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Co-existence of anti-glutamic acid decarboxylase-65 and anti-sry-like high-mobility group box receptor antibody-associated autoimmune encephalitis: A rare case report

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ABSTRACT

Autoimmune encephalitis (AE) has been increasingly recognized in children. An 11-year-old Saudi boy presented with prodromal symptoms of fever and headache followed by behavioral changes, cognitive impairment, and focal seizures. Cerebrospinal fluid (CSF) analysis showed pleocytosis. Brain magnetic resonance imaging showed T2/fluid-attenuated inversion recovery hyperintensities involving the temporal, parietal and frontal lobes. Electroencephalography revealed diffuse encephalopathy and electrographic seizures. AE was suspected; intravenous methylprednisolone and immunoglobulin were administered. Autoantibodies against glutamic acid decarboxylase-65 were detected in his serum and CSF and against Sry-like high- mobility group box 1 in his serum only. The patient was diagnosed with seropositive AE and favorably responded to intensive immunosuppressive therapy.

Introduction

Autoimmune encephalitis (AE) is a rapidly progressive encephalopathy caused by antibodies targeting cell-surface or intracellular antigens in the central nervous system (CNS) [1]. Neurological manifestations of AE in children include acute or subacute onset of behavioral changes, cognitive impairment, language dysfunction, psychiatric manifestations, seizures, movement disorders, and autonomic dysregulation [1–3]. The most commonly reported autoantibodies in children are targeted against *N*-methyl-D-aspartate receptor, myelin oligodendrocyte glycoprotein (MOG), glutamic acid decarboxylase-65 (GAD65), and γ-aminobutyric acid type A receptors [1–4].

GAD65 is an intracellular enzyme involved in synthesizing gamma-aminobutyric acid, an inhibitory neurotransmitter in the CNS [1]. Antibodies against GAD65 are biomarkers for autoimmune CNS disorders, including stiff-person syndrome; cerebellar ataxia; epilepsy; and limbic and extra-limbic encephalitis [1]. To our knowledge, cases of GAD65 antibody-associated encephalitis have not been widely reported in the literature [1,2,5–9].

Sry-like high-mobility group box (SOX) 1 proteins are transcription factors essential for CNS development [10]. Anti-SOX1 antibodies are associated with various paraneoplastic and non-paraneoplastic neurological syndromes, including Lambert-Eaton myasthenic syndrome (LEMS), paraneoplastic cerebellar degeneration (PCD), and paraneoplastic limbic encephalitis (PLE) [11–13]. Anti-SOX1 encephalitis is rare in children. To our knowledge, only two pediatric cases have been reported [14,15].

Case report

A previously healthy 11-year-old Saudi boy presented to a local hospital with a history of decreased level of consciousness and seizures. He was admitted for managing suspected meningoencephalitis. The patient initially presented with prodromal fever and flu-like symptoms for 1 week, followed by sudden changes in behavior, cognitive and memory impairment, and focal seizures. Basic laboratory test results showed leukocytosis and high inflammatory marker levels. Partial septic workup, including blood and urine cultures, was performed. Intravenous

Abbreviations: AE, Autoimmune encephalitis; ASM, antiseizure medication; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FDG, fludeoxyglucose F18; GAD-65, glutamic acid decarboxylase-65; IVIG, intravenous immunoglobulin; LP, lumbar puncture; SCLC, small-cell lung cancer; MOG, myelin oligodendrocyte glycoprotein; NMDAR, N-methyl-D-aspartate receptor; PLE, paraneoplastic limbic encephalitis; SOX, Sry-like high-mobility group box.

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ceftriaxone (2 g every 12 h), vancomycin (15 mg/kg/dose every 12 h), and acyclovir (10 mg/kg/dose every 8 h) were administered for suspected meningoencephalitis. Initial brain computed tomography showed diffuse edema, and lumbar puncture was deferred. The antiseizure medication (ASM) levetiracetam 500 mg BID was initiated to control seizures. His health continued to deteriorate after 2 days, with a persistent decrease in consciousness level, accompanied by frequent focal onset seizures with impaired awareness and status epilepticus, prompting intensive care unit (ICU) admission, intubation, and infusion with midazolam and fentanyl for seizure control. Urgent brain magnetic resonance imaging (MRI) showed extensive cortical/subcortical swelling associated with diffusion restriction. Measures were undertaken to reduce increased intracranial pressure, including bed elevation, hypertonic saline, and intravenous mannitol. Routine electroencephalography (EEG) showed diffuse background slowing and frequent spike-and-wave discharges over the left hemisphere (T5, P3, and O1). The final culture results for blood, urine, and respiratory specimens, antibodies for herpes and brucella in blood, results of rapid multiplex polymerase chain reaction (PCR) of respiratory specimens, and coronavirus disease PCR results were negative.

