PUBLIC HEALTH SERVICE

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

November 2, 2016, 10:00 AM

National Institutes of Health
Building 31, Room 9A22
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. Ignazio Cali, Case Western Reserve University (by phone)
Dr. Greg Germino, NIDDK
Mary Harris, NIDDK
Dr. Ryan Maddox, CDC (by phone)
Amy Reiter, NIDDK
Dr. B. Tibor Roberts, NIDDK
Dr. Jiri Safar, Case Western Reserve University (by phone)
Dr. Robert Tilghman, NIDDK
Diane Tuncer, NIDDK

Westat Contract
Dr. Leschek reported that Westat is in the fourth year of the current 5-year contract. The NIDDK is planning to renew the contract for another 5 years.

NHPP Cohort Update
There have been no new clinically or pathologically confirmed cases since the last meeting, nor have there been any new clinically suspicious cases. The total number of confirmed cohort CJD cases therefore remains at 32, with 17 neuropathologically confirmed and 15 clinically confirmed. One case that has been under investigation was resolved as unlikely to involve CJD. There is still one confirmed US CJD case-patient who had received commercially produced pituitary hGH.

Dr. Leschek reported that the committee's source for death records is now the National Death Index (NDI) Plus database, which provides more detailed information than the standard NDI database. Use of the NDI Plus database enabled disposition of 95 additional cohort deaths because the causes of deaths became available; the causes of death had not been reported using the standard NDI database. Dr. Leschek is combing through the records for these newly discovered causes, and thus far has found one that raises low-level suspicion for CJD. She has

been unable to obtain any medical records, so Drs. Schonberger and Maddox will attempt to obtain information regarding the circumstances surrounding the death.

Dr. Leschek stated that a replacement is necessary for Dr. Rebecca Folkerth from the neuropathology review group, so she contacted Dr. Mark Cohen of the National Prion Disease Pathology Surveillance Center (NPDPSC), who accepted the position. The committee discussed whether to use the NPDPSC for future analyses of brain tissue samples in place of the neuropathology review group. Drs. Safar and Cali of the NPDPSC expressed interest in this proposal and agreed to work with Dr. Leschek to modify the existing procedure accordingly.

Dr. Leschek reported that Dr. Richard Johnson of the committee's neurological review group (NRG) recently passed away. The committee suggested inviting Dr. Arun Venkatesan to join the NRG.

Updates on Fact Sheet and Public Inquiries

Ms. Tuncer stated that the comprehensive and summary fact sheets were updated to reflect current confirmed cases and new papers discussed at the previous meeting. The general information in the fact sheets was also updated in consultation with Dr. Schonberger, and scientific papers discussed at the 2015 meeting were added to the resource list. For reference, the comprehensive fact sheet is here, the summary version is here, and the resource list is here.

Ms. Harris reported that there were five inquiries regarding hGH and CJD over the past year (compared to 12 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

Dr. Schonberger noted three recent papers of interest:

1. Cohen ML, Kim C, Haldiman T, et al. Rapidly progressive Alzheimer's disease features distinct structures of amyloid-β. *Brain*. 2015; 138: 1009-1022.

2. Coulthart MB, Geschwind MD, Qureshi S, et al. A case cluster of variant Creutzfeldt-Jakob disease linked to the Kingdom of Saudi Arabia. *Brain*. 2016; 139: 2609-2616.

3. Hughson AG, Race B, Kraus A, et al. Inactivation of Prions and Amyloid Seeds with Hypochlorous Acid. *PLoS Pathogen*. 2016; 12(9): e1005914.

Dr. Nath also noted several papers of interest:

1. Checchi M, Hewitt PE, Bennett P, et al. Ten-year follow-up of two cohorts with an increased risk of variant CJD: donors to individuals who later developed variant CJD and other recipients of these at-risk donors. *Vox Sang*. 2016; 111: 325-332.

2. Oshita M, Yokoyama T, Takei Y, et al. Efficient propagation of variant Creutzfeldt-Jakob disease prion protein using the cell-protein misfolding cyclic amplification technique with samples containing plasma and heparin. *Transfusion*. 2016; 56: 223-230.

3. Ritchie DL, Gibson SV, Abee CR, et al. Blood transmission studies of prion infectivity in the squirrel monkey (Saimiri sciureus): the Baxter study. *Transfusion*. 2016; 56: 712-721.

4. Urwin PJ, Mackenzie JM, Llewelyn CA, et al. Creutzfeldt–Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. *Vox Sang*. 2016; 110: 310-316.

5. Helbert MR, Bangs C, Bishop M, et al. No evidence of asymptomatic variant CJD infection in immunodeficiency patients treated with UK-sourced immunoglobulin. *Vox Sang*. 2016; 110: 282-284.

Report on CJD in Foreign and Commercial GH Recipients

Dr. Schonberger reported two new international hGH/CJD cases: one in France in 2015 (bringing the French total to 120 for hGH-related cases), and another in the United Kingdom in 2016 (bringing the U.K. total to 76). This brings the total to 209 foreign (non-U.S.) cases.

Presentations: Aβ Pathology in Iatrogenic CJD Cases

Drs. Cali and Safar from the National Prion Disease Pathology Surveillance Center at Case Western Reserve University discussed their recent findings that amyloid-beta (Aβ) deposits—the plaques that are associated with Alzheimer's disease—appear to be more common in brains of patients with iatrogenic CJD than in the brains of age-matched controls with spontaneous CJD. These CJD-associated Aβ plaques were smaller and less abundant than what is typically seen in Alzheimer's patients. Other markers typical of Alzheimer's disease—tau-positive neurofibrillary tangles and dystrophic neurites—were also found in patients with iatrogenic CJD, although not at levels seen in Alzheimer's patients. Drs. Safar and Cali discussed several possible causes for the presence of Aβ plaques in iatrogenic CJD patients, including the transmissibility of the Aβ agent, direct interactions between Aβ and the CJD prion protein, or the contribution of one or more preexisting conditions, such as growth hormone deficiency, radiation treatment, head injury, brain tumors, or HIV infection. Dr. Schonberger noted that thus far there have been no reports of confirmed deaths from Alzheimer's disease among the confirmed U.S. and international pituitary hGH cohorts.

Griffin P. Rodgers, M.D.
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