Antibodies Associated With Autoimmune Encephalitis in Patients With Presumed Neurodegenerative Dementia

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Abstract

Background & Objectives

Autoimmune encephalitis (AIE) may present with prominent cognitive disturbances without overt inflammatory changes in MRI and CSF. Identification of these neurodegenerative dementia diagnosis mimics is important because patients generally respond to immunotherapy. The objective of this study was to determine the frequency of neuronal antibodies in patients with presumed neurodegenerative dementia and describe the clinical characteristics of the patients with neuronal antibodies.

Methods

In this retrospective cohort study, 920 patients were included with neurodegenerative dementia diagnosis from established cohorts at 2 large Dutch academic memory clinics. In total, 1,398 samples were tested (both CSF and serum in 478 patients) using immunohistochemistry (IHC), cell-based assays (CBA), and live hippocampal cell cultures (LN). To ascertain specificity and prevent false positive results, samples had to test positive by at least 2 different research techniques. Clinical data were retrieved from patient files.

Results

Neuronal antibodies were detected in 7 patients (0.8%), including anti-IgLON5 (n = 3), anti-LGI1 (n = 2), anti-DPPX, and anti-NMDAR. Clinical symptoms atypical for neurodegenerative diseases were identified in all 7 and included subacute deterioration (n = 3), myoclonus (n = 2), a history of autoimmune disease (n = 2), a fluctuating disease course (n = 1), and epileptic seizures (n = 1). In this cohort, no patients with antibodies fulfilled the criteria for rapidly progressive dementia (RPD), yet a subacute deterioration was reported in 3 patients later in the disease course. Brain MRI of none of the patients demonstrated abnormalities suggestive for AIE. CSF pleocytosis was found in 1 patient, considered as an atypical sign for neurodegenerative diseases. Compared with patients without neuronal antibodies (4 per antibody-positive patient), atypical clinical signs for neurodegenerative diseases were seen more frequently among the patients with antibodies (100% vs 21%, *p* = 0.0003), especially a subacute deterioration or fluctuating course (57% vs 7%, *p* = 0.009).

Glossary

AD = Alzheimer dementia; **AIE** = autoimmune encephalitis; **CBA** = cell-based assays; **DLB** = dementia with Lewy bodies; **IHC** = immunohistochemistry; **LN** = live hippocampal cell cultures; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **RPD** = rapidly progressive dementia; **VGCC** = voltage-gated calcium channel.

Discussion

A small, but clinically relevant proportion of patients suspected to have neurodegenerative dementias have neuronal antibodies indicative of AIE and might benefit from immunotherapy. In patients with atypical signs for neurodegenerative diseases, clinicians should consider neuronal antibody testing. Physicians should keep in mind the clinical phenotype and confirmation of positive test results to avoid false positive results and administration of potential harmful therapy for the wrong indication.

Cognitive dysfunction can be the presenting and most prominent symptom in patients with autoimmune encephalitis (AIE).[1,2] In contrast to neurodegenerative diseases, patients with antibody-mediated encephalitis might benefit from immunotherapy and improve considerably.[3,4] The presence of neuronal antibodies has been reported predominantly in rapidly progressive dementia (RPD).[5,6] However, AIE can present less fulminantly and is therefore potentially missed, resulting in diagnosis and treatment delay or even misdiagnosis.[7,8] We hypothesized that a small—but not insignificant—part of dementia syndromes is indeed caused by antibody-mediated encephalitis and underdiagnosed, withholding these patients' available treatments. The wish to diagnose every single patient with autoimmune encephalitis is in opposition with the risk for false positive tests.[9] Therefore, we strictly adhere to confirmation of positive test results with 2 different test techniques. In this study, we describe the frequency of neuronal antibodies in a cohort of patients diagnosed with various dementia syndromes in a memory clinic. In addition, we present clues to improve clinical recognition of AIE in dementia syndromes.

