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ALZHEIMER'S DISEASE BIOMARKER PROFILE IN CEREBROSPINAL FLUID OF INDIVIDUALS WITH IMMUNE-MEDIATED ENCEPHALITIS

To the Editor: Amyloid-beta plaques are one of the neuropathological hallmarks of Alzheimer's disease (AD), but despite increasing knowledge, the precise role of this peptide and its precursor protein, amyloid precursor protein (APP), remains elusive.[1] During the last decade, much attention has been paid to the quantification of AD biomarkers in cerebrospinal fluid (CSF), resulting in their inclusion in the 2011 National Institute on Aging–Alzheimer's Association AD criteria.[2]

Low CSF Aβ1–42 levels are considered a useful diagnostic tool to determine amyloid deposition in the central nervous system. These abnormalities, accompanied by high total tau (t-tau) and more importantly phospho tau (p-tau) levels, in an individual with a cognitive impairment are highly suggestive of underlying AD pathology. The significance of an AD profile of CSF biomarkers in asymptomatic individuals is controversial.[1]

The aim of the present letter was to report six cases of immune-mediated encephalitis (IME) exhibiting a CSF biomarker profile mimicking that found in individuals with AD.

Table 1. Baseline Participant Characteristics

Case	Age	Sex	Clinical Manifestations	Etiology Antibodies	Severity, (Modified Rankin Scale)	Follow-Up, Months	Treatment	Brain Magnetic Resonance Imaging	Electroencephalography	CSF Values				CSF Biomarkers	
										Proteins, mg/dL	Glucose, mg/dL	Cytology	Aβ1–42, pg/mL	t-tau, pg/mL	p-tau, pg/mL
1	71	Male	Dementia, tremor, ataxia, myoclonus, hyperthermia	Unknown	4	19	Methylprednisolone, oral prednisone, mycophenolate	Normal	Abnormal	129	46	5	116.1	504.9	51.3
2	46	Male	Neuropsychiatric symptoms, (hallucinations, aggressive behavior), seizures	VGKC antibodies	3	20	Methylprednisolone	Unilateral hippocampal abnormality (in FLAIR)	Abnormal	20	68	0	196.7	52.4	20.0
3	60	Male	Neuropsychiatric symptoms (paranoid delusions, aggressive behavior), amnestic syndrome	Unknown	3	7	Methylprednisolone	Normal	Abnormal	120	58	2	576.4	66.3	25.0
4	48	Female	Seizures, severe mutism, akinesia	Unknown	5	18	Plasmapheresis	Cortical ribbon (diffusion-weighted imaging+FLAIR)	Abnormal	173	78	65	142.8	1253.9	19.4
5	66	Male	Dementia, faciobrachial dystonic seizures	VGKC antibodies	3	12	Methylprednisolone, plasmapheresis, oral prednisone	Mild atrophy	Abnormal	29	90	2	162.2	1127.9	37.9
6	75	Male	Cortical dementia	Unknown	3	12	Gammaglobulin, oral prednisone	Mild atrophy	Normal	40	69	0	433.2	261.5	49.4
Immune-mediated encephalitis													271.2 [a]	544.4	33.8
Individuals with Alzheimer's disease													423.8	596.4	78.5
Normal controls Argentine Alzheimer's Disease Neuroimaging Initiative[3]													824.2	207.4	37.5
Laboratory values for normal													>532	<100	<26.5

[a]AB42 immune-mediated encephalitis vs Alzheimer's disease vs control, $P < .005$.

VGCK = voltage-gated potassium channel; FLAIR = fluid-attenuated inversion recovery.

All of these individuals had rapid onset of dementia, with cognitive fluctuation, neuropsychiatric symptoms, and seizures. The individuals underwent brain magnetic resonance imaging (MRI), CSF analysis, and tumor screening. An antibody panel performed on CSF from two of these individuals was positive for voltage-gated potassium channel antibodies. All had almost complete clinical recovery after treatment with methylprednisolone or plasmapheresis. None had any evidence of malignancy at follow-up. CSF biomarker levels were compared with those of 13 individuals with a diagnosis of probable AD and 15 controls without dementia from the Argentine Alzheimer's Disease Neuroimaging Initiative[3] cohort.

Aβ42, t-tau, and p-tau CSF biomarkers were measured using commercially available enayme-linked immunosorbent assays (Innotest β- amyloid(1–42), Innotest hTAU-Ag and Innotest Phosphotau(181P), respectively; Innogenetics, Ghent, Belgium).

CSF t-tau levels in individuals with IME were higher than in individuals without dementia, which strongly suggests underlying neuronal damage. P-tau was just slightly higher; Aβ1–42 levels were low in all six cases (even lower than in individuals with AD) (Table 1).

Case 1 underwent three lumbar punctures (at onset and 2 and 12 months after treatment with intravenous corticosteroids and mycophenolate mofetil). CSF biomarker levels showed higher Aβ1–42 levels than in controls and low t-tau and p-tau. These molecular findings correlated with improvement in cognitive function

Case 1 also underwent positron emission tomography with Pittsburgh compound B (PiB-PET), which was negative for Aβ1–42 deposition. Case 4 underwent brain biopsy, which was negative for Aβ immune labeling and showed no evidence of AD neuropathology.

This is the first report, to the knowledge of the authors, on individuals with IME with a CSF biomarker profile mimicking that observed in individuals with AD. It has been generally accepted that low CSF Aβ1–42 levels indicate amyloid deposition in the central nervous system, but the same results were found in this group of six individuals with IME. The CSF biomarker levels of Case 1 showed significant fluctuation after treatment (normalization of Aβ1–42 levels and decrease in t-tau and p-tau), with a concomitant improvement in cognitive function. In addition, in two of the six individuals, Aβ1–42 brain accumulation was excluded using a second method (PiB-PET and neuropathology). These findings suggest the possibility that APP metabolism may be altered in individuals with IME. In this regard, APP cleavage by beta- and gamma-secretases may be altered in a way that results in low Aβ1–42 production. Also, it is possible to envision a scenario in which Aβ1–42 clearance, by proteases or through the blood–brain barrier, is increased.

AD biomarkers have been assessed in previous studies of individuals with multiple sclerosis and neuromyelitis optica, with contradictory findings. Most studies showed no differences between controls and individuals with the disease.[4] In the case of human immunodeficiency virus–related cognitive decline, lower CSF Aβ1–42 with lower tau and p-tau181 than in controls has been described.[5] As in individuals with AD, Aβ1–42 was low in individuals with CNS infections, suggesting an effect of neuroinflammation on amyloid metabolism.[6]

In conclusion, an AD-compatible CSF biomarker profile in individuals with rapid cognitive decline must be carefully interpreted to determine whether an immune-mediated disorder is involved. Also, the use of AD CSF biomarkers in individuals with cognitive disorders with acute onset is discouraged. A more-extensive evaluation of CSF biomarkers in individuals with IME is warranted to validate these findings.

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