Creutzfeldt-Jakob disease 38 years after diagnostic use of human growth hormone

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A 47 year old man is described who developed pathology proven Creutzfeldt-Jakob disease (CJD) 38 years after receiving a low dose of human derived growth hormone (hGH) as part of a diagnostic procedure. The patient presented with a cerebellar syndrome, which is compatible with iatrogenic CJD. This is the longest incubation period described so far for iatrogenic CJD. Furthermore, this is the first report of CJD after diagnostic use of hGH. Since the patient was one of the first in the world to receive hGH, other cases of iatrogenic CJD can be expected in the coming years.

Prion diseases are potentially transmissible. Human to human transmission was first reported in 1974, when a 55 year old woman was described who developed symptoms of Creutzfeldt-Jakob disease (CJD) 18 months after a corneal transplant. Since then, transmission has been reported after stereotactic electroencephalographic (EEG) depth recording, human growth hormone (hGH) and gonadotrophin treatment, and dura mater transplantation. More than 267 patients with iatrogenic CJD are known today and their number is growing. The most important iatrogenic cause of CJD is still contaminated cadaveric hGH. Exposure to contaminated hGH occurred before 1985, when recombinant growth hormone became available. In a recent study, incubation periods in 139 patients with hGH associated CJD were found to range from 5–30 years, with a median of 12 years. One of the factors influencing incubation time is genotype on polymorphic codon 129 of the prion protein gene. The incubation time is significantly shorter in people who are homozygous for methionine or valine on this polymorphism.

We describe the second patient with hGH related CJD in the Netherlands. The patient developed the disease 38 years after hGH injections. To our knowledge, this is the longest incubation period described for any form of iatrogenic CJD. Furthermore, our patient was not treated with hGH but only received a low dose as part of a diagnostic procedure.

CASE REPORT
This patient presented at the age of 47 years with paraesthesia in both arms for six months, difficulty with walking for four weeks, and involuntary movements of mainly the upper extremities of two weeks’ duration. He did not notice any change in cognitive function, although his twin sister had noticed minor memory disturbances. There was no family history of neurological disease. During childhood the patient had experienced a growth delay compared with his twin sister and with the average in the Netherlands. When he was 9 years old, a nitrogen retention test with 6 IU hGH over five days was performed to exclude growth hormone deficiency. Since the result was not decisive, a quantitative amino acid test was performed, which measures 30 amino acids during fasting and one, two, and three hours after growth hormone injection. No abnormal amino acid concentrations were found making the diagnosis of primordial dwarfism most likely. Therefore, no treatment with hGH was given.

On neurological examination we found a slight dysarthria without aphasia. Cranial nerve function was normal. Walking was unstable and wide based. During movements of the upper extremities myoclonic jerks were present. Sensation, muscle tone, and strength were normal. Coordination was impaired in all four limbs with a disturbed balance. Tendon reflexes were brisk at the arms and increased at the legs with a clonus in the ankle reflex. Plantar responses were both normal. On the mini mental state examination, the patient scored 30/30. Routine laboratory investigation, thyroid function, vitamin concentrations (B-1, B-6, B-12, and E), and copper metabolism were normal. Admission EEG examination showed generalised arrhythmic slow activity with diffuse spikes and spike waves. EEG examination two months later showed a further slowing of the rhythm with bilateral diphasic sharp waves but was not typical for CJD. Cerebral magnetic resonance imaging was normal. Cerebrospinal fluid examination showed 1 cell/3 μl, normal glucose and protein concentrations, and a strongly positive 14-3-3 protein test. The patient was homozygous for methionine on the PRNP codon 129 polymorphism. On clinical grounds, CJD was diagnosed.

Within one month the patient’s condition deteriorated rapidly and because of severe disturbances in coordination and progressive myoclonus he became bedridden. An eye movement disorder developed with slow saccadic and dysmetric eye movements. Temperature became unstable with peaks of 39°C without an infectious focus, for which a disorder of autoregulation was presumed. Until a very advanced stage, cognitive function was intact. The patient died five months after admission. The diagnosis of CJD was confirmed at necropsy. The brain weighed 990 g and showed clear cortical and cerebellaratrophy. Spongiosis, neuronal loss, and gliosis were found predominantly in the putamen, caudate nucleus, and basotemporal and cerebellar cortex; the cerebellum was the most severely affected of these. Vacuoles ranged from 2–12 μm. No amyloid or Kuru plaques were found. Immunohistochemical staining (3F4 antibody 1:1000, Senetek, USA) was clearly positive for prion protein accumulation in a “synaptic” distribution. Most deposition was found in the stratum molecular of the cerebellum.

DISCUSSION
We describe a 47 year old patient who developed pathology proven CJD 38 years after hGH injections. The patient was never treated with hGH but received a small dose as part of a
diagnostic procedure. The onset of CJD was signalled by pro-
dromal symptoms of paraesthesia followed by a rapidly pro-
gressive ataxia. The disease presentation and course with
predominantly cerebellar and eye movement disorders are
compatible with iatrogenic CJD caused by hGH treatment. 7,8

Growth hormone treatment was first described in 1958 but
hGH was not produced on a larger scale from human pituitary
glands until the beginning of the 1960s. In the Netherlands
growth hormone extraction started in 1963 and was soon
centrally coordinated. Until 1979 growth hormone was
extracted non-commercially from pituitaries by a pharmaceu-
tical company. In 1971 commercial products also became
available. Our patient was one of the first to receive hGH in the
Netherlands but the origin of this product was not recorded. A
causal relation can therefore not be established with full cer-
tainty, but coincidentally receiving growth hormone and
developing this very rare disease is unlikely. Since the clinical
course in this relatively young patient is in accordance with an
iatrogenic cause, we think the probability is high that the hGH
injections explain the development of CJD in this patient.

The first Dutch patient with hGH related CJD died in
1990. 9 During several periods from 1963 to 1969 she received
intramuscular injections of hGH. During an unknown period
the hGH was derived from South America. At age 39, 27 years
after starting the treatment, she developed an ataxic gait,
slurred speech, sensory disorders, and myoclonus, but her
cognitive function remained normal. Postmortem examina-
tion of the brain confirmed the diagnosis of CJD. Following
the identification of this patient, a retrospective study was
started to trace all 564 registered hGH recipients who were
treated before May 1985. Until January 1995, none of these
was suspected of having CJD. 10 Since 1993 prospective surveil-
ance for all forms of human prion disease has been carried
out in the Netherlands and, apart from the patient described
above, a further two patients with iatrogenic CJD have been
identified, who developed the disease after dura mater
transplantation. 11

An incubation period as long as 38 years had never been
reported for iatrogenic CJD. Huillard d’Aignaux et al. 12 studied
the incubation period in 35 patients with hGH related CJD in a
cohort of 1361 French hGH recipients. The median
incubation period was between 9 and 10 years. Under the most
pessimistic model, the upper limit of the 95% confidence
interval varied between 17 and 20 years. Although the infect-
ding dose cannot be quantified, it can be speculated that the
long incubation period in our patient is partly explained by the
administration of a limited amount of hGH. This hypothesis is
supported by experimental models, in which higher infecting
doses usually produce shorter incubation periods. 13 Since our
patient was one of the first in the world to receive hGH, this
case indicates that still more patients with iatrogenic CJD can
be expected in the coming years. Another implication of our
study is that CJD can develop even after a low dose of hGH.
This case once more testifies that worldwide close monitoring
of any form of iatrogenic CJD is mandatory.

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