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Case Report

Anti-IgLON5 Disease: The First Cured Paediatric Case in a Previously Healthy Child

WL ***Liu***, F ***Li***

Abstract Anti-IgLON5 disease is mainly related to elder adults. Here, we report the first cured paediatric case who was previously healthy. The patient who doesn't carry HLA DRB1*10:01 and HLA DQB1*05:01 had almost all manifestations of the disease. This is the first report of significantly increased serum IgE in this disease. Active immunotherapy (IVIG and repeated rituximab) and hyperbaric oxygen had a positive effect, in which repeated rituximab played an important role. The patient's improvement was related to IgE decrease. The pathogenesis may differ between paediatric and adult cases. The report has enlightening significance for future treatment of the paediatric disease. Study on the correlation between IgE and anti-IgLON5 disease may be beneficial for understanding the mechanism and developing effective treatment in future.

Key words Anti-IgLON5 disease; Child; Hyperbaric oxygen; IgE; Immunotherapy

Introduction

Anti-IgLON5 disease was first described as a progressive antibody-related encephalopathy in 2014.[1] This disease is mainly related to elder adults.[2] Here, we report the first cured paediatric case who was previously healthy.

Case Report

A 9-year-old girl presented with a 2-month history of mild memory decline, bad temper, and attention deficit after an infection (Table 1). She was previously healthy. She is allergic to grass carp and shrimp. From the 71th day, her condition rapidly deteriorated, with seizures, hyperhidrosis on extremities, fasciculations in right face, and sleep disturbances due to numbness of toes. It was rapidly followed that new symptoms were delirium, motor disorders (involuntary movements, drunken gait, chorea, upper limb stiffness and cramps, and right limb tremor), dysarthria, sialorrhoea, tachycardia, casual urinating, and staying awake all day. At that point, a neurological examination showed confusion. The interictal video electroencephalogram (VEEG) revealed excessive δ activities in left posterior head. Brain magnetic resonance imaging (MRI) was normal. Six leukocytes/mL and IgG-oligoclonal bands were in cerebrospinal fluid (CSF). Detection of humoral immunity showed significantly increased serum immunoglobulin E (IgE) 1410 IU/mL (0-90). IgLON5 antibodies (IgG) with cell-based assay in serum and CSF were 1:100 and 1:10, respectively (Figures 1 A & B). Other antibodies of autoimmune encephalitis and central demyelinating diseases were negative. Anti-IgLON5 disease was diagnosed. She was treated with intravenous immune globulin (IVIG), high dosage of methylprednisolone (HDMP), and rituximab (RTX). Her

Department of Pediatrics; Affiliated Hospital of Guizhou Medical University, Guiyang 550004, China
WL **Liu** (劉維亮) *MD*

Department of Ophthalmology, Affiliated Hospital of Guizhou Medical University, Guiyang 550004, China
F **Li** (李芳) *MM*

Correspondence to: Dr WL **Liu**
Email: liuweiliang205@aliyun.com

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symptoms partially improved, including involuntary movements, stiffness and cramps, tremor, fasciculations, sialorrhoea, and sleep disturbances, with no perspiration on extremities but hyperhidrosis on head, after IVIG. She still had incontinence, excitement, involuntary walking, and disturbed sleeping pattern, after HDMP. Immune work-up showed elevated CD19+ lymphocytes (B cells), 28.5% (9.23-18.15%), 600/μL (247-578), before RTX. Brain MRI before three courses of RTX (RTX3) showed symmetric cerebral hemisphere atrophy (Figure 2A), in which significant manifestations were bilateral hippocampal atrophy (Figure 2B), cortical atrophy, and enlarged lateral ventricles, without atrophies of brainstem and cerebellum. Most symptoms recovered after RTX4, but there was only dementia characterised by failure in solving simple addition and subtraction within 10, not knowing own name, repetitive speech, and poor people recognition. After RTX4, serum anti-IgLON5 IgG decreased to 1:30, and CSF anti-IgLON5 IgG was 1:10 (Figures 1 C & D). Serum IgG subclass analysis revealed IgG1 and IgG4 were normal. Human total tau protein in CSF was normal. Human leukocyte antigen (HLA) typing revealed HLA A*11:01, 11:01; B*13:01, 15:02; C*08:01, 03:04; DRB1*11:01, 15:01; DQB1*03:01, 06:01; DPB1*/,/. She doesn't carry HLA DRB1*10:01 and HLA DQB1*05:01. High-throughput nucleic acid sequencing of pathogenic microorganisms in CSF was negative. VEEG showed the background α activities mixed with θ waves. Chest and abdominal CT scans were normal. After hyperbaric oxygen and RTX5, dementia improved significantly, she was able to do addition and subtraction within 60, normal people recognition, normal communication, normal self-care, significant long-term memory recovery, and gradual short-term memory recovery. Serum anti-IgLON5 IgG decreased to 1:10 (Figure 1E). IgE decreased to 531 IU/mL. Allergen by screening was dust mites. Afterwards, hyperbaric oxygen was administered once every 15 days per month. After RTX6, the patient had normal cognition, with mild dysarthria, and laboratory tests showed negative CSF IgLON5 IgG, serum IgLON5 IgG at 1:10 (Figure 1F) and IgE at 116 IU/mL. After RTX7, she fully recovered, and results of examinations revealed negative serum IgLON5 IgG, normal VEEG and brain MRI.

