Remarks to the Author:

Feeney et al argue that we have not excluded other explanations of our finding of extensive amyloid beta (Aβ) deposition in relatively young individuals who received extracts of human pituitary glands. They argue that this may have been a consequence of their underlying pathology that led to cadaveric pituitary-derived human growth hormone (c-hGH) treatment and propose that GH deficiency and Aβ pathology in these patients may have resulted from traumatic brain injury (TBI).

Firstly, as we made clear in our article, we did not argue that the patients we described had developed Alzheimer's disease, rather we reported the neuropathological finding of Aβ pathology. As also made clear in our letter, our study was observational rather than an epidemiological or experimental one. These patients, as acknowledged by the authors who present a table summarising our clinical findings, received c-hGH for various reasons and those who developed Aβ deposition were treated for pathogenetically unrelated conditions, including short stature of no obvious cause, making a common mechanism leading to Aβ pathology unlikely. The patients we reported were referred to us with CJD. We think it is unlikely that we missed significant common aspects of the medical history as all patients were under our direct care, medical records were reviewed and this issue was explored in detail with families. We identified no publications that report a causal relationship between panhypopituitarism, short stature, or craniopharyngioma and Alzheimer's disease or increased Aβ deposition. Multiple series of age-matched controls have been published previously and our cohort was compared to the largest series[1]. We did not have access to autopsies on patients treated after 1985 with synthetic GH. We agree such a comparison will be of interest although difficult as these necessarily represent different age cohorts.

One alternative hypothesis proposed by the authors is that traumatic brain injury (TBI) in childhood may have been responsible for the Aβ deposition. There is no evidence for the suggestion by Feeney et al that these patients had TBI in early childhood and thus it remains entirely speculative that the Aβ pathology may have been a long-term consequence of trauma.

Feeney et al also refer to a study of 6874 patients treated with synthetic GH due to isolated idiopathic growth hormone deficiency or short stature, where eleven patients developed an intracerebral haemorrhage, ischemic stroke or subarachnoid haemorrhage [2]. None of these patients had pathologically confirmed cerebral amyloid angiopathy (CAA) and five were known to have aneurysm, vascular malformation or arterial dissection, an unsurprising finding in such a large cohort.

The rationale of our publication was to raise the awareness that human to human transmission of proteopathic seeds may not be restricted to prions. Investigating the role of seeded protein aggregation (often referred to as "prion-like" mechanisms) is one of the most active current areas of neurodegeneration research[3]. There is already a substantial body of experimental data *in vitro* and *in vivo* demonstrating Aβ seeding, including as we cited in our letter that peripheral inoculation of laboratory mice with Alzheimer's disease brain extracts leads to CAA. We agree with Feeney et al that our study does not prove human transmission of Aβ pathology and further studies are needed. As we note, it will be important to examine archived batches of c-hGH for presence of Aβ seeds by animal inoculation studies and this work is planned. In addition, we argued in our manuscript that our findings should also prompt investigation of whether other known iatrogenic routes of prion transmission (unrelated to c-hGH treatment or the underlying conditions for which it was given) may

also be relevant to Aβ seeding. The commonest other cause of iatrogenic CJD is use of dura mater grafts. Importantly, an Austrian/Swiss series of dura mater graft recipients has now been reported which also found frequent vascular and parenchymal Aβ pathology consistent with our hypothesis[4].

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1 Braak, H. & Braak, E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* **18**, 351-357 (1997).

2 Poidvin, A. *et al.* Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. *Neurology* **83**, 780-786, doi:10.1212/WNL.0000000000000737 (2014).

3 Jucker, M. & Walker, L. C. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. *Nature* **501**, 45-51, doi:nature12481 [pii] 10.1038/nature12481 (2013).

4 Frontzek, K., Lutz, M. I., Aguzzi, A., Kovacs, G. G. & Budka, H. Amyloid-beta pathology and cerebral amyloid angiopathy are frequent in iatrogenic Creutzfeldt-Jakob disease after dural grafting. *Swiss Med Wkly* **146**, w14287, doi:10.4414/smw.2016.14287 (2016).