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LETTER

Frontotemporal dementia associated with intrathecal antibodies against axon initial segments

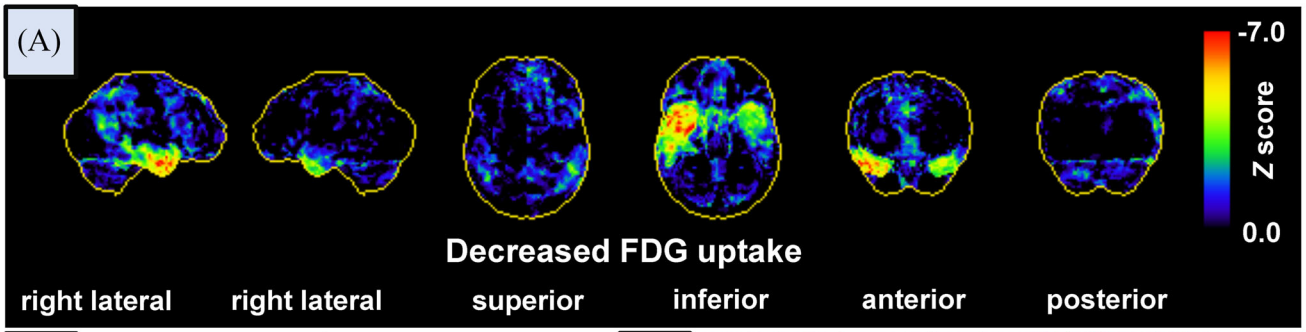
A recent publication by del Campo and colleagues (2022) summarized the current evidence of cerebrospinal fluid (CSF) biomarkers in frontotemporal dementia (FTD).[1] In addition to the established CSF biomarkers of neurodegeneration,[1] autoimmune mechanisms could be associated with FTD.[2,3] Underlying autoimmune encephalitis or autoimmune psychosis can be treated with immunotherapies.[3,4] The present article illustrates a paradigmatic case study in which routine diagnostic findings revealed the presence of neurodegenerative FTD[5] and novel neuronal autoantibodies leading to the conclusion of possibly autoimmune-modulated neurodegenerative FTD.

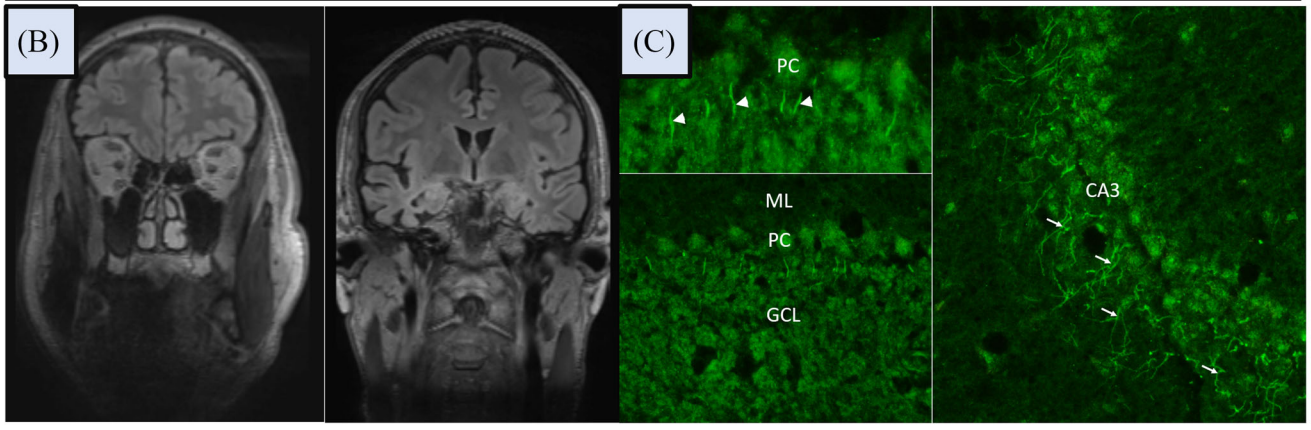
The 57-year-old male developed cognitive deficits, including substantial memory impairment, over 5 months, followed by a first acute severe psychotic decompensation, including auditory hallucinations, disorganized thinking, and suicidality due to the stress of hearing his own thoughts. His productive psychotic symptomatology regressed under treatment with aripiprazole (15 mg). Mirtazapine (30 mg) led to normalization of his sleep disturbances. However, the patient still suffered from concentration deficits, memory problems, anxiety, flat affect, and reduced energy levels. Neuropsychological testing revealed deficits in reaction time with or without sound and deficits in verbal learning and memory abilities. Further diagnostic work-up resulted in findings reminiscent of neurodegenerative FTD. Magnetic resonance imaging (MRI) demonstrated right-sided anterior temporal lobe atrophy. [^{18}F]Fluorodeoxyglucose positron emission tomography (FDG-PET) of the brain revealed right-ward asymmetric temporal polar hypometabolism compatible with right temporal variant of FTD (rtvFTD).[6] CSF showed blood–CSF barrier disturbance and tauopathy. All well-characterized neuronal autoantibodies were negative. However, in tissue-based assays,[7] a strong autoantibody staining against axon initial segments (AIS) was identified in the CSF (+++) and also weaker in serum. The binding pattern was reminiscent of anti-tripartite motif-containing protein 46 (TRIM46) autoantibodies, a marker of paraneoplastic neurological syndromes.[8] However, testing for TRIM46 autoantibodies remained negative using a cell-based assay. Therefore, novel autoantibodies against another AIS antigen can be assumed to exist.

