

PUBLIC HEALTH SERVICE

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

November 13, 2015, 10:00 AM

Democracy II, NIDDK Conference Room 694
Bethesda, Maryland

Committee Members Attending

Dr. Patricia Bright, CDC (by phone)
Dr. Judith Fradkin, NIDDK
Dr. Ellen Leschek, NIDDK
Dr. James Mills, NICHD (by phone)
Dr. Avindra Nath, NINDS
Dr. Griffin Rodgers, NIDDK, Chairman
Dr. Lawrence Schonberger, CDC (by phone)

Also Attending

Dr. Joe Abrams, CDC (by phone)
Dr. Greg Germino, NIDDK
Dr. Ryan Maddox, CDC (by phone)
Amy Reiter, NIDDK
Dr. B. Tibor Roberts, NIDDK
Diane Tuncer, NIDDK

Westat Contract

Dr. Leschek reported that Westat is in the third year of the current 5-year contract.

NHPP Cohort Update

The total number of confirmed cohort CJD cases is now 32, including two more neuropathologically confirmed cases. Because the 30th case, discussed in the 2014 minutes, was subsequently neuropathologically confirmed, the totals are now 17 neuropathologically confirmed and 15 clinically confirmed.

Case 31, resulting in death in 2014, was discussed at the previous meeting, but the neuropathological confirmation we have now was not yet available. This case increases the maximum known incubation period: 44.8 years from the start of hGH therapy to the onset of CJD symptoms; 42.8 years from the midpoint of therapy to the onset of symptoms; and 40.7 years between the end of hGH therapy and the onset of symptoms.

Case 32 came to the Committee's attention because Dr. Schonberger was in contact with the [National Prion Disease Pathology Surveillance Center](#) (NPDPS) at Case Western Reserve University to identify any potential information or samples that might help provide evidence for Alzheimer's disease (AD) pathology transmission. The NPDPS data included this case, but Dr. Schonberger noted that it was not among our known cases. Westat confirmed that the individual was a recipient of NHPP-distributed hGH, but found that the individual was listed in their records as still alive, even though he had been deceased since 2005. Evidently, Westat had received report of the death, noting that the name matched an individual in the cohort, and attempted to obtain a death certificate (DC). Because they were unable to do so, they continued

to list the individual as alive, per their protocol. (The National Death Index, NDI, does not provide sufficient details to confirm a match, absent confirming information from the death certificate, and occasional false positives have arisen in the past.)

Drs. Schonberger and Leschek requested a change in Westat procedure to record apparent deaths as deaths unless the DC proved otherwise. And upon further investigation, it was determined that there were more than 50 other possible deaths for which DCs were not obtained. An effort to determine the status of these individuals is currently underway. Westat is instructed to re-investigate with the total cohort using NDI-Plus, a more comprehensive service that includes DC-listed causes of death, potentially suggesting instances where a more vigorous (and potentially CDC-bolstered) effort to obtain the DC is advisable. Results from the initial NDI-Plus search are not yet available. Drs. Schonberger and Leschek noted that case 31 might also have been missed—due to an adoption that resulted in a name change—if it had not been brought to Dr. Schonberger’s attention by the individual’s mother, who was aware of the growth hormone treatment and potential CJD risk. NDI-Plus would not have been a help in identifying this individual, so it is still possible to miss a case.

As with all other confirmed cases, the new cases occurred in patients who began treatment before Dr. Albert Parlow’s lab began preparing hGH in 1977. Dr. Rodgers suggested that it would be helpful to get an annual report on the status of the living cohort members, potentially tracking how many have passed the maximum known incubation period since their last treatments. Dr. Fradkin noted that it might also be helpful to group them into three categories: those who received NHPP-supplied hGH entirely before 1977; those who received hormone both before and after 1977; and those treated exclusively after 1977.

One case under investigation remained so: a man who was not in the cohort, but who received hormone according to eyewitness accounts, and is linked to the program by other circumstantial evidence, and who is said to have declined rapidly in his last year of life. His death certificate lists hypotension, pneumonia, septic shock, and musculodegenerative disease. Dr. Maddox had been in contact with the state health department, which declared there was no evidence of CJD being the cause of death; however, it is possible that this is because the final health care efforts were focused more on the pneumonia and sepsis. Dr. Maddox agreed to re-contact the state officials to obtain permission to speak directly to the area neurologists who may have treated the man for his musculodegenerative condition.

Discussion of Potential for A β 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- \$\beta\$ Pathology and Cerebral Amyloid Angiopathy.](#)” Amyloid- β (A β) 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 A β 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 A β 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: A β 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 NPDPS of five specimens that the NPDPS had on-hand from US hGH/CJD cases did not support or refute the idea that A β amyloid could be transmitted by pituitary growth hormone preparations: four of the patients based on available tissues lacked clear signs of A β plaques, while the fifth case that did have A β plaques was also HIV positive raising the question about whether the HIV infection could have been responsible for the A β pathology. To try 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 also provided names of pathologists who had completed autopsies of individuals in the cohort who had died without evidence of CJD, in case there is any evidence of A β transmission in the absence of CJD, noting that at present there is no reason to think there would be. Dr. Schonberger noted that he pared this list to exclude people who were only treated post-1977, on the theory that the purer preparations were less likely to have A β 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.

Updates on Fact Sheet and Public Inquiries

Ms. Tuncer confirmed implementation of the fact sheet and resource list as discussed at last year's meeting and stated that they will be further updated to reflect the cases confirmed in the past year. For reference, the [comprehensive fact sheet is here](#), and the [summary version is here](#), and the [resource list is here](#).

Ms. Reiter reported that there were 12 inquiries regarding hGH and CJD over the past year (compared to 10 the year before). Two were from confirmed cohort members. None of the calls were suggestive of potential new cases of CJD.

Recent Progress in CJD Research: Experimental Diagnostic Tests

Dr. Nath noted the unfortunate dearth of new or ongoing clinical research on CJD in the United States, which he attributed primarily to a lack of promising agents capable of preventing aberrant protein folding that are also bioavailable and capable of crossing the blood-brain barrier.

Dr. Schonberger noted two 2015 papers of interest:

1. Orru, CD, Groveman BR, Hughson AG, et al. [Rapid and Sensitive RT-QuIC Detection of Human Creutzfeldt-Jakob Disease Using Cerebrospinal Fluid](#). *MBio* 2015; 6: e02451-14.
2. Prusiner SB, Woerman AL, Mordes DA, et al. [Evidence for \$\alpha\$ -synuclein Prions Causing Multiple System Atrophy in Humans with Parkinsonism](#). *Proc Natl Acad Sci USA*. 2015; 112: E5308-E5317.

Report on CJD in Foreign and Commercial GH Recipients

Dr. Schonberger reported that he had not learned of any new international hGH/CJD cases in the previous year. The total therefore remains 207 international cases.

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