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RECURRENT ANTI-GAD65 LIMBIC ENCEPHALITIS IN A PEDIATRIC PATIENT

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ABSTRACT

CASE REPORT

Limbic encephalitis (LE) associated with anti-glutamic acid decarboxylase (GAD) 65 antibodies is an autoimmune condition characterized by signs and symptoms of limbic system inflammation. Herein we present the case of an 8-year-old girl with recurrent anti-GAD65 limbic encephalitis with a past history of viral infection.

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INTRODUCTION

Limbic encephalitis (LE) is an autoimmune condition characterized by signs and symptoms of limbic system inflammation [1]. Glutamic acid decarboxylase (GAD) is an intracellular enzyme, concentrated in presynaptic terminals, responsible for the synthesis of gamma-aminobutyric acid (GABA), a central nervous system (CNS) inhibitory neurotransmitter [2]. GAD antibodies are known to be associated with autoimmune health conditions, including limbic encephalitis [3,4]. Herein we present a case of recurrent autoimmune limbic encephalitis associated with anti-GAD65 antibodies in an 8-year-old girl, with a past history of viral infection.

CASE PRESENTATION

First episode

History: The 8-year-old girl, with a normal psychomotor development, came to our clinic accompanied by her parents with the

following complaints: initially, she presented abrupt behavioral changes, irritability and emotional lability, deficiency of speech, lack of concentration and memory loss, and one week later she presented headache and morning vomiting additionally. A viral infection 10 days prior to the early complaints was reported. She had no history of other acute/chronic disorders, trauma or substance abuse.

Physical examination: During inspection, slow and unbalanced gait, expressionless face (hypomimia) and hand automatisms were noticed. She looked tired and was apathetic and detached to the surrounding environment. While being interrogated, the girl was space, time and self-disoriented and showed a lack of concentration. She had global dysphasia with a slow rate, low volume, and monotonous speaking. Her speech content was poor and incoherent. She was unable to name her parents and ordinary objects. She could identify letters but couldn't read full words. The girl presented a loss of previous ability to write (agraphia), was not able to copy drawings of basic two-dimensional geometric shapes, and was not able to solve simple arithmetic operations (dyscalculia). She had both anterograde and retrograde amnesia. On neurological examination, bilateral pyramidal syndrome with patellar hyperreflexia and Babinski signs were present.

Laboratory and imaging investigation: Blood tests (complete blood count, biochemical panel, C-reactive protein, leukocyte immunophenotyping) were unremarkable of any metabolic or infectious etiology. Cerebrospinal fluid (CSF) biochemistry and cytology tests were within normal ranges. Electroencephalogram (EEG) recording showed spiked and slow right frontotemporal alpha waves, even though clinically the girl never presented convulsions. Brain computed tomography (CT) imaging showed no significant findings.

***Treatment and outcome*:** Empirical treatment was started with acyclovir, ceftriaxone, intravenous immunoglobulin (IVIg), high dose methylprednisolone pulse therapy, phenobarbital and valproic acid to which she was responsive. She was prescribed valproic acid after being discharged home.

Second Episode

After 18 months of remission the patient was hospitalized again in our clinic as the neuropsychiatric complaints were once more present 5 days after a spontaneous fall while standing, with immediate complete recovery (drop attack). On admission she displayed face blindness (prosopagnosia); she could only identify her mother by smelling her scent. Brain imaging studies (CT and MRI) were normal. CSF examination was within normal ranges. EEG showed epileptiform brain activity with no clinical seizures. Meningitis/encephalitis panel was proposed which resulted in negative for all 14 bacterial, viral and fungal most common organisms that affect the nervous system. Central nervous system vasculitis was suggested as a possible diagnosis, therefore a serum antibody/autoimmunity panel was requested; only anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (anti-SMA), anti-Sjogren Syndrome A (Ro) (anti-SSA/Ro) antibodies resulted positive (Table 1). Protein immunoelectrophoresis and complement system proteins were within normal range. The history, physical examination, laboratory and imaging findings were unremarkable of any systemic autoimmune disorders or malignancies. Autoimmune encephalitis (AE) was then proposed as a suspected diagnosis, therefore an anti-neuronal autoantibody panel was requested; only enzyme-linked immunosorbent assay (ELISA) detected anti-glutamic acid decarboxylase (GAD) 65 antibodies (Table 1). She was administered methylprednisolone, IVIg and valproic acid; clinical improvement was evidenced. She was

again prescribed valproic acid after being discharged home.

Third Episode

After 12 months of remission, the patient was hospitalized again as the neuropsychiatric complaints were present spontaneously for the third time. Blood tests, MRI, and CSF examination were within normal ranges. EEG showed epileptiform activity without clinical seizures. At this point, we administered the second-line treatment with rituximab to which she was responsive.

