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LETTER TO THE EDITORS

Intravenous immunoglobulins as first-line therapy for IgLON5 encephalopathy

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Dear Sirs,

A 56-year-old man presented with a 6 month history of dysarthrophonia, orofacial dyskinesia and chorea of both hands. His wife reported snoring, day sleepiness, insomnia and limb movements during sleep. The patient and his wife negated a cognitive impairment at the time of presentation. Mood was unimpaired.

Neurological examination showed oculomotor dysfunction (saccadic pursuit, absent vertical optokinetic nystagmus and delayed horizontal optokinetic nystagmus in routine examination), dysarthrophonia, orofacial dyskinesia and chorea.

The patient scored 28 of 30 points on the Montreal Cognitive Assessment Score (MoCA). Additional neuropsychological assessment showed abnormalities in alertness, information processing speed, selective attention and verbal memory. Unified Huntington's Disease Rating Scale motor score (UHDRS-MS), used as a measure for hyperkinesia, was 17 of 124 points.

Cerebral MRI showed a macroadenoma of the pituitary gland but was otherwise unremarkable. Screenings for systemic autoimmune diseases, neuroacanthocytosis and Wilson's disease were negative. CSF showed elevated total protein, IgG and albumin without pleocytosis. No malignant cells, intrathecal immunoglobulin synthesis or oligoclonal bands were found. Autoantibody screening was positive for IgLON5 IgG in serum (+++, 1:1000) and CSF (+++, 1:100). HLA typing showed HLA-DQB1*05:01. Hyperphosphorylated tau protein was elevated in CSF. Polysomnography showed reduced sleep efficiency with 69.4%, reduced REM sleep and NREM sleep showed increased arousals with periodic limb movements (PLM index: 75.1/h). There were signs of severe obstructive sleep apnea (Apnea–Hypopnea index of 58.0/h). Mean oxygen saturation was 93% with a nadir of 76%.

Symptomatic treatment with tiapride reduced hyperkinesia, but induced hyponatremia and hypokinesia, leading to readmission 1 month later. Cognition declined (MoCA 21 points). Immunosuppressive therapy with high-dose corticosteroids for 5 days was ineffective. Tiapride was discontinued temporarily. 3 months after baseline, MoCA was 20 points, while UHDRS-MS had worsened to 24 points.

The first IVIg cycle was initiated with a dosage of 2 g/kg body weight 4 months after the first presentation of the patient, and the second cycle was administered 4 weeks later, followed by repeated infusions with a reduced dosage of 1 g/kg body weight and prolonged intervals (see Fig. 1). The IVIg therapy led to a significant improvement in cognition and chorea (see Fig. 1). The titer of Anti-IgLON5-antibody in serum decreased to 1:320 and in CSF to 1:32 6 months after baseline. Cognition and hyperkinesia improved (MoCA 27 points, UHDRS-MS 15 points) 4 and 8 months after IVIg treatment initiation, respectively.

Four phenotypes have been identified: predominant sleep disorder, bulbar syndrome, PSP-like and cognitive impairment associated with chorea [1, 2]. Thus, our case was presented as "cognitive impairment associated with chorea" phenotype.

The first reports of IgLON5 encephalopathy questioned the relevance of immunotherapy, since most of the patients showed progressive impairment leading to death irrespective of immunotherapy [3]. Tau deposition and the absence of treatment response suggested that IgLON5 encephalopathy is a primary neurodegenerative disorder and that the antibodies are a rather secondary phenomenon [3, 4]. However, treatment with IVIg led to a dramatic improvement in our

