



Figural Memory Impairment in Conjunction With Neuropsychiatric Symptoms in IgLON5 Antibody-Associated Autoimmune Encephalitis

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OPEN ACCESS

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Specialty section:

This article was submitted to
Aging Psychiatry,
a section of the journal
Frontiers in Psychiatry

Received: 11 March 2020

Accepted: 05 June 2020

Published: 03 July 2020

Citation:

Hansen N, Hirschel S, Stöcker W,
Manig A, Falk HS, Ernst M,
Vukovich R, Zerr I, Wiltfang J and
Bartels C (2020) Figural Memory
Impairment in Conjunction With
Neuropsychiatric Symptoms in
IgLON5 Antibody-Associated
Autoimmune Encephalitis.
Front. Psychiatry 11:576.
doi: 10.3389/fpsy.2020.00576

Background: IgLON5 disease is an autoimmune disorder that shares neuropathological aspects with a tauopathy. Its clinical spectrum is heterogeneous, and figural memory impairment as an initial phenomenon of IgLON5 syndrome has not yet been described. The rationale of this report is to highlight symptoms related to IgLON5 disease that have not been reported to date. This case report will thereby emphasize how important it is to initiate thorough diagnostic methods including cerebrospinal fluid analysis (CSF) before starting early immunotherapy.

Methods: We examined a 65-year-old Caucasian male *via* neuropsychological tests, magnetic resonance imaging (MRI), electroencephalography (EEG), neurography and polysomnography. He also underwent two lumbar punctures from which we determined specific autoantibodies in cerebrospinal (CSF) and peripheral blood (PB).

Results: The patient presented initially complaining of memory loss, gradual dysphagia and sleeping dysfunction. Neuropsychological testing at first presentation and follow-up revealed subtle figural and working memory impairment. At onset and at his 6-month follow-up, we detected IgLON5 antibodies in CSF and PB. Furthermore, we identified in the CSF a blood–brain barrier disturbance at disease onset and follow-up, and markers of neuroaxonal damage such as mildly elevated phosphorylated Tau-181 protein with 86 pg/ml (normal range ≤ 61 pg/ml) at onset. Three months after his initial presentation, he was suffering from axonal neuropathy and transient ataxia in the extremities. Assuming a definitive autoimmune encephalitis-associated with anti-IgLON5 antibodies, we applied high-dose steroids monthly (1g methylprednisolone i.v. for five consecutive days) and his memory complaints, ataxia of extremities and peripheral neuropathy as well as sleeping dysfunction decreased.

Conclusions: Our findings broaden IgLON5 disease's clinical spectrum to include predominant and discrete figural memory impairment together with sleeping dysfunction at disease onset. In addition, our report illustrates how important taking an elaborated diagnostic approach is to assuring an accurate diagnosis and the appropriate therapy if a patient presents with a persisting figural memory impairment and sleeping abnormalities so as to avoid overlooking IgLON5 disease and a potentially poor outcome.

Keywords: encephalitis, IgLON5 antibodies, memory impairment, figural memory, autoimmunity

INTRODUCTION

IgLON5 antibody-associated encephalitis is a rare autoimmune-mediated disorder of the central nervous system often presenting with a tauopathy. Various clinical features have been described about anti-IgLON5 antibody-mediated encephalitis, such as sleep dysfunction (e.g. sleep-apnea, insomnia, and/or parasomnia), brainstem and/or cerebellar dysfunction (e.g. ataxia, abnormal ocular movements, dysphagia, or respiratory dysfunction), and neuropsychiatric symptoms like cognitive dysfunction (1, 2). The IgLON5 antigen is a cell-adhesion molecule whose functions are incompletely understood. We here describe for the first time the clinical case of a male patient presenting a subtle figural memory impairment in conjunction with numerous subjective cognitive complaints and additional neuropsychiatric symptoms associated with cerebrospinal fluid (CSF) anti-IgLON5 autoantibodies as an early manifestation of IgLON5 disease. This report's rationale is to highlight the subtle figural memory impairment together with other neuropsychiatric features as a relevant indicator for taking a sophisticated diagnostic approach encompassing the investigation of IgLON5 autoantibodies in CSF. We believe that the decision for initiating elaborated diagnostic methods in our case was essential, as the mortality of IgLON5 encephalitis can be high (1, 3).

