

IATROGENIC CREUTZFELDT-JAKOB DISEASE FOLLOWING HUMAN GROWTH HORMONE THERAPY

Case report

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ABSTRACT - We report the case of a 41-year-old man with iatrogenic Creutzfeldt-Jakob disease (CJD) acquired after the use of growth hormone (GH) obtained from a number of pituitary glands sourced from autopsy material. The incubation period of the disease (from the midpoint of treatment to the onset of clinical symptoms) was rather long (28 years). Besides the remarkable cerebellar and mental signs, the patient exhibited sleep disturbance (excessive somnolence) from the onset of the symptoms, with striking alteration of the sleep architecture documented by polysomnography. 14-3-3 protein was detected in the CSF, and MRI revealed increased signal intensity bilaterally in the striatum, being most evident in diffusion-weighted (DW-MRI) sequences. This is the second case of iatrogenic CJD associated with the use of GH reported in Brazil.

KEY WORDS: Creutzfeldt- Jakob disease, iatrogenic form, growth hormone, diffusion MRI, CSF 14-3-3 protein.

Doença de Creutzfeldt-Jakob iatrogênica após uso de hormônio de crescimento humano: relato de caso

RESUMO - Relatamos o caso de um homem de 41 anos com doença de Creutzfeldt- Jakob (DCJ) iatrogênica, adquirida após uso de hormônio de crescimento (GH) obtido a partir de extrato de hipófises de cadáveres humanos. O período de incubação da doença (calculado a partir do meio do tratamento com GH até o aparecimento dos sintomas) foi longo (28 anos). Além dos sinais cerebelares marcantes e dos sintomas cognitivos, desde o início da doença o paciente apresentava distúrbio do sono (sonolência excessiva), com alteração da arquitetura do sono documentada por polissonografia. Detectou-se a presença da proteína 14-3-3 no líquido cefalorraquidiano do paciente, e o exame de ressonância magnética do encéfalo mostrou hipersinal no striatum bilateralmente, mais evidente na sequência pesada em difusão. Este é o segundo caso registrado no Brasil de DCJ iatrogênica associada ao uso de GH.

PALAVRAS-CHAVE: doença de Creutzfeldt-Jakob, forma iatrogênica, hormônio de crescimento, ressonância magnética com difusão, proteína 14-3-3 no LCR.

Creutzfeldt-Jakob disease (CJD) may have three distinct etiologies. The most common form is sporadic in nature, whereas the hereditary form accounts for approximately 15% of cases¹. Acquired cases are rare and are represented by new variant CJD^{2,3}, which is associated with bovine spongiform encephalopathy, and by iatrogenic CJD⁴, where the transmission between humans is due to accidental iatrogenic contamination.

Iatrogenic CJD occurs following the use of inadequately sterilized neurosurgical instruments, dura mater and corneal grafting, or treatment with growth

hormone (GH) prepared from extracts of human cadaveric pituitaries. The first reported case of iatrogenic CJD occurred in 1974, in a patient who had received a corneal graft from a donor who was later known to have died with CJD⁵. The first cases of iatrogenic CJD following the use of human GH were reported in 1985^{6,7}. At that time there were great fears of a potential epidemic of iatrogenic CJD caused by use of human GH. These pessimistic expectations were later confirmed, with the new case reports that followed.

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A recent review on iatrogenic CJD⁸ has estimated a current number of 267 cases, of which 139 were caused by contaminated GH. More than half the cases attributed to use of GH occurred in France. One of the cases described emerged in Brazil, in 1991^{9,10}.

We report the case of a 41-year-old man with iatrogenic CJD, acquired following the use of GH obtained from a number of pituitary glands sourced from autopsy material. We also describe our findings following investigations which have been recently proposed for the diagnosis of sporadic CJD.

CASE

A 41-year-old man came into our care with a 5-month history of intellectual deterioration, abnormal somnolence, gait disturbance and loss of coordination.