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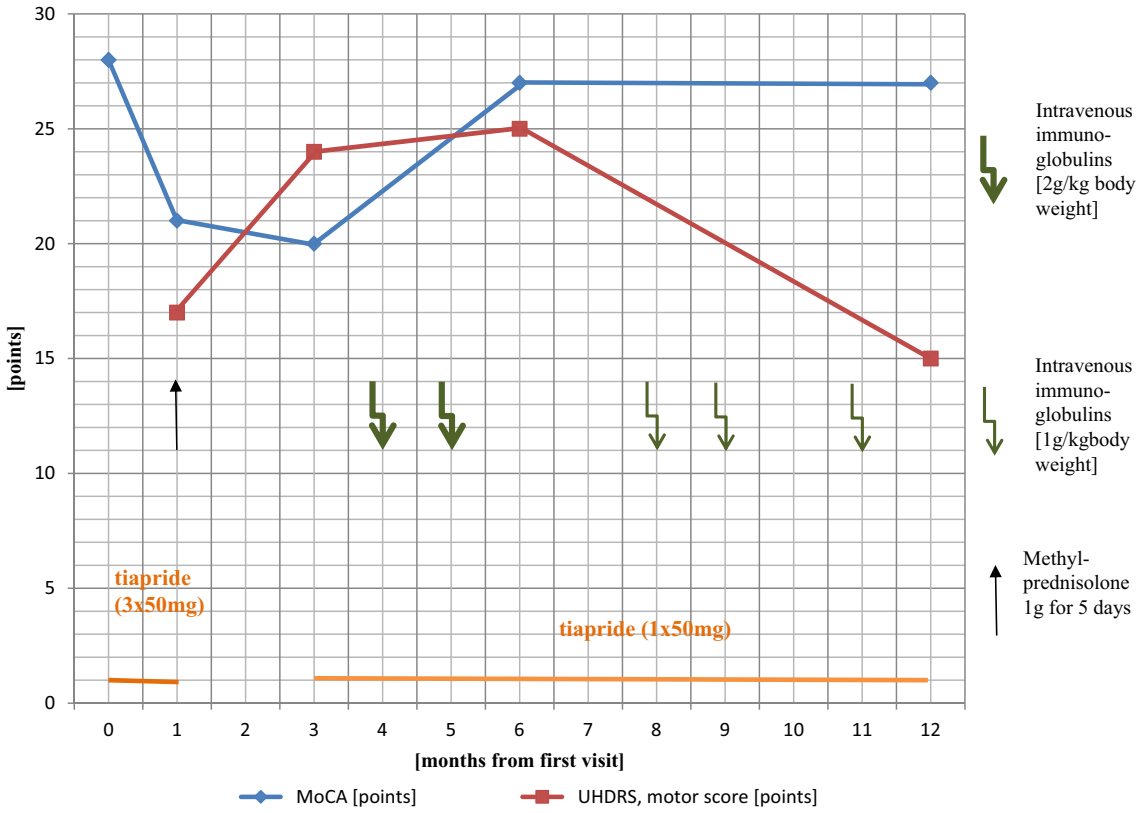

Fig. 1 Time course of UHDRS motor score and MoCA and treatment timings from baseline to 12 month follow-up. Cognitive deficits as assessed by MoCA score (*y* axis) are displayed as a blue line. Chorea as assessed by the motor score of UHDRS (*y* axis) is displayed as a red line. Duration of symptomatic treatment with tiapride is depicted with the orange line. Cortisone pulse therapy (5 days, 1 g/day) is represented by the black arrow, intravenous immunoglobulins infusions (with the dose of 2 g/kg body weight) are represented by the thick green arrow, intravenous immunoglobulins infusion (with the maintenance dose of 1 g/kg body weight) are represented by the thin green arrow

patient. Recently, two more cases and a retrospective study on IgLON5 encephalopathy identified a broad range of responsivity to immunotherapy which supported the notion of relevant pathogenic role of IgLON5 autoimmunity [4–6]. Interestingly, our case and three out of the four other prospectively investigated responsive cases can be assigned to the "cognitive impairment with chorea" phenotype [4–6]. Although it is not clear which patients benefit the most, it is possible that either certain symptoms are more responsive to immunosuppressive treatment or different phenotypes may have different underlying pathophysiologies leading to differences in treatment responses. Earlier and more consequent treatments could have led to better treatment responses as well [4, 5] and underlines the importance of early treatment initiation similar to other autoimmune-mediated encephalopathies [7, 8]. The used agent may also be of relevance, since most of the patients responding to immunotherapy were treated with IVIg [5, 6].

Taken together, we report a case of a patient with "cognitive impairment and chorea" phenotype IgLON5 encephalopathy dramatically responding to early immunotherapy with IVIg, which may be considered as the first-line therapy as early as possible.

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interests to report.

Ethical standards The study was performed in accordance with the Declaration of Helsinki.

Informed consent The patient gave his consent to publish the case report.

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