PATIENT AND METHODS

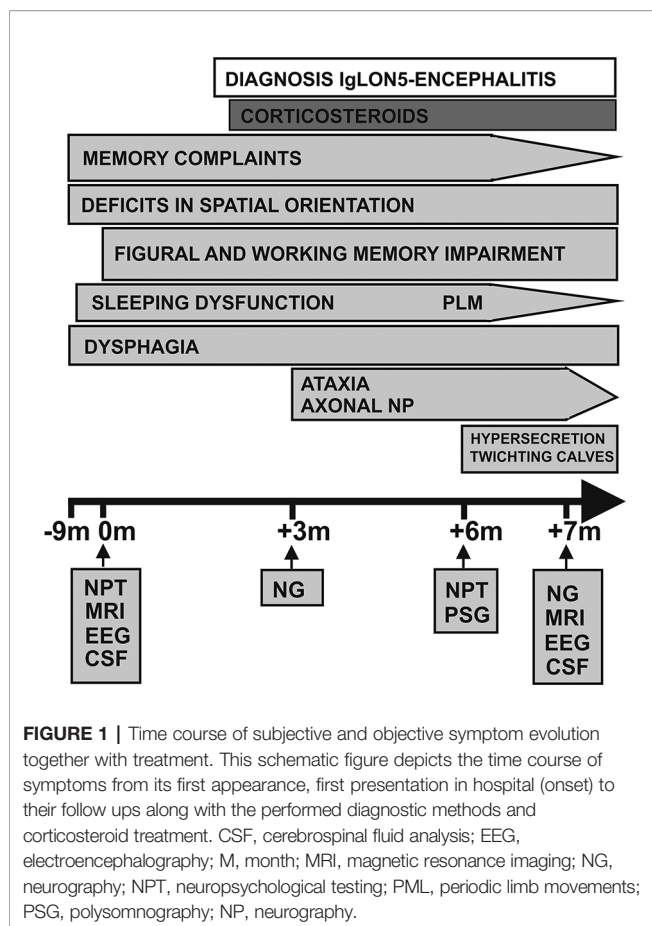
We examined a 65-year-old Caucasian male patient who presented in our tertiary memory clinic. The patient is married and father of two children. He has an educational level of 13 years and works as an administration employee. Our diagnostic schedule comprised comprehensive neuropsychological assessment, electroencephalography (EEG), magnetic resonance imaging (MRI), peripheral blood (PB) and cerebrospinal fluid (CSF) analyses including specific antibodies and markers of neuronal degeneration, polysomnography (PSG) and neurography. Neuropsychological testing and follow-up after six months – split into two sessions – covered all major cognitive domains (language, attention, executive functions, visuoconstruction, and memory) and comprised the following instruments: Beck Depression Inventory (BDI-II), CDT (Clock Drawing Test), CERAD (consortium to establish a registry for Alzheimer's disease)-plus, Mini-Mental Status Examination (MMSE), Regensburger word fluency test (RWT), Rey-Osterrieth-Complex-Figure test (ROCF), and subtests from the Wechsler Adult Intelligence Scale IV (WAIS-IV) and Wechsler Memory-Scale IV (WMS-IV). We sought specific

antibodies against paraneoplastic antigens *via* antibody blots [Amphiphysin, CV2 (cromveinten 2), GAD65 (glutamic acid decarboxylase 65), HuD, Ma1/2, Ri, Ro, SOX1, TR, Zic4] in CSF and PB. Furthermore, we did antibody testing of CSF and PB with recombinant-cell indirect immunofluorescence against neuronal antigens such as Aquaporin-, AMPAR1/2- (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1/2), CASPR2- (contactin-associated protein-like 2), DPPX- (dipeptidyl peptidase protein-like 6), GABAAR- (γ -aminobutyric acid A receptor), LGI1- (Leucine-rich glioma inactivated 1) and NMDAR- (N-methyl-D-aspartate receptor) antibodies. These antibodies were screened in the CSF laboratory in the Department of Neurology, University Medical Center Goettingen, IgLON5 antibodies were analyzed in the Euroimmun laboratory in Luebeck, Germany. We obtained informed consent from our patient and ethical approval. Our report concurs with the Declaration of Helsinki.

