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Case Report

Atypical brain MRI findings in a patient with treatment responsive anti-IgLON5 disease ☆

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ABSTRACT

Anti-IgLON5 disease is a rare autoimmune neurological condition which was relatively recently described in the literature. This syndrome encompasses a range of clinical manifestations with most cases showing unremarkable findings on brain magnetic resonance imaging (MRI). Here, we report a case of a 61-year-old female patient with unique brain MRI features that, to the best of our knowledge, has not been reported in the literature before. Following treatment including immunotherapy, the patient experienced significant improvement clinically accompanied by radiological improvement on the follow-up imaging.

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Introduction

Anti-IgLON5 disease is a rare immune disorder which was first described in 2014 and is known to be associated with antibodies directed against the neuronal cell adhesion protein IgLON5 [1]. The syndrome encompasses a range of clinical manifestations including sleep disturbances, bulbar dysfunction, gait instability, chorea, oculomotor abnormalities, and cognitive decline [2,3].

Most cases show unremarkable brain magnetic resonance imaging (MRI) findings [1,2,4], with only few cases reported in the literature featuring positive brain imaging manifestations. Here, we describe a case with notable MRI brain changes and its subsequent improvement following treatment.

Case presentation

A 61-year-old right-handed female patient was admitted with a 10-day history of progressively worsening neurological symptoms. These symptoms initially included dysarthria and right-sided facial paraesthesia, which progressed to bilateral

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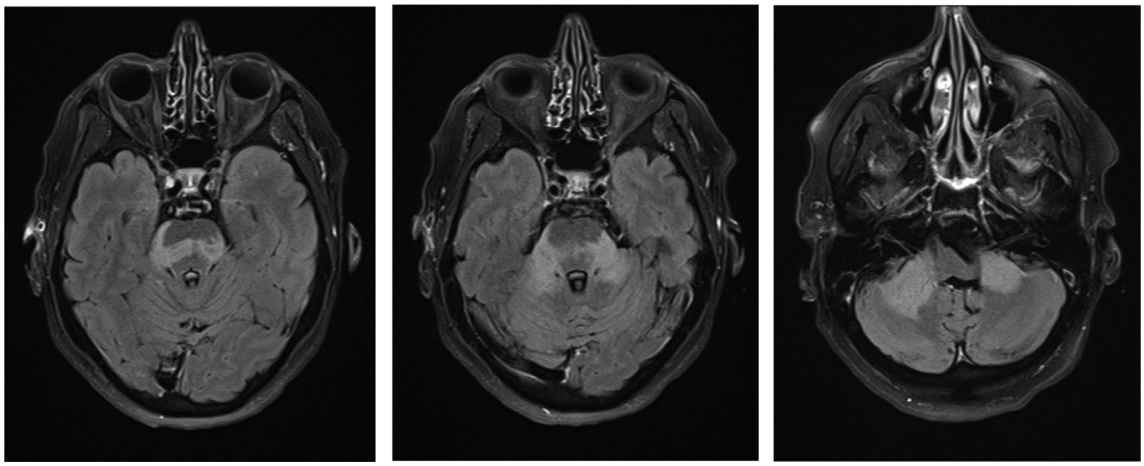

Fig. 1 – MRI brain on admission. T2 FLAIR sequences demonstrating confluent and symmetrical hyperintensity in the pons, middle cerebellar peduncles and anteromedial cerebellar hemispheres.

facial numbness, gait ataxia, diplopia, vertigo, and insomnia. Approximately 2 weeks prior to the onset of these symptoms, the patient had experienced episodes of diarrhea and fatigue. Her background medical history otherwise consisted of hypertension and migraine.

The neurological examination revealed bilateral upper limb dysmetria, right dysdiadochokinesis, heel-shin ataxia, right leg spasticity, and sustained right ankle clonus. She had generalized brisk reflexes with right positive Hoffmann's sign and right extensor Babinski reflex. Right abducens nerve palsy and horizontal jerk nystagmus were also noted, and she was unable to walk unassisted due to severe ataxia. In addition, she scored 19 out of 30 on Montreal Cognitive Assessment (MOCA), suggestive of cognitive impairment, with deficits in attention, visuospatial, executive, language, and delayed recall.