Discussion

Main features of anti-IgLON5 disease are movement disorders, sleep problems, bulbar dysfunction, oculomotor

Table 1 Course and treatment of the present case

D1-3	**D5**	**D71**	**D75**	**D78**	**D80**	**D82-86 IVIG**	**D82-87 HDMP**
Upper respiratory tract infection	Memory decline, touchy. D20, attention deficit. D59, fever for 1 day	Seizures (tonic of upper limbs and right lower limb, foaming at the mouth) for 3 minutes 5 times in a week, perspiration, limb rigidity, silence	Fasciculations, poor sleep	Delirium, involuntary movements, limb stiffness and cramps, tremor, drunk gait, casual urinating, no sleep	Chorea, dysarthria, sialorrhea, tachycardia, mania	D86, symptoms improved partially	D97, poor treatment effect

D98 RTX1	**D105 RTX2**	**D112 RTX3**	**D119 RTX4**	**D137-149 Hyperbaric oxygen**	**D150 RTX5**	**D203 RTX6**	**D368 RTX7**
D104, limb tremor improved	D111, no hyperhidrosis, normal movement and temper, improved consciousness	D118, restored consciousnes	D136, dementia	D149, repetitive speech improvement, knowing own name, partial addition and subtraction subtraction within 10, improved recognition, poor communication, poor self-care, partial memory recovery	D202, dementia improved obviously	D210, normal cognition, mild dysarthri	D419, normal

D, day; HDMP, high dosage of methylprednisolone; IVIG, intravenous immune globulin; RTX, rituximab

abnormalities, dysautonomia, cognitive impairment, neuromuscular symptoms, and progressive supranuclear palsy-like phenotype in adults.[3] Previously, an untreated paediatric individual of the disease with Langerhans cell histiocytosis was first reported.[4] Sleep problems and movement disorders are main manifestations in above patient.[4] Our patient is the first cured paediatric case who was previously healthy. Our patient had cognitive impairment, movement disorders, sleep disorders, psychosis and behaviour changes, seizures, dysautonomia,