RESULTS

Our patient presented at first with a striking subjective memory decline. He reported having experienced difficulty finding words, naming things and persons. Both his forgetfulness and high distractibility often resulted in misplacing everyday items such as keys, as his wife reported. He had great difficulty concentrating, and experienced sleep disturbances (sleeping less than 3–4 h and waking up early). Furthermore, he reported mild dysphagia, and problems with spatial orientation in a novel environment during the previous 9 months (**Figure 1**). His wife also reported an increase in snoring over the last 9 months without its having interfered with his sleep. His daily living activities were unaffected. His medical history revealed no relevant comorbidities nor any relevant past or recurrent treatments. His mother suffers from parkinsonism. His physical examination exposed no pathological findings, but his neurologic examination revealed a known left-sided anisocoria. The patient found his cognitive deficits most afflicting; they had developed with a subacute onset, but no further deterioration. Cognitive screening results applying the MMSE and CDT were normal (MMSE=30/30, CDT=1), and the patient's self-report indicated a euthymic affective state (BDI-II=4) (**Table 1**).

Most interestingly, cognitive impairment was detected in figural memory parameters in the CERAD-plus test battery, but not in the immediate and delayed recall in WMS-IV Visual Reproduction subtests, although the latter relies on more complex stimuli and entails a longer delayed recall interval. A slight impairment was also observed in his verbal memory span



(WAIS-IV Digit Span forward), while all other cognitive functions appeared unaffected (**Table 1**). At neuropsychological follow-up six months later, we detected a similar pattern with stable, subtle impairments in figural memory and working memory (**Figure 1**, **Table 1**). Modest improvements in other cognitive parameters must be interpreted cautiously and while considering practice effects.

For differential diagnosis, we performed lumbar puncture, analyzed CSF, and detected a pleocytosis of leukocytes (for specifications see **Table 1**). Specific antibodies (see methods) in PB and CSF were not detected. Furthermore, we identified in the CSF a blood-brain barrier disturbance and markers of neuroaxonal damage such as mildly elevated phosphorylated Tau-181 protein with 86 pg/ml (normal range ≤ 61 pg/ml). Peripheral inflammation was indicated by elevated C-reactive protein (CRP) with 42.5 mg/l (normal range < 5 mg/l) and an elevated blood sedimentation rate (1h: 86/2h: 88 mm according to Westergren). MRI revealed frontal subcortical lesions on the right-side and a few unspecific periventricular white-matter lesions. EEG recordings showed neither epileptic potentials nor focal slowing (**Figure 2**).

CSF diagnostics revealed a pleocytosis, a blood-brain barrier disturbance together with mild unspecific neurodegeneration, elevated phosphorylated tau-protein, and negative standard panel of specific autoantibodies (see *Methods*, **Table 1**). Our patient had reported sleeping dysfunction in addition to his figural and working memory impairment. Sleeping dysfunction is a prominent symptom of IgLON5 disease (4–6). His clinical

