# Growth Hormone and Cerebral Amyloidosis

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Key words
- somatotropin
- amyloid
- Alzheimer's disease
- bioinformatics
- pituitary
- microadenomas

## 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 had 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-occurring of Creutzfeldt–Jakob disease and Alzheimer's disease.

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## 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. Both contain 11 amino acids identical/homologous to the 14 invariable residues of 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**). Reinforcing our data, the Aggrescan software [5] predicts sequences 100–132 and 184–193 of GH precursor (sequences 74–106 and 158–167 of mature protein, respectively) to be amyloidogenic.

| Amyloid protein | aa | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CK5 | 416-468 | D | A | E | Q | R | G | E | L | A | L | K | D | 11 | L | Q | K | 4 | M | 5 | E | Y | Q | E | L | M | N | T | | K | L | | A | L | D | V | E | I | | | A |
| CK1 | 428-480 | D | A | E | Q | R | G | E | N | A | L | K | D | 11 | L | Q | Q | 4 | L | 5 | D | Y | Q | E | L | M | N | T | | K | L | | A | L | D | L | E | I | | | A |
| CK14-a | 140-184 | N | A | D | L | E | V | K | I | R | D | W | Y | Q | R | Q | R | 3 | I | 5 | Y | F | K | T | I | E | D | L | | R | N | K | I | L | T | A | T | V | D | N | A |
| CK14-b | 215-266 | E | A | D | I | N | G | L | R | R | V | L | D | 10 | M | Q | I | 6 | L | A | Y | L | K | K | N | H | E | E | | E | M | N | A | L | R | G | Q | V | G | | G |
| CK10-a | 190-250 | Q | G | E | P | R | D | Y | S | K | Y | Y | K | 9 | L | N | L | 6 | I | 5 | N | A | R | L | A | A | D | D | F | R | L | 6 | A | L | R | Q | S | V | E | | A |
| CK10-b | 335-382 | D | A | E | A | W | F | N | E | K | S | K | E | 4 | I | D | N | 4 | I | 2 | Y | K | S | E | I | T | E | L | R | R | N | 2 | A | L | E | I | E | L | Q | S | Q |
| Apo-AI | 25-69 | D | | E | P | P | Q | S | P | W | D | R | V | 7 | V | D | V | | L | K | D | S | G | R | D | Y | V | S | Q | F | E | 2 | A | L | G | K | Q | L | N | L | K |
| Apo-AII | 24-64 | Q | A | D | G | Q | D | M | Q | S | L | F | T | 2 | F | Q | S | | M | 2 | Y | G | K | D | L | V | E | K | A | K | T | S | E | I | Q | S | Q | A | K | A | Y |
| Apo-AIV | 57-105 | Q | L | N | A | L | | | F | Q | D | K | L | 9 | L | Q | K | 2 | V | P | F | A | T | E | L | H | E | | | R | L | 5 | K | L | K | E | E | I | G | K | E |
| Apo-E4 | 254-304 | V | A | E | V | R | A | K | L | E | E | Q | A | 4 | L | Q | A | 6 | L | 3 | F | E | P | L | V | E | D | M | Q | R | Q | 2 | G | L | V | E | K | V | Q | A | A |
| AL-λ | 4-42 | L | T | Q | P | P | S | A | S | G | T | P | G | | | Q | R | | V | 3 | C | S | G | G | N | F | D | I | G | R | N | S | V | N | W | Y | Q | V | H | P | G |
| AL-κ | 15-64 | V | G | D | R | V | T | I | T | C | Q | A | S | 3 | T | N | H | | L | 2 | Y | Q | Q | K | P | G | K | A | P | K | L | 10 | G | V | P | S | R | F | S | | G |
| SAA | 72-107 | A | A | E | A | I | S | D | A | R | E | N | | | I | Q | R | | F | | F | G | H | G | A | E | D | S | L | A | D | Q | A | A | N | E | W | G | R | S | G |
| β2M | 21-49 | | | | | | | | | | | | | | I | Q | R | | T | 5 | Y | S | R | H | P | A | E | N | G | K | S | N | F | L | N | C | Y | V | | S | G |
| TTR-a | 38-73 | D | A | | V | R | G | S | P | A | I | N | V | A | V | | H | | V | | F | R | K | A | A | D | D | T | W | E | P | F | A | S | G | K | T | S | E | S | G |
| TTR-b | 92-137 | E | I | D | T | K | | S | Y | W | K | A | L | 5 | H | E | H | 2 | V | V | F | T | A | N | D | S | G | P | R | R | Y | 3 | A | L | L | S | P | Y | S | Y | S |
| CysC | 41-80 | D | A | S | V | E | E | E | G | V | R | R | A | | L | D | F | | A | 3 | Y | N | K | A | S | N | D | M | Y | H | S | R | A | L | Q | V | V | R | A | R | K |
| Gel | 174-208 | S | G | | F | K | H | V | V | P | N | E | V | V | V | Q | R | | L | | F | Q | V | K | G | R | R | V | V | R | | | A | T | E | V | P | V | S | W | E |