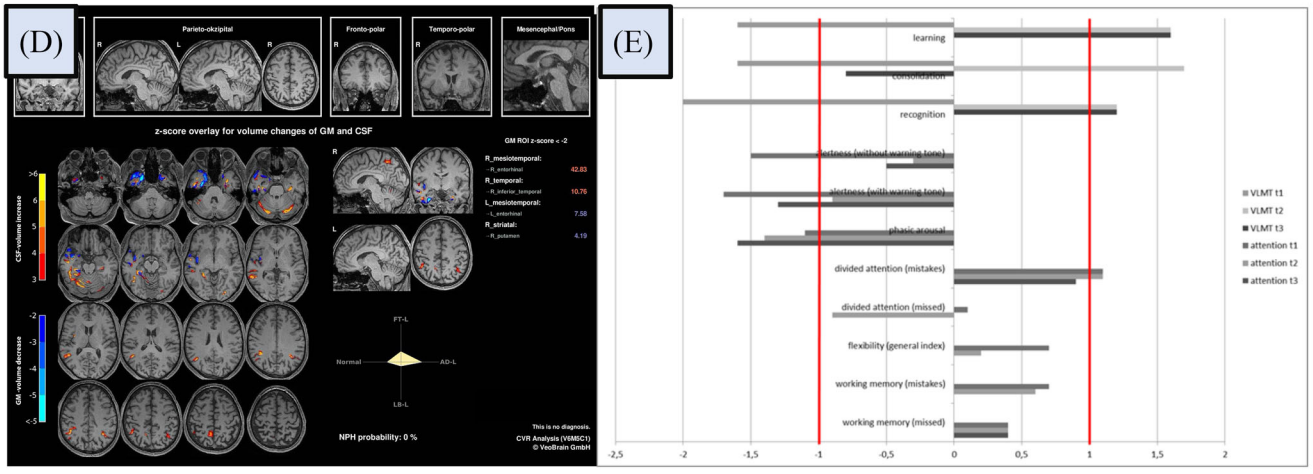
After a multidisciplinary case discussion, immunotherapy with plasmapheresis (five sessions across 5 days) followed by azathioprine (up to 150 mg per day) was initiated. After plasmapheresis, mood and concentration improved (the patient felt "more receptive"), and anxiety disappeared. Neuropsychological follow-up after 3 months showed improvements, and the patient returned to work. Glutamate levels (measured using MR spectroscopy) in the right insula were decreasing parallel to the clinical improvement. Affective flattening and partially reduced energy persisted. The FDG-PET follow-up showed no relevant change (Figure 1).