Her initial brain MRI with gadolinium contrast showed bilateral symmetric areas of hyperintense T2-weighted/FLAIR and hypointense T1-weighted signal involving the pons, middle cerebellar peduncles, and anteromedial cerebellar hemispheres with no associated enhancement, restricted diffusion, or hemorrhage (Fig. 1). On day 3 of admission, her serum limbic encephalitis panel was strongly positive for the anti-IgLON5 antibody. Subsequently, her cerebrospinal fluid (CSF) analysis was weakly positive for the anti-IgLON5 antibody and negative for neurotropic infections including Human Herpesvirus 6 (HHV-6), listeria monocytogenes, arboviruses including Japanese encephalitis, treponema pallidum, and mycobacterium tuberculosis. CSF oligoclonal bands were also negative, with normal CSF flow cytometry and cytology. The serum vasculitis and connective tissue disease screen were negative, as were the remainder of the anti-MOG, anti-neuronal and limbic encephalitis antibody panels. Furthermore, human leukocyte antigen (HLA) tissue typing was performed and the patient was HLA-DQB1*05:01 positive and HLA-DRB1*10:01 negative which has association with anti-IgLON5 disease [3].

The patient was commenced on immunomodulatory treatment for IgLON5 autoimmune encephalitis, which included high-dose intravenous methylprednisolone, plasmapheresis, rituximab (anti-CD20 monoclonal antibody) and intravenous immunoglobulin (IVIG).

Dramatic improvements in the patient's gait ataxia, cerebellar signs and somnolence were noted 4 weeks after treatment, around the second of 5 planned plasma exchanges. After 6 weeks, she regained the ability to walk with a normal gait, and her diplopia and nystagmus had resolved. However, she still had residual mild right upper limb dysmetria and facial numbness. Furthermore, there was notable improvement in her cognition, as evidenced by a repeated MOCA score of 25 out of 30, with the loss of points primarily attributed to attention and visuospatial-executive tasks, while language and memory function remained intact. A neuropsychological testing at 6 months following treatment revealed normal executive function, information processing speed and verbal recall; low average complex figure recall and confrontational naming and below average visuospatial ability.

A follow-up brain MRI, conducted 3 months post-treatment, revealed radiological improvement in the disease, characterized by reduction in the degree of previously shown hyperintense regions (Fig. 2).

Discussion

Anti-IgLON5 disease is a relatively recently described autoimmune neurological condition which presents a diagnostic and management challenge for clinicians due to its heterogenous clinical manifestations, diverse progression, and limited understanding of its underlying mechanisms [2,3].

In 2014, Sabater and colleagues were the first to describe the disease, focusing on characterizing its sleep disturbances and identifying the associated antigen [1]. Subsequently, it was suggested that suspicion of anti-IgLON5 disease arises when distinctive sleep disorders occur alongside one or more of the following symptoms: bulbar dysfunction, gait abnormalities, oculomotor abnormalities, chorea, or cognitive decline [2]. One of the interesting features of this progressive

