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A complex case of young child with ADHD, developmental delay who developed seronegative autoimmune encephalitis exacerbated by stimulants

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ABSTRACT

Autoimmune encephalitis (AE) is a group of disorders characterized by a wide clinical spectrum ranging from the typical limbic encephalitis to more complex neuropsychiatric symptoms including abnormal movements, psychosis, deficits in memory and cognition, dysautonomia, seizures, or coma. Psychiatric symptoms can occur early in the disease progress or manifest during its course. These symptoms are challenging and often slow down the diagnosis of AE. This is a crucial aspect considering that early diagnosis and management of AE are critical for a good outcome. However, there is a lack in studies outlining the exact symptomatology and specific appropriate care that would allow clinicians to achieve an early diagnosis and management. Additionally, AE in children mostly presents with neuropsychiatric symptoms and diagnosis is especially challenging in kids because of their limited capacity in describing their symptoms, the normal childhood behavioral changes and the possibility of a comorbid psychiatric diagnosis. We present a complex case of seronegative AE with comorbid ADHD (Attention Deficit Hyperactivity Disorder) and anxiety in a young six-year-old girl.

1. Introduction

Autoimmune encephalitis (AE) is a group of disorders characterized by a wide clinical spectrum ranging from the typical limbic encephalitis to more complex neuropsychiatric symptoms including abnormal movements, psychosis, deficits in memory and cognition, dysautonomia, seizures, or coma occurring in association with antibodies against neuronal cell surface proteins and synaptic antigens (Leypoldt et al., 2013). Seronegative autoimmune encephalitis is a subgroup without established autoantibodies or targeted neural autoantigens (Najjar et al., 2011; Storey et al., 2011). In children, AE presents as an acute or subacute onset of neuropsychiatric symptoms that can overlap with symptoms of other inflammatory brain diseases, metabolic diseases, infections and psychiatric disorders (Van Mater, 2014). It is particularly challenging in younger children because of their limited ability to describe their symptoms and the complexity of typical behavioral changes during childhood. We present a case of seronegative AE with comorbid ADHD and anxiety in a young girl.

2. Case

This is a 6-year-old girl with a history of developmental speech delay, sleep difficulties, anxiety and ADHD diagnosed in August 2020. She initially presented at the age of 4 in September 2020 to the young child clinic at Mayo Clinic in Rochester Minnesota, where she was started on methylphenidate hydrochloride (Ritalin IR-total dose of 12.5 mg) and clonidine 0.1 mg. The medications prescribed were helpful, but in February 2022, mother continued to report hyperactive behaviors that were difficult to manage. She was then switched to Dexmethylphenidate (Focalin XR 10 mg). A higher dose of the stimulant was helpful, but mother continued to report that there was room for improvement both at home and school. With patient's weight being 20.7 kg dose of Focalin XR was titrated to 20 mg. In May 2022, the patient's mother reported episodes of staring spells that started in March 2022 to the psychiatrist who directly referred the patient to neurology. In June 2022 the patient presented to neurology with worsening daily dystonic posturing of her upper limbs and abnormal orofacial movements which were reported by the mother to have started in mid-April 2022. The mother also mentioned unusual crawling sensation on her skin, subtle personality

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changes and language regression that started mid-May 2022. Initially the movements were subtle and difficult to notice. They have worsened over time to the point where parents were not able to ignore them.

A routine awake EEG was performed and did not reflect any seizure activities. A brain MRI without and with contrast was arranged but the results were normal. Infectious etiologies were excluded with negative antistreptolysin-O and Anti-DNase titers and normal CSF cell count and differential (Table 1). Serology was negative for all autoantibodies. However, three oligoclonal bands were found in the cerebrospinal fluid (CSF). Considering the acute nature (<3 months) of the patient's symptoms of staring spells, worsening dystonic posturing, abnormal orofacial movements, language regression, subtle personality changes and crawling sensation on her skin and the presence of three oligoclonal bands in the CSF, the diagnosis of seronegative AE was considered as she fills the criteria for probable autoimmune AE for the pediatric population (Dalmau and Graus, 2023). Coincidentally, the patient underwent an evaluation at another facility for autism spectrum disorder (ASD) in mid-April 2022, around the time frame when her symptoms of seronegative AE started and was diagnosed with ASD with intellectual impairment.