syndrome, which comprised cognitive deficits together with sleeping abnormalities in conjunction with signs of CNS inflammation was our rationale to search for anti-IgLON5 antibodies (Euroimmun Laboratory, Luebeck, Germany) beyond the standard antibody panel. Anti-IgLON5 antibodies in serum (1:320) and CSF (1:3200) were detected *via* indirect immunofluorescence assay. Finally, we diagnosed an autoimmune encephalitis associated with anti-IgLON5 antibodies according to the Graus criteria (7) and started high-dosage therapy with methylprednisolone (1g/d i.v. over five days), to be continued over 6 months with 5 days of corticosteroids administered monthly as first therapy of choice in autoimmune encephalitis. Two weeks after having starting this well-tolerated corticosteroid treatment with no report of any adverse event, the patient complained at follow-up of dysphagia that he had noticed for several months but which he had ignored until then. In addition, he reported at follow-up (and after 3 cycles of corticosteroids) that he had been sleeping better (for 6 h uninterrupted), although he still suffers daytime sleepiness. His subjective memory impairments were less pronounced at follow-up, but he complained further of increased hypersalivation, his calves twitching, and of worse subjective dysphagia at follow-up. An endoscopic examination of his throat revealed no cause for his dysphagia. We decided to continue monthly intravenous administration of high-dose corticosteroids due to his improved cognitive and sleeping function. A follow-up neuropsychiatric examination 3 months after his initial presentation revealed ataxia of extremities (**Figure 1**) that had disappeared by his final follow-up 7 months after initial presentation. In the meantime, he was diagnosed with axonal sensorimotor polyneuropathy *via* neurophysiologic measurements 3 months after his initial presentation (**Figure 1**), but another investigator could not confirm that finding neurographically at his last follow-up. PSG given over three nights 6 months after his initial presentation (**Figure 2**) revealed central (and mainly in supine position) obstructive sleep apnea and oxygen desaturation as low as 89% (**Table 1**, **Figure 2E**). However, after being given an additional pillow to discourage back sleeping, his obstructive apnea lessened. We also observed increased period limb movements (PLM) in PSG. At his last follow-up 7 month after initial presentation, MRI showed known frontal subcortical lesions on the right side and periventricular white matter lesions (**Figures 2A–D**) and a previously undescribed mild global atrophy. His last follow-up EEG still revealed no pathological signs. Subsequent CSF analysis showed a pleocytosis (**Table 1**) and a blood-brain barrier disturbance. Again, indirect immunofluorescence assay revealed anti-IgLON5 antibodies in serum and CSF at follow up.

DISCUSSION

With our patient's cognitive testing results, the clinical IgLON5 syndrome's spectrum is expanded to include figural memory impairment. Very few patients with IgLON5 antibody-positive encephalitis and cognitive dysfunction have been reported in the literature so far (1, 2, 8–11). This could be due to both the lack of neuropsychological testing and IgLON5 disease's broad clinical

TABLE 1 | Results of individual investigations at first visit and follow-up.

Parameter	First visit	Follow-up
CSF analysis		
Cell count /ul (pathological: >5 µl)	8	8
Lymphocytes in %	93	92
Monocytes in %	5	.
Plasma cells in %	2	2
Albumin mg/L	518	615
IgG mg/L	69.3	62.5
IgA mg/L	10.7	9.6
IgM mg/L	0.97	0.84
QA1b %	11.5	15.4
Q1gG %	7.3	8.9
Q1gA %	4.3	5.2
Q1gM %	2.4	2.4
Lactat mmol/L	2	2
Oligoclonal IgG	–	–
NSE ng/ml (pathological: >30 ng/ml)	19.3	.
S100 µg/ml (pathological: >2.7 µg/ml)	2	.
Tau pg/ml (pathological: >450 pg/ml)	409	.
P-Tau 181 pg/ml (pathological: > 61 pg/ml)	68	.
Aβ1-42 pg/ml (pathological: >450 pg/ml)	715	.
Aβ1-40 pg/ml	9565	.
Aβ ratio pg/ml (pathological: >0.5 pg/ml)	0.75	.
Serum		
Oligoclonal IgG	–	–
CRP mg/l	42.5	1.1
Leukocytes 10 ³ µl	5.63	4.29
Neuropsychological testing*		
MMSE	30	29
CDT	01	01
CERAD Boston Naming Test	PR 31	PR 82
CERAD semantic fluency	PR 50	PR 66
CERAD phonemic fluency	PR 82	PR 62
TMT part A	PR 76	PR 99
WAIS-IV Digit Symbol Test	PR 84	PR 95
TMT division part B/A	PR 84	PR 58
RWT semantic fluency (alternating)	PR 30	PR 75
RWT phonemic fluency (alternating)	PR 63	PR 54
WAIS-IV Digit Span forward	PR 05*	PR 05*
WAIS-IV Digit Span backward	PR 16	PR 16
CERAD List Learning (trials 1-3)	PR 34	PR 34
CERAD List Recall (savings)	PR 46	PR 54
CERAD List Recognition/discriminability	PR 21	PR 79
WMS-IV Logical Memory I	PR 50	PR 50
WMS-IV Logical Memory II	PR 16	PR 50
CERAD Figure recall (savings)	PR 01*	PR 12*
WMS-IV Visual Reproduction I	PR 25	PR 75
WMS-IV Visual Reproduction II	PR 50	PR 50
CERAD Figure Copy	PR 73	PR 18
ROCFT Copy	PR>16	PR>16
WAIS-IV Block Design	PR 25	PR 75
Psychopathology		
BDI-II	04	05
Polysomnography		
Apnoe-Hypopnoe-Index	.	9.7
PLMI	.	64.6
Basal O ₂ desaturation %	.	94
Minimal O ₂ desaturation %	.	89.0
O ₂ desaturation index %	.	13