Methods

Patients and Laboratory Studies

In this retrospective multicenter study, we tested for the presence of neuronal antibodies in serum and CSF samples from patients diagnosed with neurodegenerative dementia diagnosis, included earlier prospectively in established cohorts at 2 large Dutch academic memory clinics (Erasmus University Medical Center, Amsterdam University Medical Centers, location VUmc)[10] between 1998 and 2016 (84% last 10 years). All patients fulfilled the core clinical criteria for dementia, as defined by the National Institutes of Aging-Alzheimer Association workgroups.[11] Patients were classified into 4 subgroups (based on diagnostic criteria): Alzheimer dementia (AD), frontotemporal dementia (FTD; both behavioral variant and primary progressive aphasia [PPA]), dementia with Lewy bodies (DLB), and other dementia syndromes.[11-14] Rapidly progressive dementia was defined as dementia within 12 months or death within 2 years after the

appearance of the first cognitive symptoms.[15] Patients with vascular dementia were not included. Clinic information was retrieved from the prospectively collected data. A subacute deterioration was defined as a marked progression of symptoms in 3 months and a fluctuating course as a disease course fluctuating over a longer period (e.g., weeks to months; different from the fluctuations within a day as seen in some patients with DLB). Dementia markers were scored according to the reference values (per year and per center; included in Table 1).

All samples, stored in both cohorts' biobanks, were screened for immunoreactivity with immunohistochemistry (IHC), as previously described.[16] Preferably, paired serum and CSF were tested for optimal sensitivity and specificity. Samples that were showing a positive or questionable staining pattern were tested more extensively using validated commercial cell-based assays (CBA) and in-house CBA (eTable 1, links.lww.com/NXI/A869). In addition, these samples were tested with live hippocampal cell cultures (LN).[16,17] To ascertain specificity, only samples that could be confirmed by CBA or LN were scored as positive because there is a higher risk for false-positive test results in this population with a low a priori chance to have encephalitis.[9,18] If IHC was suggestive for antibodies against intracellular (paraneoplastic) targets, this was explored by a different IHC technique.[19] Anti-thyroid peroxidase (TPO), voltage-gated calcium channel (VGCC), or low titer glutamic acid decarboxylase antibodies were not tested for because these are generally nonspecific at these ages and are not associated with dementia syndromes.

Antibody-positive patients were described exploratory and compared with a randomly selected antibody-negative group (ratio 1:4) matched for memory clinic, dementia subtype, sex, and age (±5 years). For these comparisons, medical records were additionally assessed for both the antibody-positive and antibody-negative patients. All antibody-positive patients were reviewed by a panel consisting of neurologists specialized in neurodegenerative (F.J., H.S., J.S.) or autoimmune diseases (J.V., P.S.S., M.T.), and a consensus classification of AIE vs AIE with a neurodegenerative dementia comorbidity was reached.

Table 1 Patient Characteristics of Auto-antibody Positive Patients

	1	2	3	4	5	6	7
Antibody	IgLON5	IgLON5	IgLON5	DPPX	LGI1	LGI1	NMDAR
Sex	F	F	F	M	F	M	F
Age at onset, years	53	66	71	61	61	68	74
Clinical dementia diagnosis	AD	AD, primary progressive aphasia	AD, posterior cortical atrophy	DLB	AD	FTD with ALS	AD, primary progressive aphasia
Duration onset to dementia diagnosis, months	108	18	60	12	36	49	42
Presenting symptom	Memory disorders	Language disorders	Visual disorders	Memory disorders	Memory disorders	Behavioral disorders	Language disorders
Symptoms during disease course	Slow progressive memory disorders. Subacute deterioration in months, severe apraxia, aphasia, myoclonus, hallucinations, delusions, and behavior problems. Admission to a closed psychiatric ward.	Word retrieval and phrase difficulties. Mild cognitive decline.	Progressive visuoperceptual and spatial disorders, apraxia, dyscalculia, mild behavioral disturbances, restless legs syndrome, and myoclonus. No sleep disorders.	Memory disorders, altered gait, slurred speech, orthostatic hypotension, obstipation, axial rigidity, asymmetric hypokinetic-rigid syndrome, possible OSAS. Fluctuating disease course.	Slow progressive memory disorders. Five years after onset subacute deterioration with progressive cognitive disorders, behavior disturbances.	Slow progressive behavior problems. Four years after onset right-sided hand disability, fasciculations, cognitive decline, and speech problems.	Slow progressive language disorder followed by behavior problems, right-sided hand clumsiness and 1 generalized seizure.
Cognitive tests	MMSE 5/30 CDR 2	MMSE 13/27 CDR 0.5	MMSE 28/30 CDR 0.5	MMSE 22/30 CDR 0.5	MMSE 23/30 CDR 1	MMSE 27/30 CDR 1	MMSE 10/30 CDR 1
NPA	Severe cognitive and language disorder. Problems with concentration, executive function, praxis.	Severe speech problems. No apparent other cognitive disorders.	Disturbances on visual tests.	Learning disability and problems in speed, concentration, planning.	Memory disorder and mild speech problems.	Preoccupation hand function, severe speech problems, mild memory disorder.	Severe language disorders, decreased memory.
History of autoimmune disease	No	Rheumatoid arthritis	Ankylosing spondylitis	No	No	No	No
CSF	5 WBC, normal protein; tau and p-tau normal, AB42 ↓	Not performed	1 WBC, normal protein; tau ↑, p-tau ↑, AB42 normal	8 WBC, normal protein; tau ↑, p-tau ↑, AB42 normal	2 WBC, normal protein; tau ↑↑, p-tau ↑, AB42 normal	Not performed	0 WBC, normal protein; tau ↑, p-tau ↑, AB42 ↓
MRI	Diffuse atrophy	Mild medial temporal atrophy. Old hemorrhage left parietal-occipital. Superficial siderosis, multiple lobair microbleeds	Extensive posterior atrophy	Posttraumatic atrophy and gliosis left temporal lobe	Diffuse and hippocampal atrophy	Bilateral hippocampal temporal lobe atrophy	Not performed. CT severe atrophy left temporal lobe

