the right greater than left caudate heads, without definite corresponding FLAIR abnormality. The areas of increased DWI signal within the cerebellum and cortex showed reduced signal on the apparent diffusion coefficient map, confirming that the abnormal DWI signal represents reduced free water motion, not T2 “shine through.”

Electroencephalogram was normal; results of a paraneoplastic antibody panel were normal.

Figure. Magnetic resonance image of a patient with human growth hormone--related (hGH) Creutzfeldt-Jakob disease (CJD) showing an abnormal cerebellum. A, Axial fluid-attenuated inversion recovery (FLAIR) demonstrates increased signal within the superior cerebellar vermis, best visualized by increasing image contrast. B, Corresponding axial diffusion-weighted magnetic resonance imaging (DWI) more clearly shows increased cerebellar signal. C, Decreased signal within the cerebellum on the apparent diffusion coefficient map confirms that the DWI signal abnormality is the result of reduced free water motion, not T2 “shine through.” D, Coronal FLAIR image shows possible mild hyperintensity in the cingulate and insula and no clear abnormality in the basal ganglia. E, Corresponding coronal DWI reveals increased signal within the paramedian frontal cortex bilaterally, extending superiorly over the convexities (arrows) and mildly increased signal within bilateral caudate heads (solid arrowheads). Note the susceptibility artifact from skull base secondary to air-bone interface (open arrowheads). Corresponding coronal FLAIR (F) and DWI sequences (G) show increased signal within the superior cerebellar vermis (arrows).

About 3 months after onset, he was severely dysarthric, using a wheelchair and having memory lapses and occasional urinary incontinence. His ataxia worsened; myoclonus, seizures, and dementia developed later. He died 7 months after disease onset. Autopsy confirmed iCJD, with the most extensive deposition of prions in the brainstem, cerebellum, and thalamus, with significant involvement, although to a lesser extent, in the insula, basal ganglia, anterior cingulate, and caudate. There was heavy vacuolation in the cerebellar molecular layer and cingulate, followed by the basal ganglia, thalamus, brainstem, and insula. The frontal and parietal cortices had mild pathologic features, but the temporal and occipital cortices were largely spared.

There are more than 310 known cases of iCJD worldwide. Sources have included contaminated neurosurgical equipment, depth electrodes for stereotactic electroencephalography, cadaveric dura mater and corneal grafts, human pituitary-derived gonadotrophin, and hGH. Human gonadotrophin– and hGH-related iCJD differ from most other forms of iCJD because they are due to peripheral inoculation, rather than direct inoculation of prions into the central nervous system. Human gonadotrophin– and hGH-related iCJD also share the unique propensity to manifest signs and symptoms early in the disease course as a largely isolated cerebellar syndrome. Visual symptoms are also variably present; however, dementia and myoclonus, if present, are usually mild and occur late in the disease course.

Starting in 1963, the National Hormone and Pituitary Program, the main source of hGH in the United States, sponsored the centralized collection of extracted human pituitary tissue for the production of hGH. This program was discontinued in 1985 after cases of CJD were reported. All US cases of hGH-related CJD occurred in individuals who began hGH treatment prior to 1977, before a new purification step was added to the protocol. Most hGH-related CJD cases have occurred in France and these cases were traced to a particularly high-risk treatment period from 1983 to mid-1985. The reason for the high incidence of iCJD in patients treated during this...
critical period is unclear, but may stem from cross-contamination by one or several highly infectious batches of pituitary tissue during the manufacturing process. An important factor influencing the incubation period and clinical manifestation in all forms of CJD is the polymorphism at codon 129 of the prion protein (PrP) gene. In healthy white populations, genotype frequency at codon 129 is 50% heterozygous, 40% homozygous for methionine, and 10% homozygous for valine; homozygosity increases the risk for CJD. In hGH-related CJD, the frequency of homozygous valine is especially high, with a codon 129 distribution of 23% heterozygous valine, 48% homozygous for methionine, and 29% homozygous for valine. Our patient was homozygous for valine at codon 129.

To our knowledge, this pattern of abnormal FLAIR and DWI signal with significant cerebellar involvement has not yet been reported in iCJD. In case reports of FLAIR and DWI abnormalities in hGH-related iCJD, cerebellar signal changes are not mentioned despite abnormal findings in the basal ganglia, thalami, or cortex. Abnormal cerebellar signal by FLAIR and DWI was reported in a patient with the Brownell-Oppenheimer variant of sporadic CJD; patients with this form of sporadic CJD exhibit predominantly cerebellar features both clinically and pathologically.

Specific FLAIR and DWI abnormalities, particularly cortical and basal ganglia hyperintensities, have been well demonstrated in sporadic and familial forms of CJD. Although cerebellar symptoms are common in these patients, cerebellar abnormalities on MRI, including FLAIR and DWI, rarely occur. This may be owing to the involvement by prions of cerebellar connections, rather than the cerebellum itself. Billette de Villemeur et al reported that of 33 MRIs in 34 hGH-related iCJD cases in France, all were normal or unchanged from prior studies when performed at the time of symptom onset. Fifteen patients’ MRIs remained normal, while the others developed cerebellar or diffuse cerebral atrophy following a period of 3 to 8 months. Although Billette de Villemeur et al did not specify MRI sequences, given the period it is unlikely that FLAIR and DWI were used in most, if not all, cases. This may explain the lack of MRI findings other than atrophy.

In our patient, the neuropathology correlated very well with the MRI, particularly in the cerebellum, cingulate, and insula. The significant neuropathological changes in the basal ganglia, brainstem, and thalami, with minimal, if any, corresponding involvement on MRI in these areas, may be because of these analyses being performed 5 months apart. Why hGH-related iCJD spreads in this manner, with a predilection for the cerebellum and sparing certain cortical regions, is an interesting research question that requires further study. Nevertheless, this case report suggests that in cases of suspected iCJD, invariably seen with early cerebellar signs, the finding of associated cerebellar FLAIR and DWI abnormalities may aid in earlier diagnosis, prompt initiation of supportive care, and possibly even treatment.

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