*For better comparison, cognitive data is presented as percentiles (PR) unless otherwise indicated. Asterisk denote performance below the normal range (PR<16). . = data not available. - = not present. Polysomnography data are derived from the second night.

AHI, apnoe-hyperpnoe index; Aβ ratio, β amyloid 1-42/1-40 ratio; Aβ1-40, β amyloid 1-40; Aβ1-42, β amyloid 1-42; BDI-II, Beck Depression Inventory; CSF, cerebrospinal fluid; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; MMSE, Mini-Mental Status Examination; CDT, Clock Drawing Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; TMT, Trail Making Test; RWT, ROCFT, Rey-Osterrieth-Complex-Figure test; WAIS-IV, Wechsler Adult Intelligence Scale IV; WMS-IV, Wechsler Memory-Scale IV, NSE, neuron specific enolase; O₂ desaturation, oxygen desaturation; PLMI, periodic limb movement index; P-tau181, phosphorylated tau protein 181; QA1b, quotient albumin; Q1gA, quotient immunoglobulin A; Q1gG, quotient immunoglobulin G; Q1gM, quotient immunoglobulin M; T-tau, total tau protein.

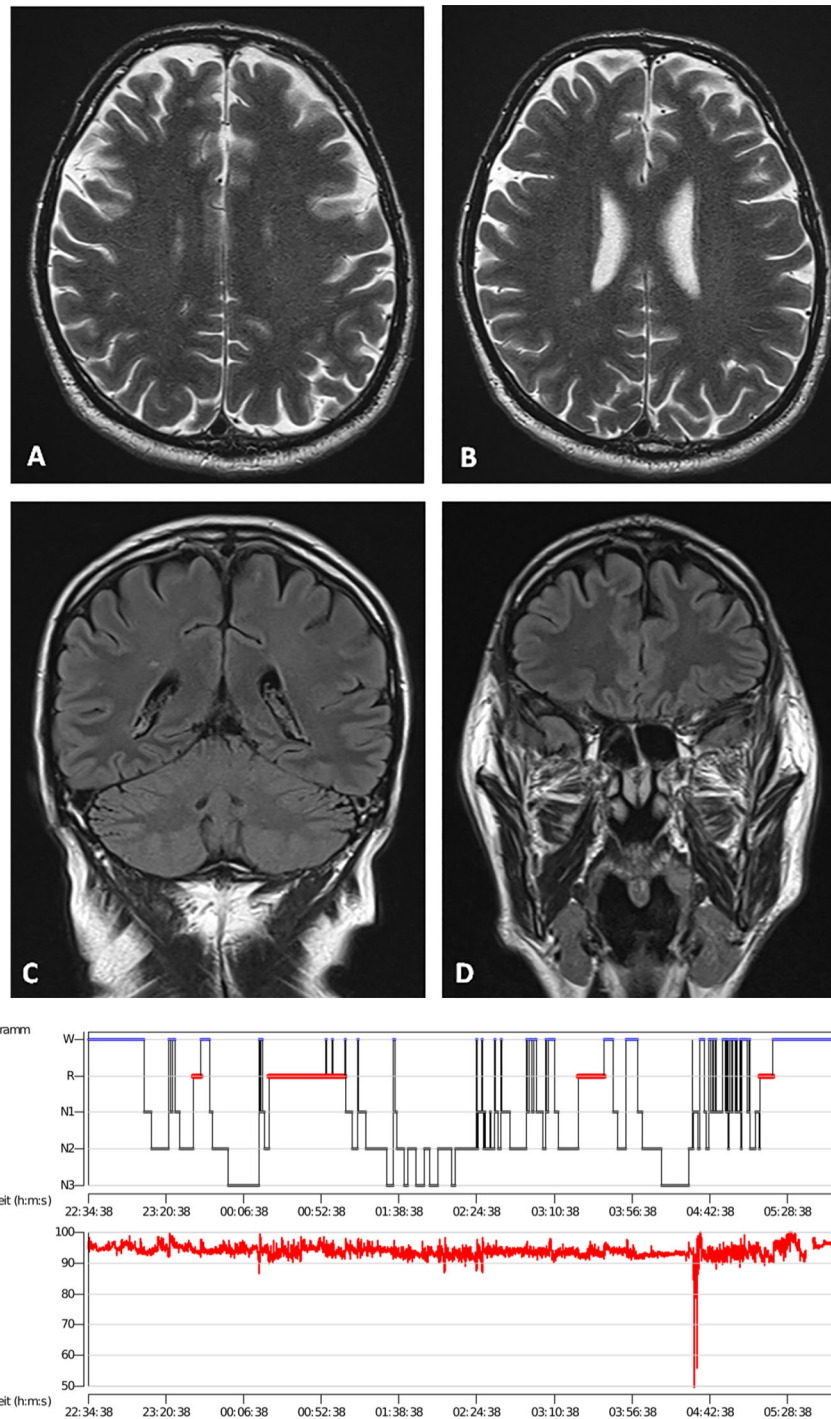


FIGURE 2 | Brain magnetic resonance imaging and polysomnography. Brain magnetic resonance imaging (Siemens Avanto 1.5 T). Axial T2w (**A, B**) and coronal FLAIR (**C, D**). Hyperintense periventricular and juxtacortical white matter lesions. No specific MRI findings for IgLON5-associated encephalitis. (**E**) In the upper graph the hypnogram is shown as a function of time of the day (hours: minutes: seconds) with W representing wakefulness, R representing rapid eye movement (REM) sleep and N1-3 representing non-REM-sleep stages 1 to 3. In the lower graph oxygen saturation measured via pulse oximetry is depicted as a function of time of the day (hours: minutes: seconds) ranging from 50 to 100%.

spectrum—often presenting with predominant sleep dysfunction and motor impairment (9). So far, the cognitive spectrum of IgLON5 disease covers deficits in attention, information-processing speed, disinhibition and executive dysfunction, as well as impaired verbal memory performance (1, 2, 8–11), often progressing from mild cognitive impairment to dementia (10, 11). The pathophysiological mechanism of figural memory dysfunction in IgLON5 disease remains unclear. However, we hypothesize that IgLON5 autoantibodies result in phosphorylated Tau-deposits within the right hippocampus, as this structure is involved in figural memory function (12). A recent study demonstrated phosphorylated Tau-protein pathology in temporal regions including specific hippocampal subfields such as the cornu ammonis 1 (CA1) and the subiculum (13) concurring with a hypothetical mechanism for our patient's figural memory impairment.