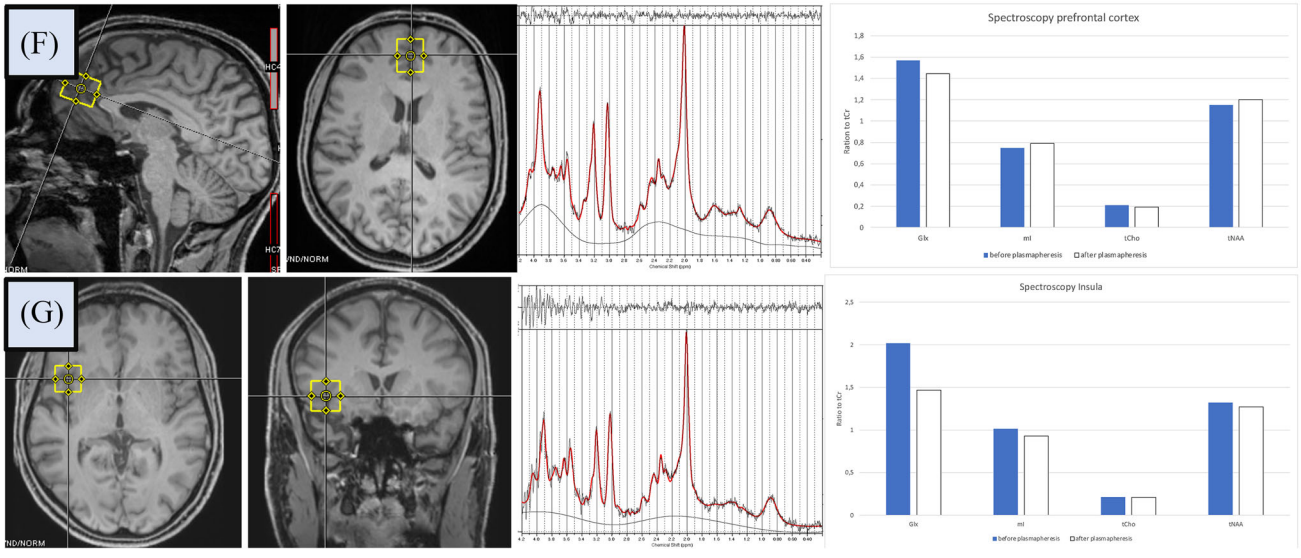
There are three different scenarios on how autoantibodies against AIS could play a role in the presented case with FTD syndrome: (1) the autoantibodies may directly cause a new variant of autoimmune encephalitis, (2) they could be irrelevant concomitant phenomena, or (3) they could have a disease-modulating effect.

1. The acute psychotic exacerbation[4] and findings of autoantibodies against AIS similar to those directed against the antigen TRIM46 (with comparable tissue-based assay findings, but a different target antigen)[9] suggest a possible autoimmune encephalitis.[4,9] TRIM46 antibodies against AIS have previously been described in patients with paraneoplastic autoimmune encephalitis.[8,9] Since TRIM46 is a cytosolic protein, neurological symptoms are likely caused by a T-cell-mediated response against TRIM46.[8,9]
2. In contrast, the absence of TRIM46 as a target antigen, lack of an underlying malignancy, and brain imaging findings well compatible with neurodegenerative rtvFTD suggest that the autoantibodies could be mere just by coincidence and unrelated with the pathophysiology of the presented patient. The absence of inflammatory CSF routine markers and the lack of FDG-PET improvement after plasmapheresis may support such a conclusion. Accordingly, the clinical improvement could represent a placebo effect.
3. Finally, and favored by the authors, autoantibodies against AIS could modulate underlying neurodegenerative FTD. This pathophysiological possibility was discussed most recently in the context of anti-IgLON5 encephalitis, where disruption of the neuronal cytoskeleton by IgLON5 antibodies was reported.[3] Thus, exposure to newly developing antigens in AIS-proteins in the context of a neurodegenerative process such as FTD could be causative for the formation of autoantibodies against AIS. Increasing evidence supports the concept that autoantibodies binding to intracellular targets can clearly reach and bind to their antigen in vivo.[10] Accordingly, immunotherapy could provide delay in the progression of the disease or even clinical improvement (as objectified in









neuropsychological testing in our patient and which was associated with decreasing glutamate levels in the insula) by removing autoantibodies; but without reversing the underlying neurodegenerative FTD.

This case presentation suggests that future studies on FTD should include screening for novel neural autoantibodies from CSF. Such an approach could expand the current arsenal of CSF biomarkers in FTD[1] and optimally improve treatment approaches in similar patients.

AUTHOR CONTRIBUTIONS

D.E., K.N., K.R., N.V., H.P., and L.T.vE. were involved in the treatment of the patient. K.N. was responsible for the vision tests. K.R. performed the olfactory tests and a lumbar puncture. A.S. performed the neuropsychological testing. K.D. critically revised the manuscript. H.U. and T.L. performed the MRI measurements and interpreted the findings. N.V. was responsible for the immunological co-assessment. J.B. and P.T.M. performed the FDG-PET measurements and interpreted the findings. H.P. performed the tissue-based assays. H.P. and B.B. were responsible for the neurological co-assessment. All authors were critically involved theoretical discussion and composition of the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