Due to continuous clinical worsening a decision was made to discontinue dexmethylphenidate, which improved her AE symptoms but exacerbated her hyperactivity and inattentive behaviors. She was then prescribed a 5-day course of intravenous (IV) methylprednisolone infusion 500 mg, followed by a trial of 20 g IV immunoglobulin (IVIG). No clear improvement was seen after she received the IV methylprednisolone, and her IVIG trial was withheld due to lack of insurance coverage. Because her ADHD symptoms were not controlled, under neurology supervision patient was started on lisdexamphetamine (Vyvanse) at 20 mg (dose equivalent to her last effective dose of Focalin XR). However, it significantly worsened the bug crawling sensation on her skin and the dystonic movements which started to occur during sleep and could last for hours. The severity of her AE symptoms diminished again after discontinuing the stimulant. Similarly, the trial of methylphenidate hydrochloride (Ritalin IR) at a very low dose of only 5 mg-test dose, exacerbated her symptoms, hence a decision was made to stop all stimulants and prescribe atomoxetine to control her ADHD. Despite increasing the dosage of the non-stimulant, the patient was still struggling with hyperactivity and inattention. Therefore, she was put on a trial of methylphenidate hydrochloride extended release (Jornay PM) at lowest possible dose 20 mg which did not exacerbate her AE symptoms and controlled her ADHD symptoms. The patient was then admitted to the pediatric epilepsy monitoring unit where she underwent a video-EEG (VEEG) monitoring for two days. After administering short acting methylphenidate, abnormal posturing of her upper extremities was recorded on video, but she did not have any seizure like EEG changes or decreased alertness. She then received two rounds of 20 g IVIG treatment which improved her symptoms quickly over the course of subsequent days. However, the patient still had occasional but less severe episodes of abnormal orofacial and upper extremity movements, therefore she is planned to continue the therapy of monthly 1 g/kg IVIG infusion for a minimum of 3 months. The patient also underwent a reevaluation for her ASD diagnosis at school and she did not meet criteria for autism. A full testing will be done at the developmental clinic to reassess her autism diagnosis. See Fig. 1 for a timeline of the case.

Table 1
CSF differential.

Fluid type	CSF
CSF gross appearance	Clear
Erythrocytes	0
Neutrophils % Reference value 4% ± 4%	0
Lymphocytes % Reference value 60% ± 20%	67
Monocyte/Macrophages % Reference value 30% ± 20%	33
Eosinophils	0
Basophils	0
Oligoclonal bands Reference value < 2	3
Pyruvic acid mmol/L Reference value 0.06–0.19 mmol/L	0.13
Lactic acid mmol/L Reference value 1.1–2.8 mmol/L	2
Glucose mg/dL	59
Protein total mg/dL Reference value 0–35 mg/dL	15

