PUBLIC HEALTH SERVICE

Interagency
Coordinating Committee on
Human Growth Hormone and Creutzfeldt-Jakob Disease

October 16, 2024, 9:00 am

- Virtual Meeting -
Hosted by the National Institutes of Health
Bethesda, Maryland

Committee Members Attending
Dr. Ellen Leschek, NIDDK
Dr. James Mills, NICHD
Dr. Avindra Nath, NINDS
Dr. Griffin Rodgers, NIDDK, Chair
Dr. Lawrence Schonberger, CDC
Dr. Aida Kuzucan, FDA

Absent
Dr. William Cefalu, NIDDK
Dr. Gregory Germino, NIDDK

Also Attending
Ms. Leslie Curtis, NIDDK
Dr. Ryan Maddox, CDC
Dr. B. Tibor Roberts, NIDDK
Ms. Lisa Yuan, NIDDK

Westat Contract
Dr. Leschek reported that in July, Westat started the second year of their current 5-year contract to support the Committee's work.

National Hormone and Pituitary Program (NHPP) Cohort Update
Dr. Leschek reported that, as expected (see below), one neuropathologically confirmed case of CJD from the cohort was added since the 2023 meeting. Therefore, the total number of official cases (*i.e.*, those either neuropathologically or clinically confirmed) increased to 36.

The 36th case is a cohort member who died due to CJD shortly before the 2023 meeting. As discussed by the Committee in 2023, there was strong clinical evidence that this individual had died of CJD, but the autopsy results were not yet available. Thus, this case could not yet be made official and we did not count it toward the total. Now, having received neuropathological confirmation, this case has officially been added to the total. Symptoms were thought to have begun about 51.5 years after initiation of hGH treatment, meaning this case increased the longest known incubation time for a cohort case by more than 6 years.

Dr. Leschek discussed 4 cases under investigation, where cohort members had neurological issues at death that did not seem to be fully explained by other known diagnoses. In two cases she is working with family members who had medical power of attorney and agreed to release

the medical records of the final years of life. For the other two cases, Dr. Leschek was not able to find living next of kin, so the CDC is attempting to obtain more information.

Potential Link Between Alzheimer's Disease and Pituitary hGH

In response to the published claim from the UK that there have been 8 cases of transmitted Alzheimer's disease (AD) in their 1800-person cadaveric GH cohort (which also had a much higher rate of CJD transmission than the US cohort), Drs. Nath, Leschek, and other experts have expressed skepticism that the published data establish clear evidence for Alzheimer's, and they recently published a commentary to this effect. That said, the Committee members discussed how best to investigate whether there is evidence for AD transmission in the US cohort. Dr. Leschek initiated another chart review to identify death certificates that indicate either AD or unspecified dementia. Of the approximately 1,400 cohort deaths to date, 4 indicate AD. Of those, three show evidence that is reasonably suspicious for AD, while the fourth case seems highly unlikely. There is also one known case of a living cohort member who has a clinical diagnosis of AD. Nine additional death certificates list unspecified dementia. Of these, 4 were considered suspicious for CJD and/or AD, 2 were potentially AD only, and 3 were unlikely to be either CJD or AD. Records are being reviewed for those considered suspicious for CJD and/or AD. Dr. Nath suggested examining all tissue blocks from our neuropathologically confirmed CJD cases for co-occurring amyloid beta and/or tau protein deposits. (Amyloid beta and tau together would indicate AD; amyloid beta alone would suggest cerebral amyloid angiopathy (CAA).) Dr. Leschek noted that none of the autopsy reports mention presence of either protein deposit. Dr. Nath suggested that they may not have looked for this pathology.

Dr. Schonberger said that unfortunately, very few tissue blocks were preserved, but that in 2015, a paper was published that examined 8 U.K. cases of iCJD, finding CAA-like amyloid deposits in 4 of them; in contrast, no CAA was found in 19 individuals with non-iatrogenic prion disease. This paper was supported by a subsequent investigation that examined tissue from 13 US iCJD cases from the NHPP and 14 international iCJD cases associated with dura mater grafts. Although 52 percent of these individuals had evidence of CAA-like amyloid deposits (in addition to PrP^{Sc}), tau deposits were not found at levels indicative of AD. The authors of this later paper discussed some of their data, pre-publication, at the 2016 meeting of this Committee. (See the final item in the 2016 minutes.) Dr. Nath suggested trying to obtain better data by examining tissue samples from any autopsy of a cohort member. He suggested discussing with Jonathan Green to confirm that (as he recalled) next-of-kin permission is not normally required. Dr. Leschek said she would review records to develop a list of the individuals who had autopsies.

Updates on Fact Sheet and Public Inquiries

Ms. Curtis stated that the fact sheet resource list was updated to reflect the new scientific papers discussed at the 2023 meeting. For reference, the comprehensive fact sheet is here, and the resource list is here.

Ms. Curtis also reported that there were 25 inquiries regarding hGH and CJD over the past year, compared to 12 the year prior. She noted that 25 was the highest number of inquiries received in the last 4 years. Five were from confirmed cohort members, three of whom received follow-up contact from Dr. Leschek. Most calls related to concerns about the finding of possible AD

transmission discussed above; none of the inquiries were suggestive of potential new cases of CJD.

Report on CJD in Foreign and Commercial Growth Hormone Recipients
Dr. Schonberger reported no new international iCJD cases associated with pituitary hGH treatment. The total number of foreign cases therefore remains 217.

