Growth Hormone and Cerebral Amyloidosis

Abstract

Great interest has recently been focused on a paper reporting characteristic deposits of amyloid-β protein associated with Alzheimer’s disease in brains of adults who died of Creutzfeldt-Jakob disease. As they had contracted such disease after treatment with prion-contaminated human growth hormone extracted from cadaver-derived pituitaries, the authors have suggested that interhuman transmission of Alzheimer’s disease had occurred. Our previous research led us to find that amyloid-forming peptides share amino acid sequence homology, summarized by a motif. Here, we probed the amino acid sequence of human growth hormone for such a motif, and found that 2 segments fit the motif and are potentially amyloid-forming. This finding was confirmed by Aggrescan, another well-known software for the prediction of amyloidogenic peptides. Our results, taken together with data from the literature that are missing in the aforementioned paper and associated commentaries, minimize the contagious nature of the iatrogenically-acquired coexistence of Creutzfeldt-Jakob disease and Alzheimer’s disease. In particular, the above mentioned paper misses literature data on intratumoral amyloidosis in growth hormone- and prolactin-secreting adenomas, tumors relatively frequent in adults, which are often silent. It cannot be excluded that some pituitaries used to extract growth hormone contained clinically silent microadenomas, a fraction of which containing amyloid deposits, and patients might have received a fraction of growth hormone (with or without prolactin) that already was an amyloid seed. The intrinsic amyloidogenicity of growth hormone, in the presence of contaminating prion protein (and perhaps prolactin as well) and amyloid-β contained in some cadavers’ pituitaries, may have led to the observed co-occuring of Creutzfeldt–Jakob disease and Alzheimer’s disease.

Introduction

Recently, Jaunmuktane et al. [1] found the characteristic deposits of amyloid-β protein associated with Alzheimer’s disease (AD) in brains of 36 to 51-year old adults who died of Creutzfeldt-Jakob disease (CJD). These subjects were not genetically predisposed to AD and had no clinical signs of AD, but contracted CJD after treatment with prion-contaminated human growth hormone (GH) extracted from cadaver-derived pituitaries. The authors suggested that interhuman transmission of AD had occurred, because of the amyloid-β that was present in the injected extracts [1]. In previous experiments, mice developed plaques when brain extracts containing amyloid-β were injected in their brains or abdomens [2]. Amyloidoses are heterogeneous systemic or localized diseases, and they are characterized by pathological extracellular deposition of peptides derived from autologous proteins. At least 33 of these proteins, belonging to distinct, unrelated superfamilies, and with different localizations and functions, are known [3]. We have been interested in providing a unifying theory that would explain why proteins so diverse can precipitate and deposit as amyloid. We found that they share the amino acid sequence homology, as summarized by the motif “D/E/N/Q, A/G, D/E/N/Q, 4–20X, V/I/L/M, D/E/N/Q, R/K/H, 0–6X, V/I/L/M, 0–5X, F/Y/W, 4–5X, D/E/N/Q, 0–2X, R/K/H, 0–12X, A/G, V/I/L/M, 0–3X, V/I/L/M, 0–2X, A/G” [3]. Here, we searched for the occurrence of such a motif in the amino acid sequence of GH. Our results, together with the literature data missing in both the paper by Jaunmuktane et al. [1] and subsequent commentaries, minimize the contagious nature of the iatrogenically-acquired coexistence of CJD and AD.
Materials and Methods
Following our usual bioinformatics approach [4] we extracted the amino acid sequence of GH from the Entrez Protein database (http://www.ncbi.nlm.nih.gov/protein) and probed it for the presence of the aforementioned motif.

Results
Similar to cytokeratins 14 and 10, transthyretin, semenogelin I, and prion protein, GH has 2 sequences (residues 89–131 and 180–216 of the precursor, corresponding to residues 63–105 and 154–190 of the mature protein, respectively) that fit the motif. Either sequence shares 9 such residues with the amyloid-β precursor sequence 672–709 (sequence 655–692 of the mature protein). Additionally, either sequence shares 2 noncrucial residues with the amyloid-β sequence, and one to 4 noncrucial residues with the prion protein sequences (Fig. 1).

The topic of "infectious" interhuman transmission of AD through cadaver-derived GH extracts contaminated with neurodegenerative disease-associated proteins (NDAPs) is controversial. Before the publication of the paper by Jaunmuktane et al. [1], Irwin et al. [6] had found "no evidence to support concerns that NDAPs underlying AD transmit disease in humans despite evidence of their cell-to-cell transmission in model systems of these disorders".

A number of hormones are involved in amyloidoses: atrial natriuretic factor, found in isolated cardiac atrial amyloidosis; insulin – bovine [7], porcine [8] or even recombinant human [9] –, which form subcutaneous nodules at sites of injection; and amylin, calcitonin, GH, and prolactin (PRL), found in amyloidosis associated to insulinoma or type 2 diabetes mellitus, medullary thyroid cancer, GH-secreting and PRL-secreting pituitary adenomas, respectively [10–12].

The paper by Jaunmuktane et al. [1] misses literature data on intratumoral amyloidosis in various polypeptide hormone producing tumors [13], including GH-secreting and PRL-secreting adenomas [14,15]. These tumors account for over 3-fourths of pituitary adenomas. Pituitary adenomas are detectable in 4–20 % of pituitary adenomas. Pituitary adenomas are detectable in 4–20 % of pituitary adenomas.

In brief, the intrinsic amyloidogenicity of GH, in the presence of contaminating prion protein (and perhaps PRL as well) and amyloid-β seeds injected into the abdomens of mice, rather than amyloid-β contained in some cadavers' pituitaries, may have led to the co-occurring CJD and AD observed by Jaunmuktane et al. [1]. This is similar to the experimental condition in which amyloid-β seeds injected into the abdomens of mice, rather than directly into the brain, cause cerebral amyloid-β deposition [2]. Injected GH (or fragments thereof) may find its/their port of entry into the brain [17]. Here, the overload of misfolded GH (or its amyloidogenic fragments) would catalyze aggregation and fibrillar deposition of both itself and any contaminating amyloid-related protein (prion protein and amyloid-β, in this case).

The driving force of the excess GH would explain the early onset of AD in the patients receiving the contaminated GH [1]. Possible contamination of cadaver-extracted GH by another amyloidotic pituitary hormone (PRL) would provide further burden to the overall amyloid deposition, and add to the explanation of why AD occurred at a relatively young age.

Conflict of Interest

The authors declare no conflict of interest.

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