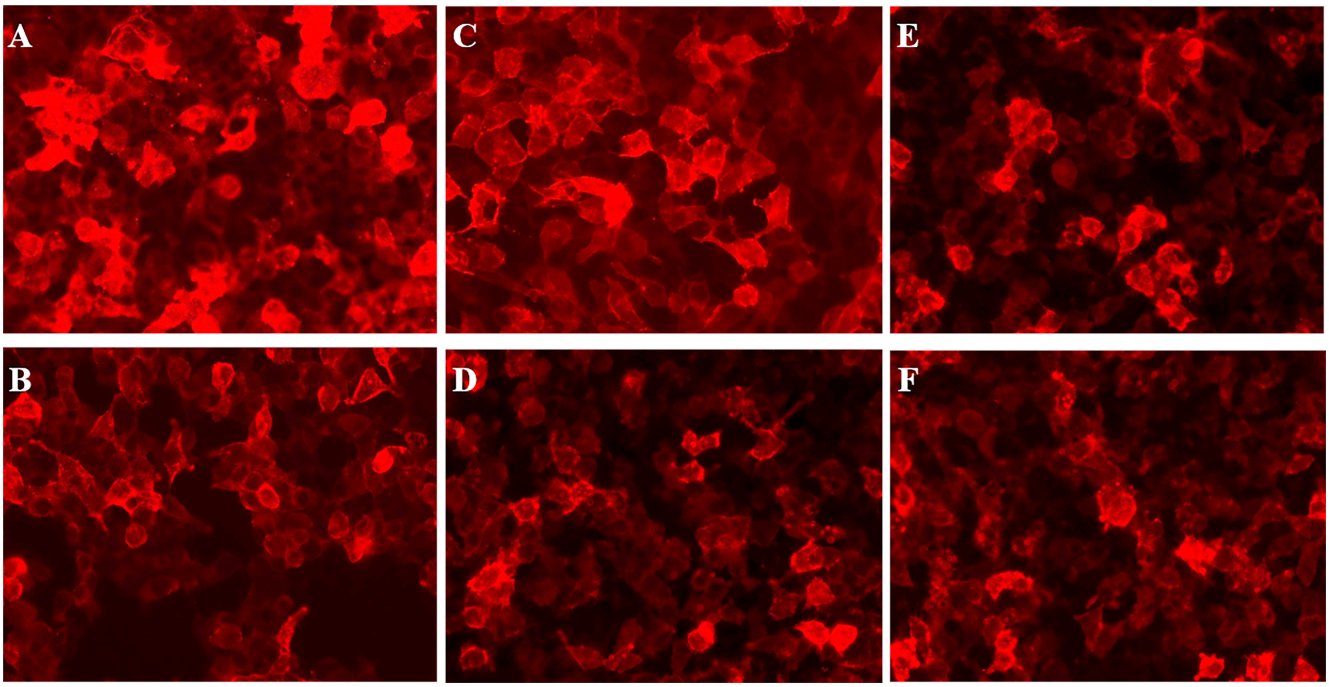

Figure 1 IgLON5 IgG. (A) Serum IgLON5 IgG 1:100, (B) CSF IgLON5 IgG 1:10, (C) Serum IgLON5 IgG 1:30, (D) CSF IgLON5 IgG 1:10, (E) Serum IgLON5 IgG 1:10, (F) Serum IgLON5 IgG 1:10.

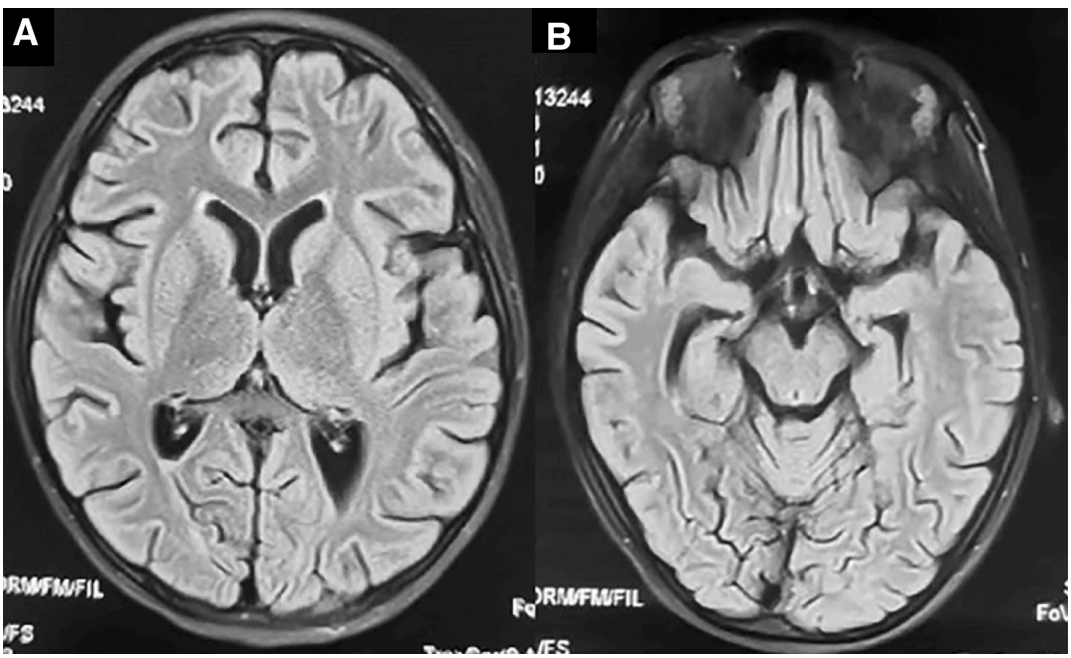

Figure 2 Brain MRI. (A) T2W-Flair MRI showing symmetric cerebral hemisphere atrophy, (B) T2W-Flair MRI showing bilateral hippocampal atrophy.

peripheral neuropathy, neuromuscular symptoms, and bulbar dysfunction, in which cognitive impairment was the most severe and persistent. The patient with chronic insidious onset may have an acute exacerbation process.