Continued

**Table 1** Patient Characteristics of Auto-antibody Positive Patients *(continued)*

	1	2	3	4	5	6	7
Antibody	IgLON5	IgLON5	IgLON5	DPPX	LGI1	LGI1	NMDAR
EEG	Diffuse slowing, right parietal sharp waves	Multifocal slow wave activity predominantly left hemisphere	Mildly slow activity at temporal areas	Mild slowing background activity	Not performed	Not performed	Normal
Antibody tests, serum	IHC positive CBA positive	IHC positive CBA positive	IHC positive CBA positive	IHC negative CBA negative LN negative	IHC positive CBA positive LN positive	IHC positive CBA positive LN positive	N.A.
Antibody tests, CSF	IHC positive CBA positive	N.A.	IHC negative CBA negative	IHC positive CBA weak positive LN positive	IHC negative, CBA negative LN negative	N.A.	IHC positive CBA positive LN weak positive
Clinical FU	Progressive cognitive decline. Died 1.5 y after diagnosis	Deceased	Progression of visual disturbances. Died 4 y after diagnosis	Spontaneous gradual improvement and stabilization of cognitive disturbances	Gradual progression of cognitive disturbances. Unable to communicate. Requirement of help for personal care	Subacute deterioration, died 6 mo after diagnosis	Deceased
FU from onset (mo)	127[a]	120[a]	108[a]	87	158	55[a]	54[a]
Additional tests/ information	SPECT: bilateral parietotemporal hypoperfusion			DAT-SPECT: inconclusive	Mother rapidly progressive Alzheimer disease. Genetic analysis (including APP, C9orf72, PRNP) no abnormalities	EMG: axonal damage, fasciculations. No fulfillment El Escorial criteria No C9orf72 repeat expansion	
Final diagnosis	Anti-IgLON5 encephalitis	Anti-IgLON5 encephalitis and potentially comorbid neurodegenerative dementia (AD with vascular pathology)	Anti-IgLON5 encephalitis and PCA	Anti-DPPX encephalitis	Anti-LGI1 encephalitis	Anti-LGI1 encephalitis	Anti-NMDAR encephalitis and Alzheimer disease

Abbreviations: AB42 = amyloid beta 42; AD = Alzheimer disease; ALS = amyotrophic lateral sclerosis; CBA = cell-based assay; CDR = clinical dementia rating; DAT-SPECT = dopamine receptor-single-photon emission CT; DLB = diffuse Lewy body dementia; DPPX = dipeptidyl aminopeptidase-like protein 6; EEG = electroencephalography; F = female; FTD = frontotemporal dementia; FU = follow-up; IgLON5 = Ig-like domain-containing protein family member 5; IHC = immunohistochemistry; LGI1 = leucin-rich glioma inactivated protein 1; LN = live neurons; M = male; MMSE = mini-mental state examination; N.A. = not applicable; NMDAR = N-methyl-D-aspartate receptor; NPA = neuropsychological assessment; PCA = posterior cortical atrophy; p-tau = phosphor tau; WBC = white blood cells.
Bold text indicates significant *p* values (<0.05).
[a] Deceased.