The patient had a past of postpartum respiratory distress, having required ventilatory assistance for about a week. He was discharged from the hospital and had no further medical problems until the age of five, when his parents noticed stunted growth, and sought medical advice. At that time pituitary dysgenesis was diagnosed, and the patient was subsequently placed on a regimen of thyroid and growth hormone (GH) replacement. GH was being imported from the USA, where it was obtained from a number of pituitary glands sourced from autopsy material. Treatment with GH continued from the age of five to 21.

Despite abnormal growth, the patient had normal intellectual development. He completed his basic education and college, and was admitted to an engineering school in Michigan, USA. After graduation, he came back to Brazil and started to run a computer devices firm which he owned.

Five months prior to admission the patient began to exhibit signs of rapidly progressive cognitive decline. A memory deficit became evident, as the patient had great trouble in recalling recent facts and information (such as

what he had had for lunch on that very same day, or who had come to visit him or who he had talked to over the telephone). The family also noticed behavioral changes, on being a childlike demeanor. He showed excessive distractibility, paying no attention to any of his usual activities. In a short space of time he was no longer able to work at his firm. In parallel with these mental changes, the patient showed strikingly excessive somnolence; a remarkable fact was that he could fall asleep even while talking on the phone or while eating his meals. At the same time he also presented gait instability leading to frequent falls, loss of coordination, and slurred speech.

The remainder of the patient's medical history was deemed irrelevant to the current disease. There was no family history of neurologic or psychiatric diseases.

On admission to hospital, physical examination showed the patient to be alert, but showed bouts of extreme somnolence. The patient's language was intact, but he was disarthric, with slurred speech. His facial expressions were reduced. There was no apparent loss of visual field; both horizontal and vertical gazes being full, with no nystagmus. His gait was markedly ataxic and all muscles tested had normal strength. Cerebellar testing showed uncoordination, dysmetria and slow distal alternating movements in both arms and legs, the right being worse than the left. An action tremor was noted in both arms. No myoclonus was observed. The deep tendon reflexes were slightly decreased in the limbs, and the plantar responses were flexor. The glabellar reflex was exaggerated, and a snout reflex was elicited. Testing of all modalities of sensibility was unremarkable.

He scored 20/30 in the Mini-Mental State Examination due to impaired orientation, recall and drawing. In a comprehensive neuropsychological examination he scored 111/144 in the Dementia Rating Scale, with greatest impairment in memory (13/25) and initiation/perseveration (25/37) subscales. There was severe impairment in verbal