Subsequently, after 2 weeks, the patient's seizures were partially controlled, and he was transferred to the ICU of a tertiary hospital for further evaluation and management. On initial assessment, the patient had stable vital signs and was intubated and off sedation, on nasogastric feeding owing to bulbar dysfunction and encephalopathy, with a lack of interest in his surroundings. His cranial nerves showed reactive brisk pupils, limited extraocular muscle movements, and an absent gag reflex. Motor examinations revealed generalized hypotonia, brisk deep tendon reflexes, and a muted plantar response. The patient started experiencing clinical seizures, and intravenous anesthetics were resumed and levetiracetam dose was maximized. The intravenous antibiotics were upgraded to meropenem and piperacillin/tazobactam. Routine laboratory tests and full septic work up including lumbar puncture were repeated.

Further investigations included CSF analysis, brain MRI, and long-term EEG monitoring. CSF analysis revealed clear and colorless pleocytosis (white blood cell count, 11×10^6/L) with lymphocytosis; red blood cell count, 34×10^6/L; glucose level, 5.3 mmol/L; and protein level, 289 mg/L. CSF culture findings were negative. CSF PCR results were negative for *Escherichia coli* K1, H.I, *Listeria*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Cryptococcus*, *Cytomegalovirus*, Enterovirus, HSV, Varicella zoster, and human Parechovirus. Oligoclonal bands were negative. AE workup was performed.

Follow-up brain MRI showed confluent and scattered subcortical and deep white matter patchy T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in the deep gray matter nuclei, specifically the caudate heads, bilateral basal ganglia/putamen, and external capsules. Similarly, corresponding diffusion restriction, specifically in the caudate head, corresponding to T2 hyperintensities in the bilateral basal ganglia and external capsules, and foci of enhancement in the subcortical white matter along the left cerebral hemisphere were observed (Fig. 1A-D). Long-term EEG monitoring revealed left hemispheric regional slowing. Interictal spike-and-wave discharges were observed frequently over the left hemisphere (T5, P3, and O1). Multiple electrographic seizures arising from T5, P3, and O1 evolved to involve the left parasagittal head region and spread to the right frontal head region (Fig. 2). At that time, the patient was administered a loading dose of valproic acid and maintenance dose was initiated. His ASMs included levetiracetam 1500 mg BID (40 mg/kg/day) and valproic acid 250 mg BID (20 mg/kg/day), followed by topiramate 100 mg BID (6 mg/kg/day) administration, but all proved ineffective.

Owing to the acute onset, encephalopathy, refractory seizures, and MRI features of encephalitis, possible pediatric AE was suspected, and immunotherapy was initiated. Intravenous pulse therapy of methylprednisolone (30 mg/kg/d) was administered over 5 days, repeated weekly, for 4 weeks. Simultaneously, adjunctive intravenous immunoglobulin (IVIG) (0.4 g/kg/d) was administered over 5 days and repeated the following week. After the second week of immunotherapy initiation, the patient showed gradual overall improvement, including consciousness level, bulbar symptoms, and seizure control. He was able to recognize and talk to his mother and follow the simple commands of the medical team. The nasogastric tube was removed on the third week of treatment, and he was able to tolerate oral intake without swallowing difficulties as assessed by the speech and language therapist. His seizure frequency and duration improved gradually with treatment until discontinuation. He was encouraged to walk and assessed daily by physical and occupational therapists by the fourth week of treatment.

The encephalitis/paraneoplastic panels were negative for CASPR2, AMPA1, LGI1, AMPA2, $GABA_b$, CV2, PNMA2, Ri, Yo, Hu, Recoverin, and Zic4 and were positive for SOX1 in serum and negative in CSF, and GAD65 in serum and CSF (Euroimmun, Lübeck, Germany). An enzyme-linked immunosorbent assay for GAD65 showed high serum titers (>2000 IU/mL). The serum MOG antibody test result was negative. Whole-body positron emission tomography revealed abnormal fludeoxyglucose F18 (FDG) metabolism throughout the brain parenchyma with a diffuse decrease in FDG uptake in the left cerebral hemisphere. Screening for underlying malignancy by positron emission tomography was negative.