Figure Flowchart of Patient Inclusion With Antibody Results
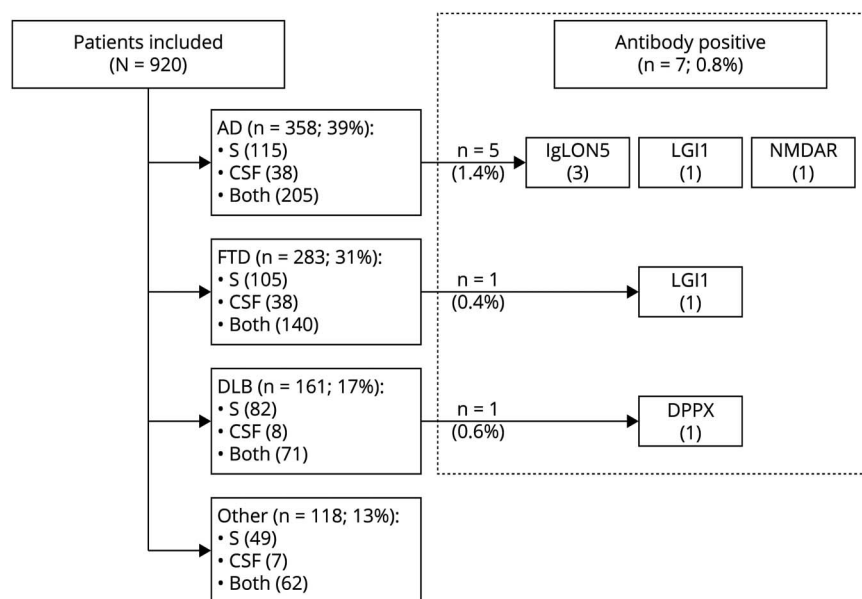
In total, 920 patients (1,398 samples) with a presumed neurodegenerative dementia syndrome were tested for the presence of neuronal antibodies in serum and CSF. Neuronal antibodies were detected in 7 patients (0.8%, 95% CI 0.2–1.3); five among the 358 Alzheimer disease patients. Subclassification of the 'other' group is provided in supplementary table eTable 2 (links.lww.com/NXI/A869). AD = Alzheimer disease; DLB = diffuse Lewy body dementia; DPPX = dipeptidyl aminopeptidase-like protein 6; FTD = frontotemporal dementia; IgLON5 = Ig-like domain-containing protein family member 5; LGI1 = leucin-rich glioma inactivated protein 1; NMDAR = N-methyl-D-aspartate receptor; S = serum.

Statistical Analysis

We used IBM SPSS 25.0 (SPSS Inc) and Prism 8.4.3 (GraphPad) for statistical analysis. Baseline characteristics were analyzed using the Fisher exact test, the Fisher-Freeman-Halton test, or the Kruskal-Wallis test, when appropriate. For group comparisons, encompassing categorical data, we used the Pearson χ^2 test or the Fisher-Freeman-Halton test, when appropriate. Continuous data were analyzed using the Mann-Whitney U test. All p-values were two-sided and considered statistically significant when below 0.05. We applied no correction for multiple testing, and therefore, p values between 0.05 and 0.005 should be interpreted carefully.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by The Institutional Review Boards of Erasmus University Medical Center Rotterdam and Amsterdam University Medical Center, location VUmc. Written informed consent was obtained from all patients.

Data Availability

Any data not published within this article are available at the Erasmus MC University Medical Center. Patient-related data will be shared on reasonable request from any qualified investigator, maintaining anonymization of the individual patients.

Results

In total, 1,398 samples from 920 patients were tested (Figure; in 478, both CSF and serum [52%]). Three-hundred fifty-eight patients were classified as AD (39%), 283 FTD (31%), and 161 DLB (17%). The fourth subgroup with other dementia syndromes consisted of 118 patients (13%), including progressive supranuclear palsy (n = 48, 5%) and corticobasal syndrome

(n = 29, 3%). The median age at disease onset was 62 years (range 16–90 years). Male patients were overrepresented (n = 542, 59%), and 60 patients (7%) fulfilled the criteria for rapidly progressive dementia (RPD; eTable 2, links.lww.com/NXI/A869).