Recent Progress in CJD Research
Drs. Schonberger and Nath noted three recent publications of interest:

1. Banerjee G, Farmer SF, et al. Iatrogenic Alzheimer's disease in recipients of cadaveric pituitary-derived growth hormone. Nat Med. 30:394-402, 2024.

2. Nath A, Holtzman DM, et al. Insufficient evidence for an association between iatrogenic Alzheimer's disease and cadaveric pituitary-derived growth hormone. Alzheimers Dement. 20:7399-7402, 2024.

3. Groveman BR, Williams K, et al. Lack of Transmission of Chronic Wasting Disease Prions to Human Cerebral Organoids. Emerg Infect Dis. 30:1193-1202, 2024.

Griffin P. Rodgers, M.D.
Director, NIDDK

The following are two excerpts of previous meeting summaries that may be helpful to the Committee either in consideration of these minutes or as a reminder of key historical information.

Excerpt from the 2015 minutes, currently found at https://www.niddk.nih.gov/-/media/Files/Advisory-Coordinating-Committees/Public-Health-hGh-CJD/hGH-CJD_summary_2015_FINAL.pdf :

Discussion of Potential for Aβ Pathology Transmission
Drs. Schonberger and Nath discussed an article appearing in the September 10, 2015 issue of Nature, titled "Evidence for Human Transmission of Amyloid-β Pathology and Cerebral Amyloid Angiopathy." Amyloid-β (Aβ) is the peptide that forms characteristic brain amyloid deposits in Alzheimer's disease, and which also form amyloid deposits in walls of blood vessels that supply the brain in cerebral amyloid angiopathy, a much rarer disease. The authors of the paper had been examining specimens from a group of patients who had developed CJD subsequent to receiving pituitary growth hormone in Great Britain. In addition to showing signs of CJD, half of them (4 of 8) also had Aβ deposits: both in the nervous tissue of the brain, as is typical of Alzheimer's, and in blood vessel walls, as in cerebral amyloid angiopathy. The observed rate of Aβ deposition in these patients, particularly in blood vessels, was much higher than would normally be expected in people of their relatively young age and was not observed in a set of 19 control patients in the same age range who developed CJD without having been

administered growth hormone. The authors note that their observations do not show that Alzheimer's disease is transmissible: Aβ plaques alone are not in themselves indicative of the disease in the absence of either clinical features or other structures called neurofibrillary tangles.

Drs. Nath and Schonberger agreed that the findings were interesting, but they were skeptical given the small sample size and the ambiguous interpretation of the plaques without tangles. Dr. Schonberger noted that an examination by the NPDPSC of five specimens that the NPDPSC had on-hand from US hGH/CJD cases did not support or refute the idea that Aβ amyloid could be transmitted by pituitary growth hormone preparations: four of the patients based on available tissues lacked clear signs of Aβ plaques, while the fifth case that did have Aβ plaques was also HIV positive raising the question about whether the HIV infection could have been responsible for the Aβ pathology. To take a wider look, Dr. Schonberger noted Dr. Leschek had provided him a list of where other existing brain specimens may be. He reported that Westat evidently does not hold samples for over a year, but returns them to the originating pathologist, so it is unclear how many relevant U.S. samples may still exist, but Dr. Schonberger is attempting to obtain those that he can. Dr. Leschek noted that she is trying to obtain release of brain tissue blocks from the next-of-kin from cohort members who died without evidence of CJD, in case there is any evidence of Aβ transmission in the absence of CJD, noting that at present there is no reason to think there would be. Dr. Schonberger noted that he this list could be pared to exclude people who were only treated post-1977, on the theory that the purer preparations were less likely to have Aβ transmission, just as they were less likely to have CJD transmission. He is also inquiring with his international contacts to see if any samples from non-U.S. cases are available for study, so that findings may be pooled for additional statistical significance.

Also note the following historical information of significance regarding the Interagency Committee, its history, and its mandate from the 2009 summary:

Dr. Rodgers asked Dr. Roberts to provide the historical background for establishment of the Committee. In February 1985, PHS officials were notified of a case of CJD in an individual who had received hGH through the National Hormone and Pituitary Program (NHPP). The NHPP notified physicians participating in the program, asked them to stop using NHPP-distributed hormones for non-therapeutic purposes, and inquired about other deaths from apparent CJD. That inquiry brought to light two additional CJD deaths. At that point, in April of 1985, a decision was made to temporarily halt the distribution of hGH for all clinical use, except to patients with life threatening hypoglycemia, and to initiate epidemiological studies to assess the full extent of the problem. The following is excerpted from the Seventeenth Report of the Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease (emphasis added):

> To facilitate the scientific review of this issue, the then Acting Assistant Secretary for Health formally established the Interagency Coordinating Committee on Human Growth Hormone and Creutzfeldt-Jakob Disease. The purpose of the Committee is to advise the Assistant Secretary for Health regarding a coordinated PHS response to the scientific questions surrounding hGH distribution in relation to CJD. The Committee originally reported at three-month intervals, and now reports annually or as significant new information becomes available.

In 2001, the Committee was notified that future reports were not needed unless an increase in the rate of new cases occurs. Since that time, the Committee has served as a coordinating body for continuing surveillance of CJD incidence and epidemiology within the cohort. In addition, the Committee provides updated information via fact sheets on the NIDDK web site to recipients of pituitary-derived hGH supplied through the NHPP to keep them informed of the progress of the study and of new developments with regard to hGH administration and CJD.