The patient was discharged in a stable condition on antiseizure medications and oral prednisolone with a taper plan. In the last clinic visit, which was a year after his discharge, he showed complete recovery. He ambulated without assistance and was entirely independent in activities of daily living. Similarly, he could formulate clear and comprehensive speech with intact cognition and memory. The patient resumed school and performed well. He had no seizures for 15 months. However, he was advised to continue ASMs. The neurological examination result was non-focal. Repeated titers were negative after treatment. Follow-up brain MRI showed significant improvement in the bilateral cerebral hyperintense lesions with mild atrophic changes (Fig. 1 E-H).

Discussion

AE is a rapidly expanding group of diseases with new subtypes appearing every 10 months over the past 10 years [1]. Herein, we diagnosed our patient with anti-GAD65 and anti-SOX1 antibody-associated AE based on the clinical presentation, neurological deficits, brain MRI findings, aberrant EEG findings, elevated anti-GAD65 and anti-SOX1 antibody levels, response to aggressive immunotherapy, and exclusion of other CNS pathologies.

AE commonly presents with a rapid onset of neurological manifestations, including behavioral changes (irritability, hyperactivity, hypersexuality, or insomnia), psychiatric disorders (mood swings, personality changes, or psychosis), seizures (focal or generalized), movement disorders (ataxia, chorea, dystonia, or myoclonus), and autonomic dysfunction [1]. Children are more likely to present with multifocal neuropsychiatric symptoms than isolated clinical syndromes [1]. Children with GAD65 antibodies may not present with the classic stiff-person syndrome or cerebellar degeneration observed in adults [1]. Thus, diagnosis is more challenging in the pediatric population.

Anti-GAD65 antibodies are the third most common autoantibodies in pediatric AE. However, they are only pathological if high serum and CSF titers are detected. GAD65 encephalitis is characterized by encephalitis, memory deficits, cognitive impairments, psychiatric manifestations, and refractory seizures. The most common presentation is seizures, first described by Malter et al., who reported nine young patients with seizures as the first sign of the disease [16]. Adams et al. described seven patients in whom psychiatric disturbances (depressive features, anxiety, and personality change), cognitive decline (concentration difficulty and memory loss), language decline (aphasia), and seizures were frequently observed with GAD65 [17]. Further studies reported similar neurological and neuropsychiatric manifestations, demonstrating the variability