Neuronal antibodies were detected in 7 patients (0.8%; 5 in the AD group: 1.4%; Figure), including anti-IgLON5 (n = 3), anti-LGI1 (n = 2), anti-DPPX (n = 1), and anti-NMDAR antibodies (n = 1; Table 1). Among these 7, 4 patients were diagnosed retrospectively with an exclusive diagnosis of AIE, while 3 patients were classified to have AIE (anti-IgLON5 [n = 2] and anti-NMDAR antibodies [n = 1]) with a neurodegenerative dementia comorbidity. No patients with antibodies fulfilled the criteria for RPD, yet a subacute deterioration later in the disease was reported in 3 patients. Atypical clinical signs for neurodegenerative diseases were present in 7 of 7 antibody-positive patients (100% vs 21% in antibody-negative patients, p = 0.0003; Table 2). These included a subacute deterioration (n = 3), myoclonus (n = 2), a fluctuating disease course over months (n = 1), a history of autoimmune disease (n = 2), and epileptic seizures (n = 1; Table 1). Brain MRI of none of the patients demonstrated abnormalities suggestive for active AIE, in particular no hippocampal swelling nor increased T2-signal intensity. CSF pleocytosis was found in 1 patient. CSF biomarkers (t-tau, p-tau, and Aβ42) were tested in 5 of 7 patients, and t-tau and p-tau were increased in 4, while a low Aβ42 was seen in 2. Of note, only 1 patient had the combination of reduced Aβ42 and increased p-tau/t-tau, and was diagnosed with a comorbid AD. No patient received immunotherapy. Two patients still alive (1 anti-LG1, 1 anti-DPPX positive) were contacted but refused to visit our clinic to try very delayed immunotherapy trials. It is of interest that the patient with anti-DPPX antibodies showed spontaneous improvement of cognitive disturbances, atypical for a pure neurodegenerative disease.

Table 2 Comparisons Between Patients With Neuronal Auto-antibodies and Antibody-Negative Patients

	Antibody-positive (n = 7)	Antibody-negative (n = 28)[a]	p Value
Sex (male)	2 (29%)	8 (29%)	1.00
Ethnicity			0.75
White	6/6 (100%)	20/22 (91%)	
Asian	0	1/22 (5%)	
African	0	1/22 (5%)	
Age at onset, median in years (IQR, range)	66 (61–72, 53–74)	62 (58–66, 53–79)	0.24
Age at diagnosis (IQR, range)	68 (63–77, 63–78)	66 (61–67, 55–82)	0.19
Onset to diagnosis, median in years (IQR, range)	3 (2–5, 1–10)	3 (1–5, 1–10)	0.44
RPD	0	1 (4%)	1.00
Atypical symptoms[b]	7 (100%)	6 (21%)	**0.0003**
Subacute deterioration or fluctuation	4 (57%)	2 (7%)	**0.009**
History of autoimmune disease	2 (29%)	2 (7%)	0.17
Family history of AID	0	0	—
Symptom onset			0.51
Memory disorders	3 (43%)	16 (57%)	
Behavioral changes	1 (14%)	1 (4%)	
Other	3 (43%)	11 (39%)	
Symptoms			
Memory disorders	6 (86%)	27 (96%)	0.37
Behavioral changes	4 (57%)	10 (36%)	0.40
Seizures	1 (14%)	0	0.20
Speech problems	5 (71%)	17 (61%)	0.69
Movement disorders	3 (43%)	4 (14%)	0.12
Muscle stiffness	1 (14%)	4 (14%)	1.00
Sleep disorder	2 (29%)	3 (11%)	0.26
Autonomic symptoms	1 (14%)	1 (4%)	0.37
Ancillary testing			
Tumor screening	0	0	—
MMSE (IQR, range)	22 (10–27, 5–28)	24 (18–26, 7–30)	0.28
NPA performed	7	27	
CSF analyzed	5/7 (71%)	27/28 (96%)	0.10
Onset to CSF, median in years (IQR, range)	3.6 (2.2–7.6, 1.4–10.2)	2.6 (1.1–4.1, 0.7–7.6)	0.20
WBC >5 cell/μL	1/5 (20%)	2/27 (7%)	0.41
Total protein >0.58 g/L	1/5 (20%)	2/26 (8%)	0.42
Total tau, high[c]	4/5 (80%)	22/27 (82%)	1.00
Phospho tau, high[c]	4/5 (80%)	20/26 (77%)	1.00
Aβ42, low[c]	2/5 (40%)	16/28 (57%)	0.64
MRI brain performed	6 (86%)	28 (100%)	0.20