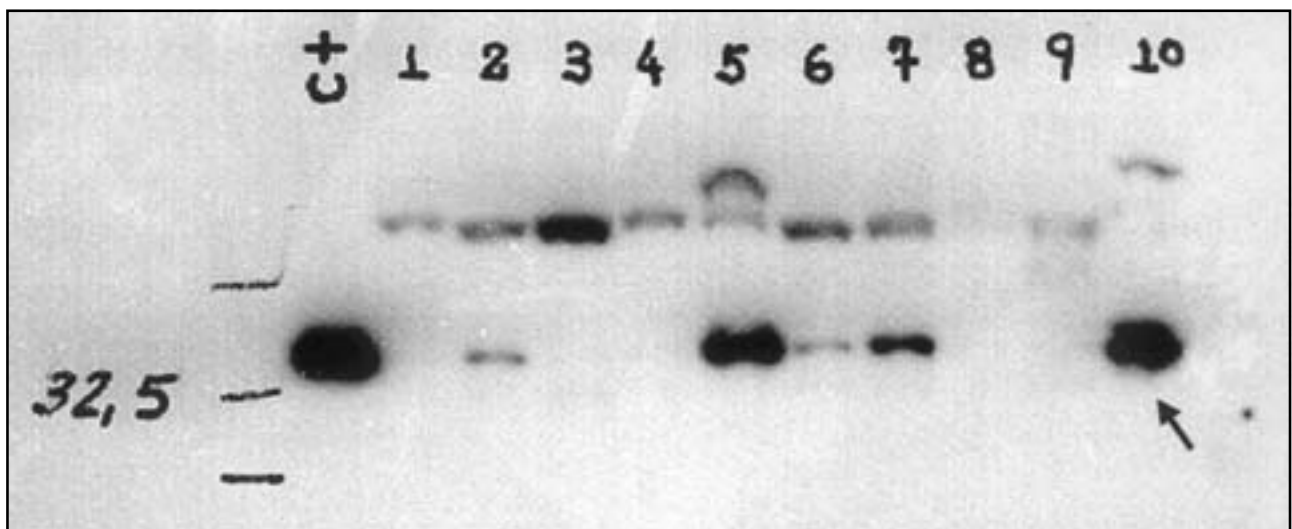


Fig 1. The arrow shows 14- 3- 3 protein band in Western blotting in the patient's CSF.

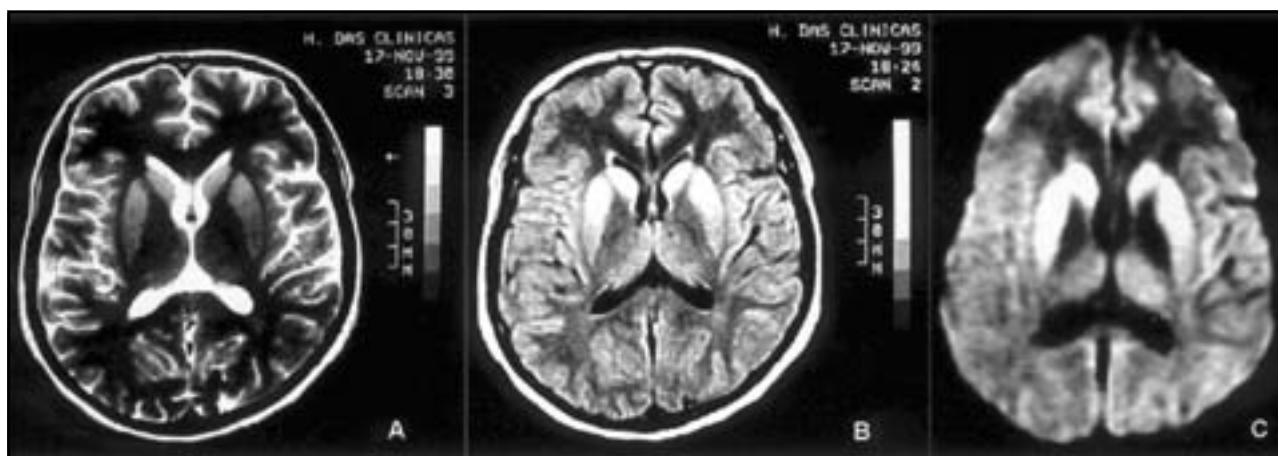


Fig 2. Magnetic resonance imaging with T2 (A), FLAIR (B) and DWI (C) weighted images, showing hyperintense sign in the striatum.

and visual learning and retention revealed by the logical memory and visual reproduction subtests of the Wechsler Memory Scale-R. He also did poorly in the trail-making tests (parts A and B). Whereas his performance was moderately impaired in the Hooper visual organization and in the block design subtest of the Wechsler Adult Intelligence Scale.

Routine blood tests showed no abnormalities.

Cerebrospinal fluid (CSF) analysis with protein electrophoresis and tests for syphilis were normal. The 14-3-3 protein immunoassay in CSF was performed as described by Zerr et al.¹¹. Fifteen μ l of CSF was applied to Western blot. Detection of the bound polyclonal antibody to the β -isoforms of the 14-3-3 protein (Santa Cruz Biotech, USA) was performed using the enhanced chemiluminescence detection kit (Amersham, USA). A positive control from the NIH3T3 cell line and a negative control were run on every gel. For this patient, 14-3-3 protein was positive in the CSF sample, with a strong positive pattern (Fig 1).