To date, 5 paediatric cases (Table 2) including our patient with the disease have been reported.[4-7] The individuals had sleep problems (100%), psychosis/behaviour changes (≈100%), movement disorders (80%), cognitive impairment (80%), oculomotor abnormalities (60%), bulbar dysfunction (40%), seizures (40%), dysautonomia (20%), and brain MRI anomalies (80%). Paediatric patients generally have psychosis/behaviour changes, which may be one of the core symptoms of the disease in children.

Active immunotherapy (IVIG and repeated RTX) and hyperbaric oxygen may had a positive effect, in which long-term repeated RTX acting by rapid and sustained B-cell depletion played an important role in our case. The lack of systematic RTX therapy in other paediatric patients may be a reason for unsatisfactory treatment. Slower short-term memory recovery in our patient may be related to hippocampal atrophy. Anti-IgLON5 disease was considered complex processes between neurodegeneration and neuroimmunology with a genetic background (HLA DRB1*10:01 and HLA DQB1*05:01) in adults.[8] The paediatric patients (patients 2, 4 and ours) don't carry any of these haplotypes. Complex processes involved in infection-induced neuroimmunologic and neurodegenerative cascades may account for the disease development, and significantly elevated IgE may aggravate above processes. The patient's improvement was related to IgE decrease. Significantly elevated IgE may be part of the clinical spectrum. IgE has abilities both to induce extremely rapid pathologic responses, and to act as a highly sensitive immunologic amplifier capable of triggering reactions.[9] IgE is associated with various autoimmune diseases.[10] Study on the correlation between IgE and anti-IgLON5 disease may be beneficial in future.

In summary, we report the first cured paediatric case with anti-IgLON5 disease. Psychosis/behaviour changes may be one of the core symptoms of the disease in children. This is the first report of significantly increased serum IgE in this disease. Immunotherapy (IVIG and repeated RTX) and hyperbaric oxygen showed good therapeutic response in our paediatric case, in which repeated RTX played an important role. The pathogenesis

Table 2 Major presentation and management in paediatric cases with Anti-IgLON5 disease

	Our case	Case 2	Case 3	Case 4	Case 5
Age and gender	9, F	2, M	13, F	2, M	16, F
Movement disorders	+	+	-	+	+
Sleep problems	+	+	+	+	+
Bulbar dysfunction	+	-	-	+	-
Oculomotor abnormalities	-	+	-	+	+
Dysautonomia	+	-	-	-	-
Cognitive impairment	+	-	+	+	+
Seizures	+	-	+	-	-
Psychosis/behaviour changes	+	±	+	+	+
Brain MRI	+	enhancement of meninges	+A	+B	-
IgLON5 antibodies	1: 100 (serum), 1:10 (CSF)	1: 30 (serum), - (CSF)	1: 100 (serum), - (CSF)	1: 30 (serum), - (CSF)	+
Management	IVIG, CS, HO, repeated RTX	NA	IVIG, CS	IVIG, CS, RTX, MMF	IVIG, CS, PE
Outcome	Cure	NA	Partial improvement	Partial improvement	Partial improvement
References	The study	4	5	6	7

A, abnormal signal in bilateral hippocampus, a choroid fissure cyst in the right hippocampus;

B, abnormal signals in the bilateral cerebellar hemispheres, basal ganglia, and dorsal thalamus, and notable cerebral atrophy after treatment;

CS, corticosteroids; CSF, cerebrospinal fluid; F, female; HO, hyperbaric oxygen; IVIG, intravenous immune globulin; M, male; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; NA, not available; PE, plasma exchange; RTX, rituximab

may differ between paediatric and adult cases. Study on the correlation between IgE and anti-IgLON5 disease may be beneficial for understanding the mechanism and developing effective treatment in future.

Declaration of Competing Interest

The authors report no conflict of interest.

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Nil.

Ethics Approval

This work was approved by the Ethics Committees of Affiliated Hospital of Guizhou Medical University.

Authors' Contributions

WLL and FL carried out the clinical studies, the data analysis and wrote the manuscript. WLL advised and guided the project. All authors read and approved the final manuscript.

Consent for Publication

Written informed consent and permission have been obtained from the legal guardians of the patient for publication of the study and accompanying images.

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