Adams et al argue that we have not excluded two alternative explanations of our finding of extensive amyloid beta (Aβ) deposition in relatively young individuals who received extracts of human pituitary glands: that this pathology may be a consequence of either the underlying diagnosis for which the treatment was given or of the treatment with growth hormone itself irrespective of whether it was contaminated. As we made clear in our letter, our study was observational rather than an epidemiological or experimental one. While by its nature it cannot exclude these hypotheses (or other possible explanations for which there is no supportive evidence), we considered them unlikely. These patients received cadaveric pituitary-derived human growth hormone (c-hGH) for various reasons and those in our cohort who developed Aβ deposition were treated for pathogenetically unrelated conditions, or simply because of short stature of no obvious cause, making a common mechanism unlikely. Also we identified no publications that report a causal relationship between panhypopituitarism, short stature, or craniopharyngioma and Alzheimer's disease or increased Aβ deposition.

We also consider the proposal that growth hormone itself (acting through the GH-IGF axis) administered through adolescence is a possible trigger of Aβ deposition to be unlikely since IGF-1 production is stimulated by growth hormone, and increased IGF levels are associated with increased Aβ clearance[1,2] and decreased risk of Alzheimer's disease[3]. Accordingly, the protracted treatment with growth hormone should have reduced accumulation of Aβ.

Adams et al refer to our hypothesis (that Aβ seeds in batches of c-hGH triggered Aβ amyloidosis in recipients) as being untested. Clearly this cannot be experimentally tested in humans but there is a substantial body of experimental data *in vitro* and *in vivo* demonstrating β-amyloid seeding, including as we cited in our letter that peripheral inoculation of laboratory mice with Alzheimer's disease brain extracts leads to cerebral amyloid angiopathy. 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[4]. As we note, it will be important to examine archived batches of hGH for presence of Aβ seeds by animal inoculation studies and this work is planned.

To refer to our comparison with patients with other forms of prion disease unrelated to hGH treatment as futile is inappropriate. Were we to have found that patients with sporadic CJD or other forms of prion disease had a similar frequency and severity of Aβ pathology at comparable ages, this would have argued strongly against our hypothesis, and indeed the two alternate hypotheses Adams et al suggest. An important question which we proposed in our letter was whether similar pathology suggestive of transmission of Aβ seeds is seen in iatrogenic CJD caused by other medical procedures. The commonest other such cause is use of dura mater grafts. Demonstration of frequent Aβ pathology in such patients, as has been reported in individual cases[5,6] would support our hypothesis and dismiss those proposed by Adams and colleagues.

However we agree with Adams et al that carefully controlled epidemiological studies are valuable and indeed we hoped that our study would stimulate such discussion and encourage precisely such work. With respect to comparing patients treated with hGH and synthetic hormone, this will be difficult as these necessarily represent different age cohorts.

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