EEG examination exhibited a diffuse slowing in the brain's electrical activity, without periodic activity.

Magnetic resonance imaging (MRI) of the brain showed increased signal intensity bilaterally in the striatum in T2-weighted, FLAIR and diffusion-weighted (DWI) sequences (Fig 2). Single-photon emitting computerized tomography (SPECT) of the brain showed a discretely heterogeneous distribution of the ^{99m}Tc -HMPAO in a diffuse manner, with no evidence of focal hypoperfusion.

Given the complaints of excessive somnolence, the patient underwent polysomnography. The exam revealed below normal sleep latency and a lack of REM sleep. A moderate number of myoclonus was observed during sleep (43.6 events per hour). The patient had a score of 16 points in the Epworth Somnolence Scale, revealing excessive daytime sleepiness.

With the diagnosis of probable CJD, the patient was discharged from the hospital to receive supporting treatment. In the months which followed his mental status deteriorated even further, and the cerebellar signs became more intense. Eventually the patient became bedridden, and five months after diagnosis he had aspirative pneu-

monia. He died ten months after the onset of the symptoms. Autopsy was not performed.

DISCUSSION

The median incubation period of GH-related CJD, calculated from the midpoint of treatment to the onset of clinical symptoms, was 12 years (range: 5-30 years) in a recent review of 139 cases⁸. The incubation period in this reported patient spanned 28 years, which is rather long but still inside the described range.

His initial symptoms and signs were those of prominent cerebellar syndrome, which is consistent with the usual clinical presentation in cases of GH-related CJD^{12,13}. However, our patient also showed precocious signs of intellectual deterioration, which are characteristically observed in cases following direct cerebral inoculation^{12,13}. Besides the cerebellar signs and the cognitive decline, the patient also showed excessive somnolence. There are reports of sleep disorders related to CJD in both experimental animal models¹⁴ and human patients^{15,16}.

EEG did not show periodic activity five months after the onset of symptoms. The absence of periodic activity is not uncommon in iatrogenic CJD following the use of human GH. In one study conducted in France, EEG was reported to be "practically normal" in 11 of the 31 patients initially recorded, and characteristic triphasic slow waves were only found in two cases after 6 and 20 months¹⁷.

MRI finding in this case - increased signal intensity bilaterally in the striatum, most evident in the diffusion-weighted sequences - is similar to that reported in sporadic^{18,19} and in a few familial²⁰ cases of CJD. We did not find other report of abnormal diffusion-weighted MRI in iatrogenic CJD in the

literature. In four cases of iatrogenic CJD following dural mater grafts, conventional MRI did not show abnormal sign in the basal ganglia²¹.

CSF was normal, but 14-3-3 protein was present, with a strong positive result. The presence of 14-3-3 protein in the CSF can be very useful for the diagnosis of CJD in patients who fulfill the clinical criteria for the disease. In such cases, this test is highly sensitive and specific marker of the disease^{22,23}. Brown et al. reported that this test was positive in 25 among 36 iatrogenic CJD cases associated with human GH use⁸.

Autopsy was not performed in this case. Series of iatrogenic CJD usually include cases of definite and probable CJD^{8,17}. In a review of 34 cases of GH-related CJD, 18 were not submitted to brain biopsy or autopsy and were hence diagnosed as probable CJD¹⁷. When patients fulfill the criteria for probable CJD based on clinical features and complementary investigation, the percentage of correct diagnoses attained 95% in a series comprising 364 patients with non-iatrogenic CJD²³. The patients were diagnosed as probable CJD either if they manifested EEG periodic activity, according to criteria established by Masters et al.²⁴ or if 14-3-3 protein was detected in CSF²³. It is likely that in cases with probable CJD with epidemiological evidence of GH treatment, the percentage of correct diagnoses would be higher than 95%.

In conclusion, this patient had epidemiological, clinical, CSF and MRI findings consistent with the diagnosis of probable CJD, and is the second case of iatrogenic CJD following use of human GH reported in Brazil.

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