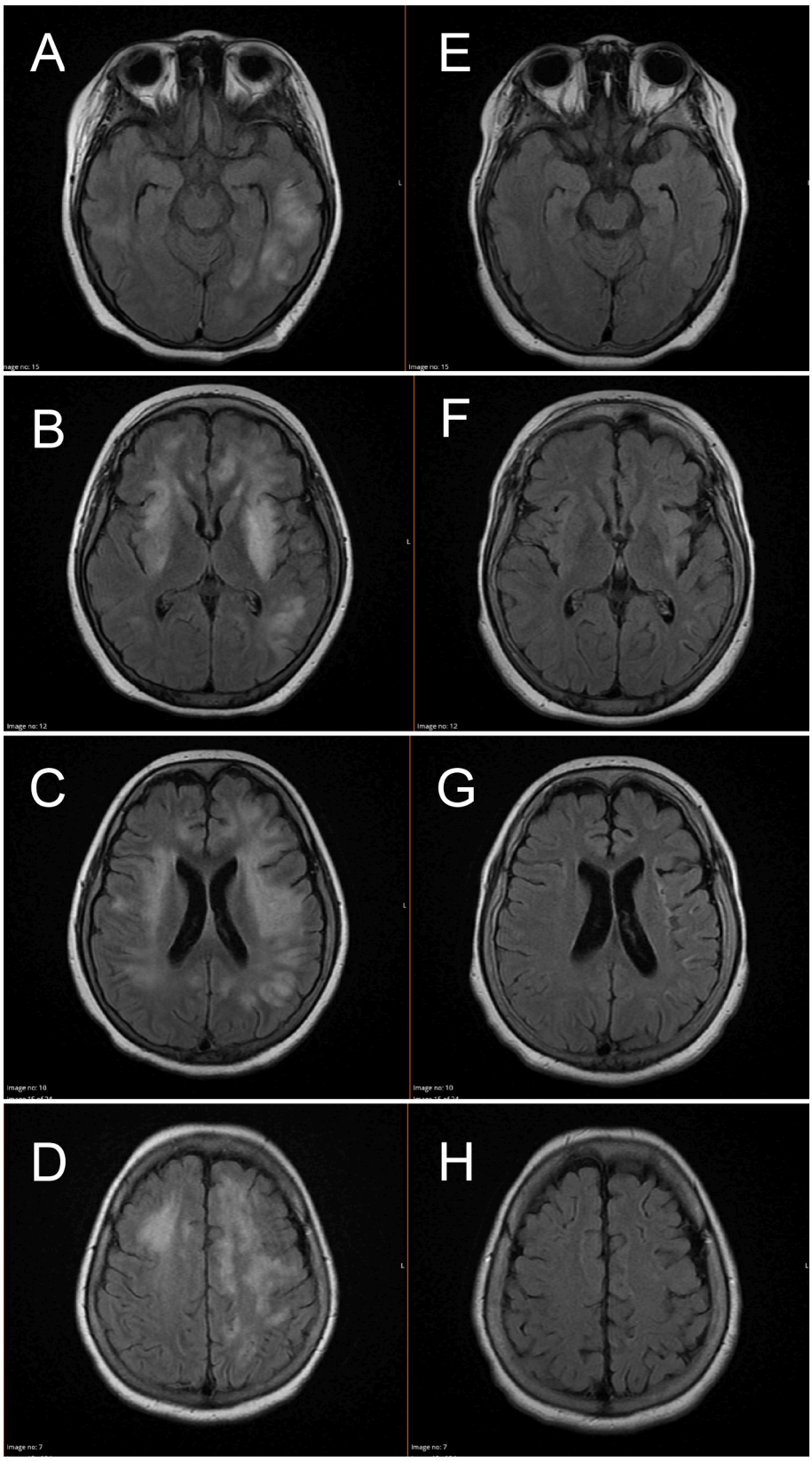

Fig. 1. (A-D) Brain MRI demonstrating confluent and scattered subcortical and deep white matter patchy T2/FLAIR hyperintensities in the deep gray matter nuclei, specifically the caudate heads, bilateral basal ganglia/putamen, and external capsules. (E-H) One year follow up brain MRI demonstrating significant interval improvement of the previously seen scattered cortical and subcortical T2/FLAIR hyperintensities most significantly involving the limbic system, bilateral frontal, temporal, and parietal lobes. In addition, mild atrophic changes noted.