Table1. Serology test results

Antibodies	Result	Method
ANA	+++; positive	IIF
AMA	negative	IIF
anti-SMA	positive	IIF
anti-dsDNA/IgG	negative	IIF
ACA/ IgM, IgG	negative	EIA
ENA screen	1.8; positive	EIA
anti-SSA/Ro	1.52; positive	EIA
anti-SSB/La	negative	EIA
anti-Sm	negative	EIA
anti-RNP	negative	EIA
anti-Scl-70	negative	EIA
anti-Jo-1	negative	EIA
Anti-neuronal antibodies		
anti-NMDAR antibodies	negative	IF
anti-GAD antibodies	15.4; positive	ELISA
anti-VGKC antibodies	negative	RIA

ACA, anti-cardiolipine antibody; anti-Jo-1, histidyl transfer tRNA synthetase antibody; AMA, anti-mitochondrial antibody; ANA,antinuclear antibody; anti-Sm, Smith antibody; anti-SCl-70, scleroderma antibody; dsDNA, double-stranded deoxyribonucleic acid; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ENA, extractable nuclear antigen; GAD, glutamic acid decarboxylase; IF, immunofluorescence; IgG, immunoglobulin G; IgM, immunoglobuline M; IIF, indirect immunofluorescence; NMDAR, N-methyl-D-aspartate; RIA, radioimmunoassay; RNP, ribonucleoprotein; SMA, anti-smooth muscle antibody; SSA, Sjogren Syndrome A; SSB, Sjogren Syndrome B; VGKC, voltage-gated potassium channel.

DISCUSSION

On the first admission, after excluding psychiatric disorders, the empirical diagnosis of encephalitis was made. On the second admission, a multidisciplinary team of medical doctors in specialties of neuropediatrics, pediatric rheumatology, pediatric psychiatry and immunology, was engaged and evaluated this clinical case – the patient's medical history, physical examination, laboratory and imaging test results – and, succeeding the differential diagnosis, the definitive diagnosis

of a recurrent autoimmune limbic encephalitis associated with GAD65 antibodies was made.

In the medical literature, data on the epidemiology of autoimmune encephalitis (AE) in pediatric patients is limited, although AE associated with N-methyl-D-aspartate (NMDA) antibodies, voltage-gated potassium channels (VGKC) antibodies or glutamic acid decarboxylase (GAD) antibodies are increasingly being diagnosed [5]. Pediatric anti-GAD limbic encephalitis (LE) is a rare condition among the spectrum of brain tissue inflammations, often misdiagnosed, thus causing serious adverse outcomes [6,7]. Different mechanisms have been proposed regarding AE, including the presence of a tumor (paraneoplastic) or a previous neurotropic infectious trigger (non-paraneoplastic) such as viruses [8,9]; in our patient, the viral infection 10 days before the initial symptoms was obviously the antecedent event.

LE is usually presented with memory deficits, behavioral changes, learning difficulties, lack of concentration, motor impairment, and seizures [1,10,11]. Relapses are infrequent in AE but not unknown; the relapse risk (one or multiple) in anti-NMDA encephalitis in children followed up for 1–5 years was 13.5%, meanwhile, in other types of AE the risk of relapse is not clearly evaluated [12].

As to the laboratory test results in our case, besides the presence of anti-GAD antibodies, ANA, anti-SMA and anti-SSA/Ro activities were also proven positive; we believe they are findings that accompany the occurrence of autoimmunity as an antigenic cross-reactivity.

Despite lacking an established treatment protocol for GAD antibodies associated LE in particular and AE in general, standard immunotherapy with corticosteroids followed by or combined with IVIg is considered the first-line treatment. Plasmapheresis (plasma exchange) should also be taken into consideration. If nonresponsive to the first-line therapy or relapses, the second-line treatment is immunotherapy with rituximab, cyclophosphamide, mycophenolate mofetil, azathiopine, either alone or combined, and if refractory to the second-line treatment, immunotherapy drugs known as third-line therapy, like daratumumab, bortezomib, tocilizumab, tofacitinib, low-dose interleukin 2 (IL-2), are recommended. [13-15].

CONCLUSION

Recurrent anti-GAD65 limbic encephalitis is an infrequent brain condition in children, therefore we believe this case report is a valuable contribution to the literature. Due to its variable clinical presentation, all clinicians should consider autoimmune encephalitis as a possible diagnosis when neuropsychiatric signs and symptoms are present in a child in order to avoid adverse outcomes. Laboratory tests and imaging examinations can provide evidence of brain inflammation, but a normal CT/MRI, EEG or CSF profile do not exclude the diagnosis.

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CONFLICT OF INTERESTS: The authors declared no conflict of interest.

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