| Gal7 | 67-105 | Q | G | S | W | G | R | E | E | R | G | P | G | 2 | F | Q | R | 5 | V | | L | I | I | A | S | D | D | G | F | K | | | A | V | | | | V | G | D | A |
| Actβ | 57-108 | E | A | Q | S | K | R | G | I | L | T | L | K | 2 | I | E | H | 6 | D | 5 | W | H | H | T | F | Y | N | E | L | R | V | 5 | P | V | L | | | L | T | E | A |
| SAP | 123-153 | I | A | E | F | W | I | N | G | T | P | L | | | V | K | K | G | L | 3 | Y | F | V | E | A | | Q | P | | K | | | I | V | | | | L | | | G |
| Tau | 603-651 | N | V | Q | S | K | | | | C | G | S | K | 11 | V | Q | | | I | V | Y | K | P | V | D | L | S | | | K | V | 7 | G | N | I | H | H | K | P | G | G |
| SGI-a | 225-281 | E | V | R | E | E | H | S | S | K | V | Q | T | 9 | L | Q | H | 4 | I | | F | S | T | Q | D | E | L | L | V | Y | N | 7 | N | L | N | Q | D | Q | Q | H | G |
| SGI-b | 282-333 | K | A | N | K | I | S | Y | Q | S | S | S | T | 11 | V | Q | K | D | V | 5 | Y | S | Q | T | E | | E | | | K | A | 2 | K | S | Q | K | Q | I | T | I | P |
| ODAM | 156-201 | Q | P | Q | Q | T | V | P | R | S | P | Q | Q | 2 | Q | Q | Y | 3 | I | P | F | Y | A | Q | F | G | Y | I | P | Q | L | 3 | A | I | S | G | G | Q | Q | Q | L |
| LF | 293-343 | Q | A | Q | E | K | F | G | K | D | K | S | P | 9 | G | Q | K | 2 | L | | F | K | D | S | A | I | G | F | S | R | V | 4 | D | S | G | L | Y | L | G | S | G |
| LAdh | 247-301 | T | A | S | S | S | Y | K | T | W | G | L | H | 10 | L | D | K | 3 | F | 2 | W | V | A | G | S | Y | G | N | D | Q | W | 5 | G | S | S | K | E | V | | T | G |
| ABri/ADan | 32-80 | D | A | V | A | V | | | D | C | K | D | P | 6 | G | Q | R | 6 | M | C | F | G | L | A | F | M | L | A | G | V | I | 2 | G | A | Y | L | Y | K | Y | F | A |
| Fibr-α | 664-705 | D | Q | E | T | S | | | L | G | G | W | L | 2 | Q | Q | R | 4 | L | N | F | N | R | T | W | Q | D | Y | K | R | G | F | G | S | L | N | D | E | G | E | G |
| LYSO | 33-73 | K | W | E | S | G | Y | N | T | R | A | T | N | 3 | G | D | R | S | T | D | Y | G | I | F | Q | I | N | S | | R | Y | W | C | N | D | G | K | T | P | G | A |
| ANF | 124-151 | | | S | L | R | R | S | S | C | F | G | G | R | M | D | R | | I | 2 | Q | S | G | L | G | C | N | S | F | R | Y | | | | | | | | | | | |
| CT | 85-116 | | | | | | | | | C | G | N | L | 8 | T | Q | D | | F | 2 | F | H | T | F | P | Q | | | | | | T | A | I | G | V | G | A | P | | |
| IAPP | 34-66 | | | | | | | | K | C | N | T | A | 3 | T | Q | R | | L | 2 | F | L | V | H | S | S | N | N | F | | | G | A | I | L | S | S | T | N | V | G |
| Ins | 14-71 | L | A | L | W | G | P | D | P | A | A | A | F | 10 | V | E | A | 3 | V | 5 | F | F | Y | T | P | K | T | R | | R | E | 5 | V | G | Q | V | E | L | G | G | G |
| PRL | 27-79 | G | G | A | A | R | | | | C | | Q | V | 5 | F | D | R | A | V | 4 | Y | I | H | N | L | S | S | E | M | F | S | 11 | F | I | T | K | A | I | N | S | C |
| Aβ | 672-709 | D | A | E | F | R | H | D | S | G | Y | E | V | H | H | Q | K | | L | V | F | F | A | E | D | V | G | S | N | K | | G | A | I | I | G | L | M | V | G | G |
| PriP-a | 215-253 | I | T | Q | Y | E | R | E | S | Q | A | Y | Y | | | Q | R | 3 | M | 2 | F | S | S | P | P | V | I | L | L | I | S | | F | L | I | F | L | I | V | | G |
| PriP-b | 91-124 | Q | G | G | G | T | H | S | | | | | | | | Q | W | | N | K | P | S | K | P | K | T | N | M | K | H | M | 3 | A | A | A | G | A | V | V | G | G |
| hGH-a | 89-131 | N | R | E | E | T | Q | Q | K | S | N | L | E | | L | L | R | 3 | L | 4 | W | L | E | P | V | | Q | F | L | R | S | 2 | A | N | S | L | | V | Y | G | A |
| hGH-b | 180-216 | D | A | L | L | K | N | Y | G | L | L | Y | C | 4 | M | D | K | | V | 2 | F | L | R | I | V | | Q | C | | R | | | S | V | E | G | S | C | | | G |
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
| Amyloid motif | | D Q E N | | A G | E Q D N | | | | | | | | | | V L I M | Q D E | R K H | | V L I M | | F Y W | | | | | | D E N | | | R K H | | | A G | L I | | | | V I L M | | | G A |

