Correspondence

Biological Psychiatry

Novel Neuronal Autoantibodies in Huntington's Disease

To the Editor:

Autoimmune encephalitis is an important differential diagnosis in psychiatry, especially for psychotic or neurocognitive syndromes (1). Novel neuronal autoantibodies with yet unknown target antigens could be essential in this context (2). Recently, overlaps between autoimmune and neurodegenerative mechanisms have been described in neurology, paradigmatically in anti-IgLON5 encephalopathy (3). The rationale of the current study is to present a patient with a neuropsychiatric syndrome, Huntington's disease (HD), and novel neuronal autoantibodies.

Case Presentation

The 30-year-old male patient had been experiencing a neuropsychiatric syndrome for 3 to 4 years with progressively deteriorating concentration and worsening attention deficits, impaired working memory, reduced energy, depressive mood, and occasionally inappropriate behavior. Referring psychiatrists diagnosed a schizoaffective disorder. The neurological examination showed evidence of a mild bilateral hypokinetic rigid syndrome with dysdiadochokinesia, mild rigidity of the arms, slow and irregular finger/foot tapping, and slowing in the Luria test with many errors. The saccades were hypometric, the tongue showed beginning motor impersistence, and the patient displayed a tic-like behavior with repeated dysfunctional sniffs. Before illness, the patient showed good school performance with the achievement of the German "Fachabitur" (higher education entrance qualification). He then successfully completed vocational training as an industrial mechanic, going on to secure a job in the field. The somatic differential diagnostics according to the Freiburg Diagnostic Protocol in Psychosis (4) revealed pathological but nonspecific findings. Blood analyses did not show any evidence of systemic immune disease (antinuclear autoantibodies/antineutrophil cytoplasmic autoantibodies/antiphospholipid autoantibodies/antithyroid autoantibodies/rheumatoid factor/complement markers/IgG/IgA/IgM concentrations were normal) or autoimmune encephalitis (no well-characterized neuronal IgG autoantibodies against intracellular [Yo/Hu/CV2-CRMP5/Ri/$Ma_{1/2}$/SOX1/Tr/Zic4/GAD65/amphiphysin], cell surface [NMDA-receptor/LGI1/CASPR2/AMPA1/2-receptor/GABA-B-receptor/DPPX], or glial [AQP4/MOG] antigens). Cerebrospinal fluid (CSF) basic diagnostics (white blood cell count/protein/albumin quotient/oligoclonal bands/IgG index) and CSF testing for well-characterized neuronal autoantibodies against cell surface antigens (NMDA-receptor/LGI1/CASPR2/AMPA1/2-receptor/GABA-B-receptor/DPPX) remained unremarkable. Electroencephalography showed continuous generalized slowing with additional intermittent generalized delta slowing. Brain magnetic resonance imaging indicated bilateral atrophy of the striatum and, less pronounced, along the midline cleft, in the cerebellar vermis, and in the left parietal cortex.

Given the severe neuropsychiatric symptomatology, extended diagnostic investigations were initiated. Tissue-based assays using serum and CSF on unfixed mouse brain sections according to our established protocols showed a strong IgG autoantibody signal against myelin structures, predominantly in the cerebellum (5). [^{18}F]fluorodeoxyglucose positron emission tomography exhibited virtually absent metabolism of both striata, highly suspicious of HD (Figure 1). In genetic testing, a pathologically extended CAG trinucleotide was detected in the *HTT* gene with 53 CAG repeats (reference ≤39). The patient is therefore a carrier of a pathological, fully penetrating Huntington's allele and was diagnosed with HD (6). Because of the anti-myelin autoantibodies in CSF and their unclear pathophysiological relationship with the basic neurodegenerative process in HD, we offered an immunotherapy trial with a steroid pulse (1000 mg intravenous methylprednisolone) over 5 days and oral tapering over 24 days (beginning with a dose of 40 mg and ending with a dose of 2.5 mg). After this treatment, the patient reported that he was able to think more clearly and had more energy. This was corroborated by follow-up neuropsychological testing after 3 months showing substantial improvements in all basic attention domains. The 44-year-old brother, who was diagnosed with schizophrenia several years prior, was then also genetically tested. He was also found to have a prolonged CAG trinucleotide in the *HTT* gene with 44 CAG repeats (reference ≤39), leading to a diagnosis of HD. CSF autoantibody testing in the brother was not possible.