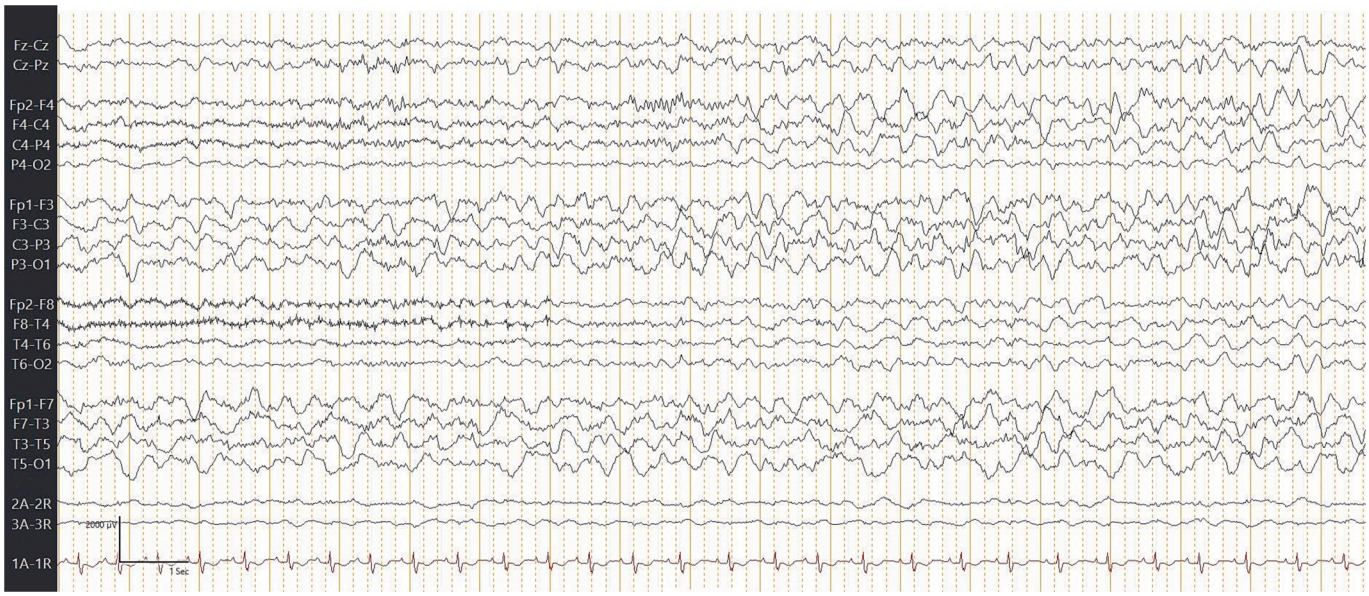

Fig. 2. Electroencephalograph recording showing an electrographic seizure arising from T5, P3, and O1 that evolved to involve the left parasagittal head region and spread to the right frontal head region.

in symptom profiles in pediatric GAD65 encephalitis (Table 1) [5–9].

Anti-SOX1 antibodies are associated with several neurological syndromes, including LEMS, polyneuropathy, PLE, and PCD. Anti-SOX1 encephalitis is a unique condition occurring in the pediatric population. Only two pediatric cases have been reported (Table 2). The first report was an unusual PLE case in a 17-year-old adolescent with classical Hodgkin lymphoma [15]. The patient presented with variable neurological deficits including memory loss and cognitive deficits along with profound B symptoms. The second case involved a 12-year-old female who presented with behavioral changes, decreased consciousness level, and distal tremors [14]. Both patients tested positive for serum SOX1 and received immunotherapy. The first patient's condition deteriorated after another antineuronal antibody was detected, while the second patient showed partial recovery.

Table 1
Clinical and diagnostic characteristics of GAD65 and SOX1 encephalitis (Cellucci et al., 2020, Douma et al., 2021, Kunstreich et al., 2017).

Attribute	GAD65	SOX1
Ages	2–17 years	12 and 17 years
Neurological manifestations	Encephalitis with memory loss, cognitive impairment, psychiatric manifestations, cerebellar ataxia, and refractory seizures	Seizures, behavioral changes, decreased level of consciousness, cognitive impairment, distal upper limb tremor, and myoclonia
Biomarker	Only pathologic if high titers in serum and present in CSF	High titers in serum and/or CSF
CSF findings	CSF leukocytosis may be mild with oligoclonal bands	Pleocytosis
MRI findings	May be normal initially, often progresses to lesions in the limbic system, extralimbic, cerebellum, and cortices with possible atrophy	Temporal lobe hyperintensities
EEG findings	Epileptiform discharges may be multifocal	NA
Tumors	Usually do not have underlying tumors	Associated with SCLC in adults
Treatment	Immunotherapy	Immunotherapy
Prognosis	Often resistant to immunotherapy	Good response

Abbreviations: GAD65, glutamic acid decarboxylase-65; SOX, Sry-like high-mobility group box; CSF, cerebrospinal fluid; EEG, electroencephalography; MRI, magnetic resonance imaging; NA, not applicable; SCLC, small-cell lung carcinoma.

AE evaluation includes neuroimaging, EEG, and CSF analyses for diagnostic clues. Brain MRI typically shows T2/FLAIR hyperintensities in AE without contrast enhancement. GAD65 encephalitis reportedly involves the temporal lobe and limbic system, denoting limbic encephalitis. However, extra-limbic involvement has also been reported [7,8]. Incecik et al. reported three children with frontal, temporal, parietal, and occipital lobe T2/FLAIR hyperintense lesions, which could be unilateral and/or bilateral. SOX1 only involves the temporal lobe [8]. EEG findings may be normal or show a focal or generalized slowing in the temporal areas [12]. GAD65 reported epileptiform discharges may be multifocal. Although CSF studies in AE are often non-contributory, they may show increased protein levels or pleocytosis [1]. AE outcome in childhood is generally good. However, it may depend on the pathogenic autoantibody, neuronal target involved, and time from symptom onset to treatment initiation [18,19]. No reports linking GAD65 and SOX1 antibodies to underlying malignancies exist in the pediatric population.

