Amyloid β Protein Species in Cerebrospinal Fluid and in Brain from Patients with Down's Syndrome

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The pathological changes of Alzheimer's disease (AD), including excessive deposition of fibrillar aggregates of amyloid β protein (Aβ) in the brain, are seen frequently in patients with Down's syndrome (DS) who survive beyond the age of 30 years. Although DS patients have been found to have increased amounts of Aβ1–42 in brain tissue[1] and increased concentrations of both Aβ1–40 and Aβ1–42 in plasma,[2] cerebrospinal fluid (CSF) Aβ concentrations in DS patients have not been analyzed to our knowledge. We used highly sensitive enzyme-linked immunosorbent assay[3–5] to measure the amounts of Aβ species in CSF and brain specimens from DS patients and compared them with specimens from previously described patients with neurological diseases not associated with dementia (diseased controls)[3] and patients with sporadic AD.

Five patients with DS diagnosed clinically or by chromosomal analyses were studied. Clinical profiles are given in the Table. Informed consent was obtained from each subject or a guardian as appropriate. We obtained CSF from patients and performed autopsies on 4 patients. Neuropathological examination showed typical AD changes.

Mean CSF concentrations of Aβ1–40 and Aβx–40 showed no statistically significant differences between DS subjects and diseased controls. On the other hand, Aβ1–42 in CSF from the DS group (181 ± 110 pM) was significantly lower than in CSF from the control group (323 ± 165 pM). Aβx–42 in CSF also was less abundant in the DS group than in controls but not significantly so (see Table). Aβ1–40, Aβx–40, and Aβx–42 as measured by enzyme-linked immunosorbent assay in brain tissue extracts were significantly more abundant in the DS group than in the AD group, although Aβ1–42 in brain did not differ significantly between the DS and AD groups (see Table).

The present observations confirmed that CSF concentrations of Aβ1–42 in DS patients in their sixth decade were significantly lower than in controls as previously reported for AD patients.[3] Enhanced deposition of Aβ in the brain resulting from adsorption of soluble Aβ1–42 to existing plaques or from decreased passage of Aβ1–42 from brain into CSF appears to be occurring in DS patients in their fifth decade. Measuring CSF Aβ1–42 concentrations might prove useful as an inverse index of cerebral Aβ deposition in DS patients. In contrast to Aβ1–42, Aβ1–40 in CSF was not decreased in DS patients even though Aβ1–40 was significantly more abundant in brain extracts from the DS group than in extracts from the AD group. Considering that Aβ1–40 shows a greater increase in plasma in DS than does Aβ1–42,[2] exaggerated production of Aβ1–40 may override enhanced deposition mechanisms in DS brain to result in CSF Aβ1–40 concentrations in DS patients that are similar to those seen in patients with other neurological diseases.

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Table. Summary of Patient Profiles, CSF Aβ Levels, and Levels of Aβ Species in the Cerebral Cortex

	CSF Aβ (pM)		Cerebral Cortex Aβ (nM/g of wet tissue)	
Age (mean ± SD [yr])	DS (n = 5) (55.3 ± 3.4 yr)	Diseased Control (n = 34) (67.9 ± 10.4 yr)	Down's Syndrome (n = 3) (53.0 ± 2.6 yr)	Sporadic AD (n = 6) (69.7 ± 8.6 yr)
Aβ1–40	1,870 ± 1,190	1,520 ± 616	124.0[b] ± 30.2	2.81 ± 4.42
Aβ1–42	181[a] ± 110	323 ± 165	4.61 ± 2.01	4.06 ± 1.65
Aβx–40	2,320 ± 926	2,560 ± 1,420	133.3[c] ± 31.1	4.89 ± 6.82
Aβx–42	201 ± 137	332 ± 178	116.3[d] ± 5.1	36.6 ± 9.40

[a–d]Significantly different from diseased control: $p < 0.05$, $p < 0.05$, $p < 0.05$, $p < 0.000001$, respectively.

Aβ = amyloid β protein; AD = Alzheimer's disease.

Basic Fibroblast Growth Factor Does Not Prolong Survival in a Transgenic Model of Familial Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting motor neurons in the spinal cord and brain. Ten percent of all ALS cases are familial; 25% of these cases have a mutation in the gene that encodes cytosolic Cu/Zn superoxide dismutase. Mice that express mutant superoxide dismutase 1 molecules die from a motor neuron degeneration resembling human ALS.[1]

Neuroprotective agents such as basic fibroblast growth factor (bFGF) may prolong survival in ALS mice. bFGF is a growth factor that crosses the blood-brain barrier when administered by subcutaneous injection and has trophic effects on neurons and glial cells.[2] bFGF also protects neurons against excitotoxicity and oxidative stress.[2] We therefore analyzed the effect of bFGF on disease phenotype in ALS mice.

Beginning at 30 days of age, mice received bFGF by intraperitoneal injection twice weekly at doses of 0, 15, 100, 200, or 500 μg/kg. Onset of disease was defined by the appearance of tremulousness and weakness in the hind limbs. Euthanasia was performed when animals were too weak to roll over in 30 seconds.

bFGF had no effect on onset of clinical disease or survival in the ALS mice. Mean lengths of survival for the trial groups were: 133.45 days (SD, 9.3; 0 μg/kg; n = 20), 129.33 days (SD, 12.8; 15 μg/kg; n = 24), 126.29 days (SD, 15.8; 100 μg/kg; n = 21), 130.75 days (SD, 11.5; 200 μg/kg; n = 8), and 132.29 days (SD, 10.4; 500 μg/kg; n = 7).

Survival has been prolonged in these ALS transgenic mice by riluzole, gabapentin,[3] creatinine,[4] and D-penicillamine.[5] *N*-Acetylcysteine and two neuronal nitric oxide inhibitors had no effect on survival in this mouse model. Our current results suggest that intraperitoneal injections of bFGF also do not delay motor neuron death in this mouse model of familial ALS.

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Reply

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We thank Drs Hattori, Higuchi, and Tsuji for their particular attention to our study. They report an interesting observation of transient cerebral arteriopathy[1] associated with delayed meningitis and IgG antibody synthesis against varicella-zoster virus (VZV) in the cerebrospinal fluid (CSF). We also observed delayed and persistent meningitis in our series. A total of 4 of 7 patients with strokes following VZV infection had CSF investigations. A delayed meningitis was observed in 2 of these 4 patients. One of them presented with a stroke 40 days after varicella and had 47 lymphocytes per microliter (day 40 after stroke). The other one presented with a stroke 40 days after varicella infection and displayed a chronic meningitis: 25 lymphocytes per microliter at day 40, 22 lymphocytes per microliter at month 4, and 9 lymphocytes per microliter at month 5. One of these 3 patients with meningitis had positive IgG synthesis in the CSF (by enzyme-linked immunosorbent assay). The protein titer in the CSF was normal in all patients. VZV DNA was not detected by polymerase chain reaction (1 patient).

Concerning the risk of recurrence, 3 of 9 patients with a transient cerebral arteriopathy[1] had one recurrence of stroke 2 to 3 months after the first one. A total of 2 of these 3 patients had VZV infection prior to the initial stroke. No recurrence of stroke was observed in our 9 patients after they received antiplatelet treatment.

The varicella arteriopathy seems to be related to a delayed inflammatory reaction resulting from either direct viral invasion as suggested by Hattori and his colleagues, indirect inflammatory mechanisms triggered by VZV, or both. Further studies are required to clarify this point.

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