Discussion

This case study demonstrates that complex neuropsychiatric disorders can conceal a genetic disease such as HD. However, the case also raises the question of the role of the detected neuronal autoantibodies. The anti-myelin binding was reminiscent of an anti-MBP pattern; these autoantibodies bind to the MBP and are discussed in the context of multiple sclerosis (8). However, anti-MBP autoantibodies in the presented patient were not confirmed using fixed cell-based assays, indicating the presence of a novel target epitope. The restriction to only a subpopulation of myelin structures indicates a specific response, rather than nonspecific white matter binding. In a previous study, the serum or CSF of patients with several neurodegenerative diseases, including 14 patients with HD, was examined. In these HD patients, no myelin signal was observed (9). Although the number of cases in the study was small, it still indicates that the present case might be unique regarding this type of myelin autoreactivity. The detection of these novel autoantibodies suggests at least two possible explanations:

First, it could be an unrelated phenomenon, in that the autoantibodies may be pathophysiologically irrelevant or may be a sign of a comorbid autoimmune encephalitis (1). A direct pathophysiological role of the autoantibodies cannot be proven based on the current case study. However, the

https://doi.org/10.1016/j.biopsych.2020.12.032
ISSN: 0006-3223

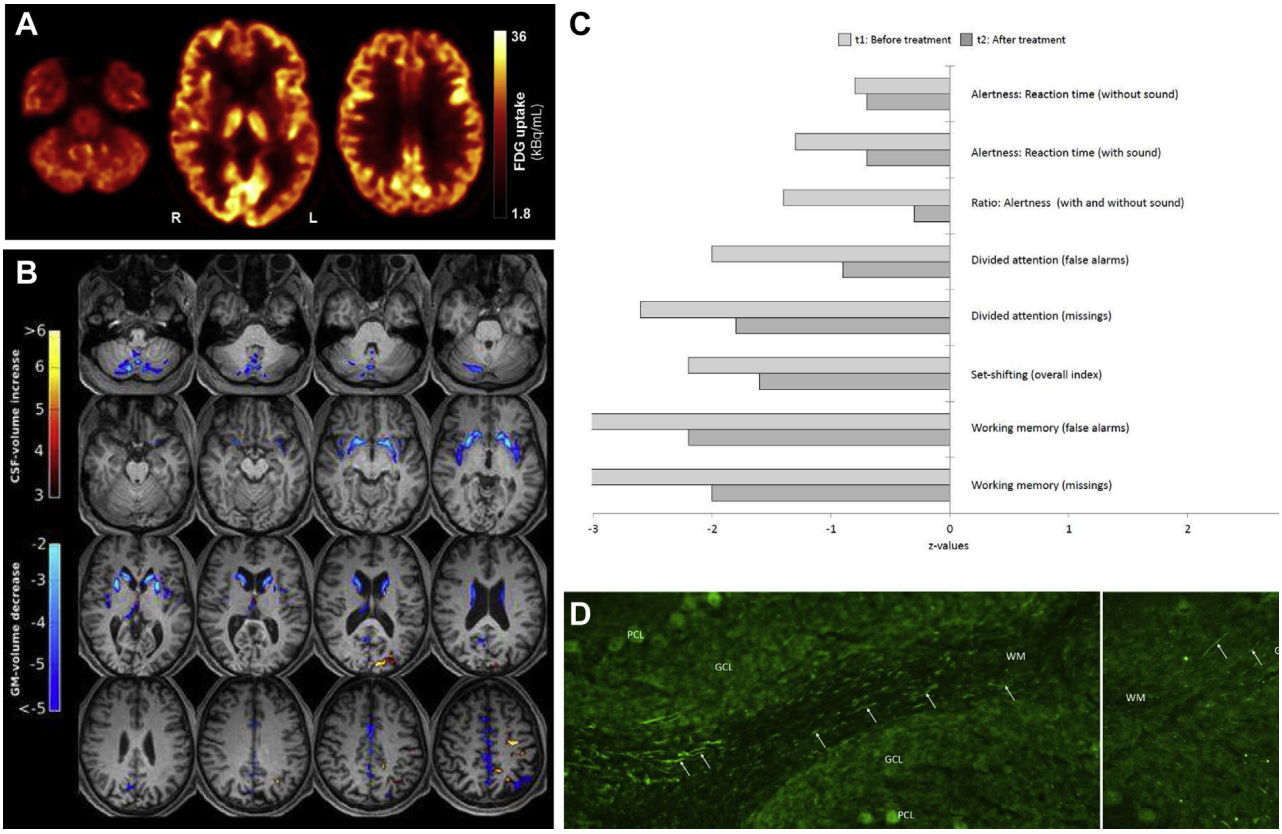

Figure 1. **(A)** Cerebral FDG-PET findings of three representative transaxial slices at the levels of the cerebellum, striatum, and cortex. **(B)** Magnetic resonance imaging and **(C)** neuropsychological findings. **(D)** Results of tissue-based assays using indirect immunofluorescence on unfixed murine brain tissue ("tissue tests"). **(A)** The FDG-PET elicits a largely absent metabolism of both caudate bodies, while cerebellar and cortical metabolism was normal, being highly suspicious of Huntington's disease. Whole-body PET/computed tomography (not shown) for exclusion of a paraneoplastic syndrome was unremarkable. **(B)** The magnetic resonance imaging analyzed by a fully automatic whole-brain volumetry using the VEObrain software (https://www.veobrain.com/?page=veomorph) showed bilateral atrophy of the striatum consistent with Huntington's disease. In addition, a less pronounced atrophy along the midline cleft, in the lower part of the cerebellar vermis, and left parietal was detected. **(C)** The initial Test for Attentional Performance at time 1 (t1) showed impairments in psychomotor processing speed (with tone) and particularly in divided attention and mental flexibility. The Test for Attentional Performance subtest for the assessment of working memory could not be performed (because of the patient's severe disability). The Test for Attentional Performance at t2 revealed substantial improvement in all attention domains and in working memory. **(D)** The autoantibody tests on unfixed murine brain slices demonstrated a clear signal against a myelin target epitope in cerebrospinal fluid (CSF) and serum (the CSF finding is presented), especially in the cerebellum, which was reminiscent of anti-MBP autoantibodies (7). Exclusion of serum and CSF anti-MBP IgG autoantibodies using fixed cell-based assays (Laboratory Stöcker, Lübeck, Germany) suggests a different myelin epitope. In detail, the figure shows the myelin fibers (left) that pass through the white matter (WM) in the cerebellum and then branch out in the granule cell layer (GCL) (right) and reach almost to the Purkinje cell layer (PCL). Some exemplary myelin fibers were marked with arrows; however, it is important to note that not all myelin fibers are affected. FDG, [^{18}F]fluorodeoxyglucose; GM, gray matter; PET, positron emission tomography; t, time.