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FIGURE 1 Functional, structural, and neurochemical imaging findings, autoantibody patterns from cerebrospinal fluid (CSF) using tissue-based assays on unfixed mouse brain slices, and neuropsychological test findings. Additional investigations (not shown), including olfactory tests (with normal results) and optical coherence tomography (crowded disc with micropapilla; norm variant), identified no specific changes. AD-L, Alzheimer dementia typical pattern; CA3, cornu ammonis 3 region of the hippocampus; CSF, cerebrospinal fluid; GCL, granule cell layer; Glx, glutamate+glutamine; FT-L, frontotemporal dementia typical pattern; GM, grey matter, L, left; LD-L, Lewy body dementia typical pattern; mI, myo-inositol; ML, molecular layer; NPH, normal pressure hydrocephalus; PC, Purkinje cell layer; ppm, parts per million; R, right; tCho, total choline; tCr, total creatine; t-NAA, total N-acetylaspartate; VLMT, verbal learning and memory test. (A) [^{18}F]Fluorodeoxyglucose positron emission tomography (FDG-PET) of the brain revealed right-ward asymmetric temporal polar hypometabolism compatible with right temporal variant of frontotemporal dementia (rtvFTD). Voxel-based statistical analysis revealed right-ward asymmetric, marked hypometabolism of the rostral temporal lobes and mild hypometabolism of the bilateral temporoparietal lobes (also right-ward asymmetric). Findings of voxel-based statistical analysis are presented as three-dimensional surface projections of regions with decreased FDG-uptake (color-coded z-score, compared with age-matched healthy control subjects; 50 min after injection of 208 MBq FDG; 10 min scan duration on a Vereos Digital PET/CT, Philips Healthcare, The Netherlands). No relevant changes of cerebral metabolism were observed at follow-up FDG-PET after approximately 3 months (not shown). Moreover, additional whole-body FDG-PET/CT excluded the possibility of a paraneoplastic syndrome (not shown). (B) Magnetic resonance imaging demonstrated right-side frontotemporal lobar degeneration with dilated external CSF spaces emphasized on the right temporal side and FLAIR hyperintensities in the parietal white matter. (C) Autoantibody staining in the CSF showed strong binding against axon initial segments (AIS) in the cerebellum (left) and hippocampus (right). Arrowheads mark the AIS of Purkinje neurons and arrows highlight the AIS of hippocampal granule cells. The well-characterized anti-neuronal autoantibodies against cell surface antigens in CSF and serum (NMDA-R/LGI1/CASPR2/AMPA1/2-R/GABA-B-R/DPPX) and against intracellular (Yo/Hu/CV2/CRMP5/Ri/Ma1/2/SOX1/Tr/Zic4/GAD65/amphiphysin) and glial (AQP4-IgG/MOG) antigens in serum were all negative. Furthermore, anti-neuronal autoantibodies against GFAP, flotillin, and TRIM46 from serum and CSF were also negative. Tau (510 pg/ml; ref.: <450 pg/ml) and phospho-tau levels in CSF were increased (105 pg/ml; ref.: <61 pg/ml) while ß-amyloid-quotient and alpha-synuclein were normal. The NSE in CSF was increased by 32.6 μg/L (ref.: from 3.7 to 16.6 μg/L). Routine CSF analysis showed a normal white blood cell count (1/μL; ref.: <5/μL), IgG index (0.45; ref.: < 0.7), and no oligoclonal bands. Blood-brain barrier dysfunction was detected with increased total protein levels of 723 mg/L (ref.: <450 mg/L) and elevated albumin quotients of 10.1 (ref.: $<6.5 \times 10^{-3}$). (D) A combined volume-based and region-based analysis method (https://www.veobrain.com/?page = veomorph) detected CSF volume increase mesiotemporal (z-score: 42.83; ref.: from -2 to +2) and temporal right (z-score: 10.76; ref.: from -2 to +2). Reduced gray matter volumes were detected mesiotemporal left (z-score: 7.58; ref.: from -2 to +2) and striatal in the putamen right (z-score: 4.19; ref.: from -2 to +2). (E) The neuropsychological testing included a test battery for attention performance (TAP) and the verbal learning and memory test (VLMT). The patient showed a significant improvement in verbal learning and memory abilities directly and 3 months after plasmapheresis. Although intrinsic alertness (without warning tone) improved in the second and third assessments, the reaction time preceding a cue stimulus (phasic arousal) deteriorated with time. Hence, deficits in basal responsiveness and reaction stability remained. Additional attentional functions were intact (average or above average) at all assessment times (ref.: from -1 to +1). (F) Single voxel spectroscopy (SVS) in the prefrontal cortex (voxel localization in the anterior cingulate cortex) showed no relevant differences in glutamate+glutamine (Glx), myo-inositol (mI), total choline (tCho), and total N- acetylaspartate (t-NAA) ratios (each related to total creatine [tCr]) before and approximately 3 months after plasmapheresis. The spectrum before plasmapheresis is shown. (G) SVS of the right insula identified a relevant decrease in Glx/tCr ratios after plasmapheresis; mI, tCho, and t-NAA ratios showed no relevant changes approximately 3 months after plasmapheresis. Again, the first spectrum before plasmapheresis is shown.

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