Continued

	Antibody-positive (n = 7)	Antibody-negative (n = 28)[a]	p Value
Atrophy	6/6 (100%)	25 (89%)	1.00
Mesiotemporal hyperintensity	0	0	
EEG abnormal	4/6 (67%)	7/11 (64%)	1.00
EEG epileptic	0	0	
EEG slow	2/3 (67%)	6/10(60%)	1.00
mRS initial	2 (2–3, 1–3)	2 (2–2, 1–3)	0.77
CDR initial	1 (0.5–1, 0.5–2)	1 (0.5–1, 0.5–2)	0.75
Deceased	5 (71%)	20/27 (74%)	0.89
Follow-up, median months from onset (IQR, range)	68 (54–120, 32–120)	60 (44–84, 17–156)	0.39

Abbreviations: AID = autoimmune disease; Aβ42 = amyloid beta 42; CDR = clinical dementia rating; EEG = electroencephalography; IQR = interquartile range; MMSE = mini-mental state examination; mRS = modified Ranking scale; NPA = neuropsychological assessment; RPD = rapid progressive dementia; WBC = white blood cells.
[a] Antibody-negative patients were matched 4:1 for memory clinic of assessment, dementia subtype, sex, and age (±5 y).
[b] Atypical symptoms were RPD, pleocytosis, subacute deterioration, fluctuating disease course, myoclonus, history of autoimmune disease, and epilepticus seizures.
[c] Dementia markers scored according to the reference values per year and per center.

Compared with the patients without neuronal antibodies, subacute cognitive deterioration or fluctuating course was present more frequently (4/7 [57%] vs 2/28 [7%], p = 0.009). Although movement disorders (myoclonus) and autoimmune disorders were present in 2 of 7 patients each, this did not reach significance (Table 2).

Discussion

In this large, multicenter, cohort study consisting of patients with a presumed neurodegenerative dementia diagnosis, we show that a small, but clinically relevant proportion (0.8%) have neuronal antibodies. In this particular group, 4 of 7 antibody-positive patients presented with an atypical clinical course (subacute deterioration or fluctuating disease course), which is considered as a clinical clue ('red flag') for an antibody-mediated etiology of dementia.[4] It is important that a fluctuating disease course was observed over a longer period (e.g., weeks or months) in AIE and should not be confused with shorter fluctuations of cognition or alertness (over the day) in DLB. Other known red flags, which we observed in these 7 patients, were myoclonus, epilepsy, pleocytosis, or a history of autoimmune disorders, as described earlier.[1,4-6] Compared with antibody-negative patients, no significant difference was found related to these symptoms alone, probably due to the low number of positive patients and related low power. However, atypical clinical signs for neurodegenerative diseases together were seen significantly more frequently in the antibody-positive group. Within this cohort mostly devoid of patients with RPD, none of the antibody-positive patients fulfilled the criteria for RPD, nor ancillary testing showed specific signs for AIE in most patients. This implicates that AIE can resemble more protracted, progressive neurodegenerative dementia syndromes, as we reported earlier.[1]

Three antibody-positive patients had IgLON5 antibodies, which is a very rare and known to have heterogeneous (chronic) clinical manifestations, including pronounced sleep problems, cognitive dysfunction, and movement disorders.[20,21] Misdiagnosis with progressive supranuclear palsy (PSP) is reported, mainly associated with the preceding movement disorders. In addition, half of the patients have cognitive impairment of whom 20% fulfilled clinical criteria for dementia.[21] It is of interest that IgLON5 disease shares features with neurodegeneration because autopsy studies showed tau deposits.[22] However, there is a strong HLA association,[20] and studies show that antibodies directly bind to surface IgLON5 on neurons and directly alter neuronal function and structure,[23] suggesting a primary inflammatory disease.