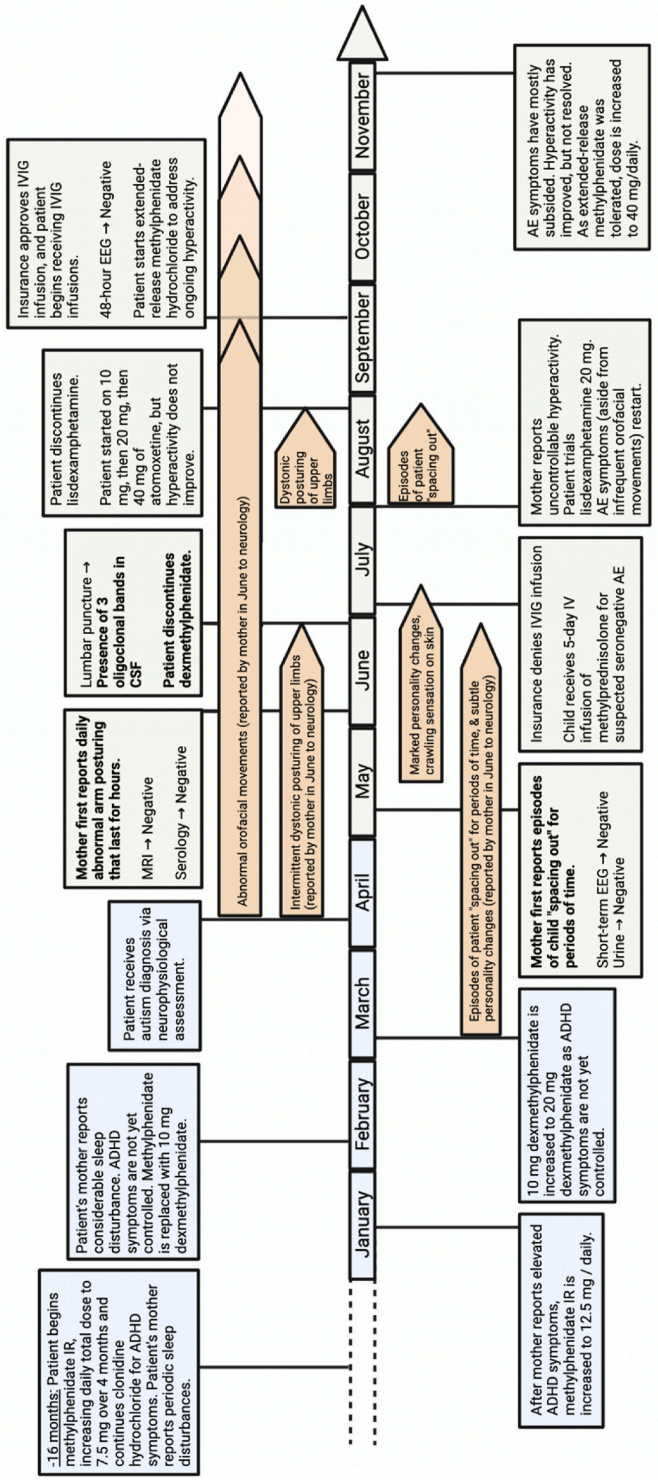

Fig. 1. Case timeline.

3. Discussion

3.1. Stimulant medication and neuroinflammation

To date, this is the first reported case of seronegative AE in which AE symptoms are exacerbated by stimulant medications. Stimulants such as amphetamine and methylphenidate are among the most effective treatments to manage ADHD but may cause movement disorders (Nam et al., 2022). Several cases of chorea, dystonic reactions, and orofacial and extremity dyskinesia exacerbated by stimulant treatment have been reported in the literature (Heinrich, 2002; Mattson and Calverley, 1968; Melvin and Heiraty, 2013; Pagliaro et al., 2022; Senecky et al., 2002; Tekin et al., 2015; Waugh, 2013; Yilmaz et al., 2013). There are two total reported cases of AE in the literature in a child and adolescent in which patients had been taking methylphenidate (Gillespie et al., 2020; Najjar et al., 2013), and one AE case in an adolescent in which the patient had been taking dexmethylphenidate (Fields et al., 2013), though there was no evidence to suggest in any of this (Aiken et al., 2002) literature that the stimulants were related to their AE diagnosis or symptoms.

Nonetheless, data from several rodent studies using therapeutic doses of methylphenidate showed that chronic treatment with methylphenidate can lead to neuroinflammation. This was evidenced by an increase in proinflammatory cytokines (Tumor necrosis factor alpha, interleukin 1 beta and interleukin 6), lipid peroxidation and mitochondrial oxidized glutathione in neurons. Additionally, it has been shown in several other rodent studies that rats administered with amphetamine display increased mRNA expression of IL-6, TNF-α, and other proinflammatory cytokines in various brain tissues compared to controls. It is well known that IL-6 stimulates B-cell differentiation, promotes antibody secretion and therefore induces and enhances autoimmunity (Bertolini and Benson, 1990; Kishimoto, 2005). A study by Byun et al. found elevated levels of IL-6 in the CSF of patients with anti-NMDAR encephalitis (Byun et al., 2016), and in a separate clinical trial, the use of tocilizumab (anti IL-6 antibody) in refractory AE showed clinical improvements (Lee et al., 2016).