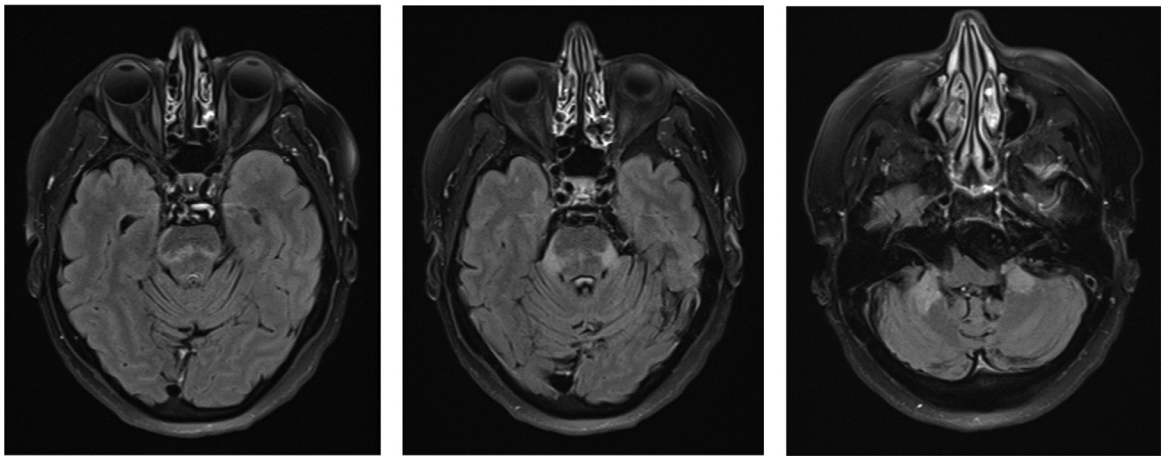

Fig. 2 – MRI brain three months post-treatment. T2 FLAIR sequences demonstrating radiological improvement in the previously known hyperintense areas.

neurological condition is the accumulation of hyperphosphorylated tau protein primarily in the brainstem tegmentum, hypothalamus, and hippocampus [5]. This places the condition in a complex overlap of neurodegeneration and autoimmunity [2,5,6]. What remains uncertain is whether the robust inflammatory response triggered by antibody activity contributes to neurodegeneration or if a primary neurodegenerative process exacerbates the immune response [6].

Most instances of anti-IgLON5 disease exhibit no significant brain MRI abnormality [1,2]. However, 2 case reports documented MRI features of atrophy in the brainstem, cerebellum and hippocampus [2,7]. Two other reports described brain MRI findings including small areas of restricted diffusion in both cerebellar hemispheres and the tegmentum of the midbrain without any significant post-contrast enhancement [8,9]. In contrast, a case reported by Montagna and colleagues showed "atypical" MRI changes, including patchy enhancement in the right temporal and frontal lobes in addition to the presence of leptomeningeal enhancement and oedema [10]. Similarly, another case demonstrated bilateral frontal and cingulate gyrus region swelling with a hyperintense lesion on the T2WI and FLAIR associated with post-contrast enhancement of frontal leptomeninges [11].

In our case, the MRI of the brain revealed the involvement of the pons, middle cerebellar peduncles, and anteromedial cerebellar hemispheres. This shares anatomical similarity with the regions described in the previous studies; However, the intriguing and unique feature of our case is the presence of confluent and symmetrical signal changes in these areas. This manifested as high-signal intensity on T2-weighted/FLAIR and low-signal intensity on T1-weighted sequences without associated post-contrast enhancement, restricted diffusion, or hemorrhage. As illustrated in the provided images (Fig. 1), the shape of the involved areas is notably distinct, resembling claws. Hence, for pattern recognition and teaching purposes, we refer to this unique appearance as "pontine claw sign" or "Zoidberg hands", the iconic fictional character with lobster-like claws.

Lastly, a notable feature of our case is the subacute presentation and rapid deterioration, as most cases of anti-IgLON5 disease are chronic in the tempo of onset, with symptoms developing over years [3]. Therefore, we believe the marked MRI brain findings in our patient was due to the level of acuity and aggressiveness of the disease. In addition, the good response to the treatment was likely due to early diagnosis and several factors known to be associated with positive clinical outcome. These factors encompass cognitive impairment, presence of HLA-DQB1*05:01 without HLA-DRB1*10:01 and atypical phenotypes [12] such as atypical Brain MRI features observed in our case.

Conclusion

In summary, anti-IgLON5 disease is a rare syndrome which can pose diagnostic challenges.

We presented a case of the disease characterized by subacute presentation, atypical brain MRI features and good response to treatment. The presence of such distinctive MRI findings should prompt clinicians to consider anti-IgLON5 disease as one of the potential differential diagnosis.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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