To monitor his figural memory impairment, we will therefore continue to examine this patient's cognitive status. What is more, our patient's concomitant features like insomnia, dysphagia, concomitant tau pathology, and mild CSF pleocytosis correspond closely with IgLON5 disease (1, 2). Our diagnostic approach entailing repeated CSF analysis providing stable proof of IgLON5 antibodies in the CSF delivers solid evidence for probable autoimmunity. In addition, the repeated confirmation of CSF antibodies together with signs of a CNS inflammation impels us to diagnose a definitive IgLON5 autoimmune encephalitis, and eliminates the consideration of IgLON5 antibodies as an epiphenomenon. Two other main differential diagnosis were initially evaluated. First, we initially considered whether this patient might have prodromal Lewy-body dementia with mild cognitive impairment, as he presented with figural memory impairment. However, what argued against the LBD assumption was his lack of core symptoms such as parkinsonism, lack of rapid eye movement (REM)-sleep behavior disorder (RBD) or REM-sleep without atonia (RWA), and his failure to exhibit fluctuating cognition. The lack of RBD and RWA was later confirmed polysomnographically (PSG). Second, cerebrovascular disease was another potential candidate causing cognitive dysfunction, as his MRI had revealed periventricular white matter lesions that might imply cerebrovascular disease, but could also be attributable to the underlying autoimmune process. However, having identified anti-IgLON5 autoantibodies within the CSF finally confirmed the diagnosis of IgLON5-autoimmune encephalitis. Further evidence for an autoimmune-based mechanism in our IgLON5 syndrome is derived from the known association between IgLON5 antibodies and human leukocyte antigen (HLA) class II (14). In addition, the subcortical right frontal cortex lesions, periventricular white matter lesions and mildly generalized atrophy on brain MRI is another potential microstructural indication of an underlying autoimmune process *via* a disturbed blood-brain barrier and the infiltration of IgLON5 autoantibodies. However, no specific IgLON5 lesions have been detected in MRI (**Figures 2A–D**). Furthermore, and although it is much less likely, a concomitant vascular pathology as differential diagnosis cannot be entirely ruled out as an additional cause for these structural brain abnormalities.

From already published data and the present case, it seems likely that IgLON5 antibody-associated autoimmune encephalitis is under-diagnosed and that affected patients are going untreated

despite the symptoms' potential (at least partial) reversibility under therapy, as various studies have shown (2, 9, 11, 15). Although self-reported improved memory is a low-evidence parameter for the efficacy of corticosteroids, lessened axonal neuropathy, no longer detectable ataxia of extremities, and less pronounced sleeping dysfunction at follow-up seem to reveal additional evidence favoring the efficacy of corticosteroids in our case. Patients presenting with cognitive impairment and IgLON5 syndrome often seem to experience better outcomes (15, 16)—an observation in line with our patient's good response to therapy so far. However, the proof of CSF IgLON5 autoantibodies and signs of CNS inflammation at follow-up support an ongoing disease state. This patient's follow-up status must therefore be carefully observed, and should his clinical condition turn progressively worse, we would consider a rationale for escalating his therapy, *i.e.*, *via* plasmapheresis. Azathioprine and mycophenolate mofetil are also known to be effective in long-term treatment for IgLON5 encephalitis (15). Nevertheless, noteworthy is our case report's inherent limitation as a single case report that enables only a low evidence level.

Taken together, even in patients presenting with subtle cognitive impairments in conjunction with sleeping dysfunction, a more specific diagnostic approach including neuropsychological assessment and CSF analysis should be taken to detect IgLON5 positive-encephalitis as a relevant differential diagnoses. The good responsiveness that this patient's cognitive impairment revealed is in line with the literature on IgLON5 syndrome (15) and concurs with our patient's encouraging prognosis.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The study involving a human participant was reviewed by the ethical committee of the University Medical Center Goettingen. The patient provided his written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NH and CB wrote the manuscript. AM, CB, HF, IZ, JW, ME, NH, RV, SH, WS revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

JW is supported by an Ilidio Pinho professorship, iBiMED (UID/BIM/04501/2013) and FCT project PTDC/DTP-PIC/5587/2014 at the University of Aveiro, Portugal.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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