

Pituitary Growth Hormone and Creutzfeldt-Jakob Disease

All clinicians who have provided human growth hormone (GH) therapy to patients in the past need to be aware of the concern that has arisen during the last several months. There is the possibility that some batches of GH extracted from human pituitaries are contaminated with an infective agent that can lead to neurodegenerative disease.

Earlier this year, the National Institutes of Health (NIH) and the FDA were notified that a patient in California who had been treated with GH between the years 1966 and 1976 had died of a rapidly progressing degenerative neurologic disease and was found at autopsy to have typical changes of Creutzfeldt-Jakob disease (CJD) in his brain. CJD is a rare condition; it is usually sporadic and usually presents between 55 and 65 years of age, with a rapidly progressive degenerative course (cerebellar ataxia leading to death over six to 18 months) and with pathognomonic spongiform changes of the brain on autopsy. It is a transmissible disease that is very closely akin to scrapie in sheep and to a specific type of encephalopathy in mink.

CJD has been studied intensively for many years because, theoretically, it would be preventable if an infective agent could be isolated and treatment developed. However, the infective agent is elusive, and it is unclear whether the disorder is caused by a slow virus or by a subviral pathogen (a protein called a prion, which is a newly defined class of proteinaceous infectious particles thought to be capable of being infective without the presence of nucleic acid). The infective agent is also resistant to the usual sterilizing procedures, such as those using formaldehyde, alcohol, or glutaraldehyde, and even to fixation, but it is susceptible to bleach (1 mol/l NaOH and one hour in an autoclave at 120 °C). Currently, there is no therapy for CJD, and no remissions have occurred. The incubation period may be several decades.

Dr. Carleton Gajdusek at the NIH, who has been involved for many years in research on CJD, estimates that one to two people per million in the general population have changes characteristic of CJD in

their brains at death. Because of the long latent period, as many as one in 6,000 to 10,000 people might carry the infective agent, although they may not manifest any symptoms. Thus, many of these people would die of other causes before CJD became manifest. GH has been produced by extracting between 5,000 and 16,000 pituitaries obtained at autopsy; there is a chance that one of these individual pituitaries carried the CJ infective agent, thus contaminating the entire lot. In North America, the average child on GH treatment will have received therapy for four years and will have received GH from several different lots. Thus, it is possible that many individuals treated with GH may have been exposed to the CJ infective agent.

Because of the potential implications of a transmitted neurodegenerative disorder in patients treated with extracted GH, several pediatric endocrinologists, officials from the NIH, the FDA, and the National Hormone and Pituitary Program (NHPP), as well as representatives of commercial suppliers of human growth hormone, assembled for an emergency meeting in April 1985. At about that time, it was recognized that two other patients who had been treated with GH had died of rapidly progressing neurologic degenerative diseases during the past year. One had not had an autopsy; the autopsy on the other patient was diagnostic of CJD. The incidence of CJD occurring in individuals under 30 years of age is less than one in 10 million; thus, to have three cases in one year in the United States, all of whom have had therapy with extracted GH, was a matter of great concern.

The technique for extracting GH changed dramatically in 1977. Prior to 1977, the method of extraction was relatively crude. It is important to point out that the three CJD patients all began their therapy before 1977 but were *not* all treated with GH from one lot. They overlap at least two extraction lots. The commercial companies and pituitary agencies in most countries feel that it is unlikely that a virus would be present in their material purified since 1977. However, CJ infective agent is not just any virus, but rather

an unusual compound that is not yet understood. Thus, it is possible that, even after 1977, extracted GH might be contaminated with the CJ infective agent.

The next question, of course, is, Will all individuals exposed to the infective agent develop the neurologic degenerative disease? There seem to be individual differences in response, both with regard to clinical presentation and length of incubation. However, as yet there is simply no answer to the question of who may develop the disease.

Because of this information and concern, in April of this year the FDA and the NHPP in the United States withdrew extracted GH for therapy of children who are GH deficient and for any other type of therapy, with the exception of children who have hypoglycemia as a result of their GH deficiency.

There have been more than 30,000 individuals treated with extracted GH since treatment programs began. What will happen to those individuals who were taken off GH therapy? They will stop growing temporarily and may have minor metabolic imbalances. However, it is well known that genetically engineered GH will be available for therapy within the next few months. It is anticipated that most individuals who have been off GH for a few months will have catch-up growth when restarted on therapy and will be minimally harmed by the hiatus in treatment.

Intensive investigation of the infective agent in CJD has been going on for many years. The application of molecular genetic techniques has allowed the isolation of the gene that produces the prion protein known to be associated with infectivity (if not the infective agent itself). This protein has been isolated and cloned. Interestingly, genetic information coding for the protein prion sequence is present in the normal human genome. However, it appears that the infective agent protein prion is more resistant to breakdown than the "normally" occurring protein. Through these investigations, it is hoped that we can develop the ability to diagnose infected individuals prior to symptoms and recognize which individuals are at risk.

These events have spurred further investigation. First, as soon as the potential danger was recognized, GH from each extraction lot was injected into various animals (hamsters, monkeys, etc) known to be susceptible to the CJ virus in the hope of identifying batches that carry the infective agent. Second, research on the infective agent (in terms of developing potential therapeutic antibodies or therapies) is rapidly proceeding. However, the results of these investigations will not be available for months or years.

It has been known from previous work on CJD and related diseases such as kuru and scrapie that animals who have had repeated injections of infective agent do mount antibodies to the scrapie-associated fibrils and associated proteins (PRP 27/30). Obviously patients treated with potentially contaminated GH have had repeated injections. For this reason, researchers at the NIH would like to receive serum samples from patients who have been given GH in the past; they will let you know what they find in your specific patient(s). They will be testing for antibodies to scrapie-associated fibrils. To participate, send 4 to 5 ml of frozen serum collect by Federal Express to Dr. Joe Gibbs, Building 36, Room 4A17, NIH, Bethesda, MD 20205 (phone: 301-496-4821); include age of patient, during what years he or she was treated and for how long, how much GH was given, and the lot number, if known. Also, please notify Dr. Paul Brown, Building 36, Room 5B25, NIH, Bethesda, MD 20205 (phone: 301-496-5291) of any patients under your care who have received GH in the past, and who have neurological symptoms suggestive of CJ disease.

In summary, it is unclear what the future holds for patients who have been treated with extracted GH. However, it is important to be aware of the concern, to continue to be informed, to apprise patients and families of the situation, and to participate in any epidemiologic studies that are undertaken. In general, it is important to be straightforward and honest with patients, but to assure them that a great deal is being done to evaluate the situation and investigate the questions that remain unanswered.