In previous research, a notably higher frequency (14%) of neuronal antibodies in patients with dementia was reported by Giannocaro et al.[24] The discrepancy with our test results is probably explained by differences in patient selection and antibody testing methodology. First, 30% of the patients in the cohort described by Giannocaro et al. demonstrated CSF inflammatory abnormalities, indicating a relatively high pretest probability of antibody-positivity compared with our study.[24] A lack of CSF pleocytosis probably better represents the population of memory clinics. Second, the previous study exclusively tested serum by cell-based assay without confirmatory tests nor testing antibodies in CSF.[24] We only considered antibody test results positive when confirmed by additional techniques to avoid suboptimal specificity and false-positive test results.[9]

Previous studies, including our own, suggested RPD as a relevant red flag for AIE,[1,4,9,25] but we cannot determine this from our study based on the design of our study. We included patients at tertiary memory clinics without overt signs or

symptoms suggestive for encephalitis. Therefore, the amount of patients with RPD included was very limited (7%), comparable with other large dementia cohort studies, as was the amount of patients with abnormal ancillary testing suggestive for AIE because this would have prompted a different approach than referral to a tertiary memory clinic. These patients with RPD and ancillary testing suggestive of AIE were not included in our study. Inclusion of those patients would have likely increased our rate of positivity.

The strength of our study is the large number of paired samples (serum and CSF combined) from a cohort with various presumed neurodegenerative diseases without AIE suspicion, representative for academic memory clinics. A limitation is the lack of neuropathologic data to support our findings and make diagnoses of neurodegeneration or inflammation definite. To confirm if the symptoms are related to the presence of antibodies, we tried to overcome this concern in different ways. First, the presence of antibodies in serum and CSF was confirmed by different techniques (cell-based assay, tissue immunohistochemistry, and cultured live neurons), indicating optimal test specificity. Second, afterward patients were thoroughly reviewed by a panel of neurologists specialized in neurodegenerative or autoimmune disease to detect atypical signs and symptoms related to AIE. This is a very large cohort of patients with dementia examined for the presence of neuronal antibodies. Nevertheless, an important limitation of this study is the small number of antibody-positive patients, underpowering the probability to identify significant differences between antibody-positive and antibody-negative patients. The low number of patients with RPD has probably added to this small number, and a prospective study including patients with RPD is recommended. Nevertheless, several probable red flags could be identified. Diagnosing AIE in patients with dementia is highly relevant because these patients might respond to immunotherapy. Therefore, clinicians should test for neuronal antibody in patients demonstrating red flags suggestive for an autoimmune etiology, if possible early in disease course. When profound temporal lobe atrophy already has developed, little effect is to be expected. Red flags identified in this study are subacute deterioration or fluctuating course. Other red flags described previously, we also see reflected in our study, are autoimmune disorders, myoclonus, seizures, and pleocytosis.[1,4-6] Preferably, both serum and CSF should be tested and confirmed by additional techniques. Always consider the possibility of a false positive test result, especially when only using a single technique (like the commercial cell-based assay). If the clinical phenotype is atypical, confirmation in a research laboratory should be mandatory. The use of antibody panels is discouraged, especially including the paraneoplastic blots, because these are associated with higher risks of lack of clinical relevance.[26] This caution is even more warranted for tests not associated with neurodegenerative syndromes, but with a history of nonspecificity, including VGKC (in the absence of LGI1 or CASPR2), VGCC, anti-TPO, and low-titer anti-GAD65.[27-30] Further research should focus on improving clinical recognition of AIE in patients with dementia determining the effect of immunotherapy in this specific patient category and assessing the frequency of AIE in RPD.

In conclusion, we have shown that a clinically relevant, albeit small proportion of patients with a suspected neurodegenerative disease and nonrapidly progressive course have neuronal antibodies indicative of AIE.

Publication History

Appendix Authors

Name	Location	Contribution
Anna E.M. Bastiaansen, MD	Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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Charlotte Teunissen, PhD	Amsterdam Neuroscience, Neurodegeneration; Neurochemistry Laboratory, Department of Chemistry, Amsterdam UMC Location VUmc, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Esther de Graaff, PhD	Department of Biology, Faculty of Science, Utrecht University, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
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Manuela Paunovic, PhD	Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands	Major role in the acquisition of data; analysis or interpretation of data
Suzanne C. Franken, MSc	Department of Neurology, Erasmus University Medical Center, Rotterdam, The Netherlands	Major role in the acquisition of data; analysis or interpretation of data
Marco W.J. Schreurs, PhD	Department of Immunology, Erasmus University Medical Center, Rotterdam, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content

Continued

Appendix *(continued)*

Name	Location	Contribution
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