We report a unique case of overlapping encephalitis in an 11-year-old boy, the first Saudi case and the youngest reported patient in the literature. His clinical presentation was classical AE. Neuroimaging showed T2/FLAIR hyperintensities involving the white and deep gray matter involving the temporal, frontal, and parietal lobes. This extensive extra-limbic involvement has been previously reported in GAD65. EEG findings showed epileptiform discharges arising from the left temporal lobe. CSF analysis showed pleocytosis. GAD65 was detected in the serum with high titers and in the CSF. SOX1 was also detected in the serum with high titers. Guidelines on treating AE do not exist. However, early immune therapy could yield a good outcome, and our patient was treated aggressively with IVMP and IVIG, which showed a favorable response and symptom recovery [18].

Overlapping encephalitis is an emerging entity in the literature. The co-existence of multiple antineuronal antibodies in AE has been reported primarily in case series and sporadic cases. The clinical significance of this finding remains unclear; however, co-existing pathologies should be addressed differently for several reasons. First, an evident association exists with an underlying malignancy. Second, the presence of multiple neuronal antibodies may indicate rapid disease progression and poor outcomes. Qiao et al. reported a case of positive NMDA, SOX1, and GAD65 antibodies associated with AE and small-cell lung cancer (SCLC) in a 46-year-old man who presented with memory loss and cognitive

Table 2
Cases associated with SOX1 encephalitis and seizures (Douma et al., 2021, Kunstreich et al., 2017).

Case	Age	Sex	Antibody + ve	Seizures	Associated features	CSF findings	MRI findings	EEG findings	Treatment
Our case	11 years	M	Anti-SOX1 in serum	Yes	Behavioral changes, decreased level of consciousness	Pleocytosis	Confluent and scattered subcortical and deep white matter patchy T2/FLAIR hyperintensities in the deep gray matter nuclei	Asymmetrical background, electrographic seizures	Methylprednisolone/ IVIG/ASM
Douma et al.	12 years	F	Anti-SOX1 in serum	Yes	Behavioral disorders, decreased level of consciousness, distal upper limb tremor and myoclonia	Pleocytosis	Increased temporal T2 signal	NA	Methylprednisolone/ IVIG
Kunstreich et al.	17 years	M	Anti-SOX1 in CSF and serum/later anti-PCA2	Yes	Reduction in short-term memory, cognitive deficits, disorientation, headache, diplopia, paresthesia in the right arm and leg, and subsequently, spastic paraparesis and profound B-symptoms	Pleocytosis/ elevated protein	Hyperintense lesions with contrast enhancement in the medial temporal lobe and limbic system	NA	Chemotherapy/ methylprednisolone/ plasmapheresis/ cyclophosphamide/ rituximab/azathioprine/ oral steroids

Abbreviations: SOX, Sry-like high-mobility group box; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; EEG, electroencephalography; M, male; F, female; IVIG, intravenous immunoglobulin; ASM, antiseizure medication; NA, not applicable.

impairment with a poor outcome [20]. Gong et al. reported a 56-year-old man with seizures and cognitive impairment diagnosed with PLE associated with SOX1 and GABAB antibodies and a poor outcome following SCLC detection [12]. Lastly, anti-GAD65 antibodies are reported to have questionable pathogenic significance and patients with autoimmune encephalitis should be evaluated for other antibodies against cell-surface antigens [21–23]. Nonetheless, overlapping encephalitis is rare, and its pathogenesis remains unclear.

Conclusions

AE is a rapidly progressive and challenging disease. Several new antibodies have recently been described. Moreover, multiple etiologies of neuronal antibody-associated encephalitis have been reported. The pathophysiological mechanisms, treatment strategies, and outcomes may differ between patients with overlapping encephalitis and those with an isolated disease, and additional differences in clinical phenotypes may exist depending on the specific profile of dual antibodies and chronology of symptom onset. This case contributes to the growing literature on pediatric non-paraneoplastic AE; we particularly observed SOX1 expression and overlapping encephalitis. Additionally, early AE recognition and appropriate treatment may prevent irreversible sequelae. Although the likelihood of a paraneoplastic etiology in children is rare, investigating it is essential. Finally, the clinical significance and therapeutic implications of multiple antineuronal antibodies require further investigation including in vitro and in vivo experiments to determine their clinical relevance.

Informed consent

Informed consent has been obtained.

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CRediT authorship contribution statement

Raneem H. Alghamdi: . **Daad Alsowat:** . **Suad Alyamani:** Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Haya Alfaris:** Writing – review & editing. **Amal Mokeem:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization.

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.

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