detection of this extremely rare pattern of autoantibodies in CSF with specific cerebellar myelin binding in combination with the atypical cerebellar atrophy may indicate pathogenic brain involvement. This is also supported by the improvement in attentional performance after immunotherapy (although nonspecific methylprednisolone effects clearly cannot be excluded, and not all neuropsychological functions did normalize, which is quite understandable because there is clearly a neurodegenerative process active in the context of HD). In contrast, [^{18}F]fluorodeoxyglucose positron emission tomography yielded no cerebellar or cortical involvement.

Alternatively, autoantibodies could have been produced secondarily to the neurodegenerative process with progressive neuronal loss in HD (6,10). Following this line of thought, a verum effect of immunotherapy may have caused a positive modulating effect on the disease course of our patient. Such effects could be limited to patients with HD and neuronal autoantibodies and deserve further study, including the identification of the underlying epitope and the characterization of the autoantibody effects in vitro and in vivo. Similar observations were made for anti-IgLON5 encephalopathy. Here, tauopathy of the brainstem in combination with autoantibodies against the neuronal cell adhesion molecule IgLON5 has been identified, autoantibodies disrupted the cytoskeletal structure, and affected patients benefited from immunotherapy (3,11).

In summary, this case study could be indicative of a contributing immunological pathomechanism, in which reactive autoimmune processes with intrathecal neuronal autoantibody production could have a modulating course on neurodegenerative diseases such as HD.

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Acknowledgments and Disclosures

This work was supported by the Berta-Ottenstein-Programme for Advanced Clinician Scientists, Faculty of Medicine, University of Freiburg (to DE) and the Berta-Ottenstein-Programme for Clinician Scientists, Faculty of Medicine, University of Freiburg (to NS).

RW and LTvE diagnosed and treated the patient. DE, HP and LTvE developed the pathophysiological considerations in this process. DE performed the data research and wrote the article. HP performed the neurological interpretation and performed the tissue-based testing on unfixed brain sections. PTM performed the nuclear medicine investigations and interpretation. HU performed and interpreted the magnetic resonance imaging. TS performed the neuropsychological testing and interpretation. MAS and KD supported the genetic interpretation. NS supported the neurological interpretation. MAS, KN, MF, and KD supported the clinical and laboratory interpretation. All authors were critically involved in the theoretical discussion and composition of the manuscript. All authors read and approved the final version of the manuscript.

KD has served on the neurosciences steering committee for Janssen. HU is shareholder for VEObrain. PTM has served on advisory boards and lectured within the last 3 years for GE, Philips, OPASCA, Curium, Desitin, and Medac. LTvE has served on advisory boards, lectured, or received travel grants within the last 3 years from Roche, Eli Lilly, Janssen-Cilag, Novartis, Shire, UCB, GSK, Servier, Janssen, and Cyberonics. All other authors report no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Nov 14, 2020; revised Dec 19, 2020; accepted Dec 21, 2020.

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