Groups of homologous aminoacids whose frequency in a column is >50% are typed in bold on a gray background; in the "Amyloidogenic motif" section, for each group, aminoacids are shown in decreasing order of frequency in the column. Alignment includes two regions (labeled as "-a" and "-b") of cytokeratin 14, cytokeratin 10, transthyretin, prion protein, semenogelin I and growth hormone because either fitted the alignment. ABri and ADan are grouped because the segments of interest are identical. CK5 = cytokeratin 5 (AC P13647.3), CK1 = cytokeratin 1 (AC P04264.6), CK14-a and CK14-b = cytokeratin 14 (AC P02533.4), CK10-a and CK10-b = cytokeratin 10 (AC P13645.6), Apo-AI = Apolipoprotein AI precursor (AC P02647), Apo-AII = Apolipoprotein AII precursor (AC AAA37248), Apo-AIV = Apolipoprotein AIV precursor (AC AAA51744), Apo-E4 = Apolipoprotein E4 (AC P02649.1) , AL-λ = Ig-lambda chain V-I region VOR (AC P01699), AL-κ = Ig-kappa chain (AC 3DVF_A), SAA = Serum amyloid A, alpha precursor (AC P0DJI8.1, formerly AC P02735; new code effective from July 13, 2012), β2M = beta2-microglobulin precursor (AC P61769), TTR-a and TTR-b = Transthyretin precursor (AC P02766), CysC = Cystatin C precursor (AC P01034), Gel = Gelsolin precursor (AC P06396), Gal7 = Galectin-7 (AC NP_002298), Actβ = Actin beta (AC AAH13380), SAP = Serum amyloid P component (AC BAA00060), IAPP = Islet amyloid polypeptide precursor (AC P10997), Tau = Tau precursor (AC P10636), SGI-a and SGI-b = Semenogelin I precursor (AC CAA87636), ODAM = Odontogenic ameloblast-associated protein precursor (AC NP_060325), LF = Lactoferrin precursor (AC AAA59511), Ladh = Lactadherin precursor (AC NP_005919), ABri/ADan = ABri/ADan precursor (AC Q9Y287), Fibr-α = Fibrinogen alpha chain precursor (AC P02671), LYSO = Lysozyme (AC CAA32175), ANF = Atrial natriuretic factor precursor (AC P01160), CT = Calcitonin precursor (AC P01258), Ins = Insulin precursor (AC AAA59172), PRL = Prolactin precursor (AC CAA38264), Aβ = region 672-709 of Amyloid beta PP770 precursor (AC P05067), PriP-a and PriP-b = prion protein precursor (AC P04156), hGH-a and hGH-b = human growth hormone precursor (AC P01241).
Aminoacids are indicated in one-letter code, as follows: A = Alanine, C = Cysteine, D = Aspartic Acid, E = Glutamic Acid, F = Phenylalanine, G = Glycine, H = Histidine, I = Isoleucine, K = Lysine, L = Leucine, M = Methionine, N = Asparagine, P = Proline, Q = Glutamine, R = Arginine, S = Serine, T = Threonine, V = Valine, W = Tryptophan, Y = Tyrosine.

**Fig. 1** Alignment of the segments of precursors of amyloidogenic proteins and of human growth hormone, which contain the amyloid motif [3].

## Discussion

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 or 10–38% of adults undergoing cranial imaging studies with computed tomography or magnetic resonance imaging for reasons other than pituitary disease, and 11% of pituitaries at autopsy [16]. Hence, it cannot be excluded that some pituitaries, which were used to extract GH, contained clinically silent GH-secreting and/or PRL-secreting microadenomas, a fraction of which containing GH-associated and/or PRL-associated amyloid deposits. The corollary is that cadaveric GH-treated patients reported by Jaunmuktane et al. [1] might have received a fraction of GH (with or without PRL) that already was an amyloid seed. Thus, Jaunmuktane et al. [1] should have looked for GH and PRL in intracerebral amyloid deposits, including pituitary. Indeed, it cannot be excluded that the injected GH preparations were contaminated by PRL.

In brief, the intrinsic amyloidogenicity of GH, in the presence of contaminating prion protein (and perhaps PRL as well) and 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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