It was noted that in this case of seronegative AE, the timing of AE symptoms became apparent when the patient was transitioned from Ritalin IR to Focalin XR and significantly worsened after increasing the dose of Focalin XR from 10 mg daily to 20 mg daily. It could be coincidental as AE is a significant illness and one would not expect a stimulant medication to have major influence over it. It is interesting that during the course of illness when psychiatrist attempted to try different stimulant medications such as Vyvanse, Ritalin IR each time AE symptoms were visibly exacerbated. Only after first dose of IVIG was patient able to tolerate a stimulant medication. Taken together, it is possible that the patient's exacerbation of AE symptoms was due to a stimulant medication. It is unclear and unlikely whether pharmacokinetic profile of stimulant formulations played a role in AE symptomatology. It is important to note that by the time Jornay PM was trialed, the patient had already received a course of high dose IV steroids and was just starting the first course of IVIG treatment. Although steroids were minimally efficacious in relief of AE symptoms, IVIG significantly improved AE symptoms.

3.2. Encephalitis and ADHD

Regarding the neuropathology behind ADHD, there has been evidence supporting the role of the immune activation in the etiology of ADHD. In the literature, observational data supports the comorbidity of ADHD and autoimmune and inflammatory disorders (Chen et al., 2017). Studies show that individuals with ADHD have a higher risk of developing diseases with an immune aspect (Hegvik et al., 2018a; Miyazaki et al., 2017). A Danish study using a national registry showed an association between ADHD and juvenile arthritis, type 1 diabetes and autoimmune thyroiditis (Nielsen et al., 2017). Another Norwegian study using a national registry found an association between ADHD and psoriasis in both males and females, and Ulcerative colitis and Crohn's disease in females (Hegvik et al., 2018b). The potential role of neuro-immune dysregulation in the pathogenesis of ADHD has been suggested after finding auto-antibodies against dopamine transporter that correlated with the severity of ADHD symptoms in a subgroup of children with ADHD (Hoekstra, 2019).On the other hand, autoimmune encephalitis is an immune mediated condition related to autoimmune antibodies targeting synaptic proteins and causing widespread inflammation (Hébert et al., 2022). One could hypothesize that overlapping entity of immune dysfunction in both ADHD and autoimmune encephalitis could justify a common pathogenic background between these two conditions.

3.3. Encephalitis and ASD

Multiple studies in the literature describe the regression of patients into an autism diagnosis after a diagnosis of encephalitis, including AE (Ghaziuddin et al., 2002; Gonzalez-Toro et al., 2013; Marques et al., 2014; Scott et al., 2014). Gonzàlez-Toro et al. report resolution of ASD symptoms in a 5-year-old girl diagnosed with anti-NMDA encephalitis after receiving IV corticosteroids, immunoglobulins and Rituximab (Gonzalez-Toro et al., 2013). Similarly, Scott et al. described the case of a 33-month-old boy who presented sleep disturbance, irritability, loss of language and social skills, and abnormal upper limb movements. The patient met the diagnostic criteria of ASD within a month but was later also diagnosed with anti-NMDA encephalitis. Treatment with IV immunoglobulins and steroids resulted in resolution of all symptoms including requisition of language and social skills (Scott et al., 2014).

Interestingly, our patient's diagnosis of ASD happened around the same time she displayed symptoms of AE. Treatment of encephalitis with IV immunoglobulins conferred improvement of her symptoms, and the reassessment at school showed that she did not meet criteria for an ASD diagnosis.

This emphasizes on the importance of suspecting autoimmune encephalitis as the cause of autistic regression. A high index of suspicion should be maintained even in an age group where the diagnosis of ASD is typically made, and specifically when symptoms present abruptly with concurrent dystonic movements.

Statement regarding informed consent

The consent to publication has been obtained by patient.

Authors' contributions

The Authors contributed equally in the preparation of the manuscript.

Prior publications

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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