Case Report

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Unexpected Time of Age with a Rare Syndrome ALERD: Case Report

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Abstract

Acute encephalopathy is a rapidly progressive neurological condition characterized by seizures, altered mental status, and other neurologic abnormalities. One rare etiology of this presentation is Acute Leukoencephalopathy with Restricted Diffusion (ALERD), which typically occurs in early childhood. However, in rare instances, it may also present in older individuals. We present the case of a 17-year-9-month-old female admitted to the emergency department (ED) with acute-onset confusion, fixed gaze, and altered consciousness following a week of diarrhea, three days of insomnia and hearing loss, and one day of disorientation. On examination, she was lethargic, with a Glasgow Coma Scale (GCS) score of 12, absent pupillary light reflexes, and extensor plantar responses. Initial CT and MRI scans were normal. Cerebrospinal fluid (CSF) analyses were unremarkable, and a comprehensive toxicology panel was negative. Despite empirical antimicrobial and antiepileptic treatment, her condition did not improve. She was treated with pulse-dose methylprednisolone, followed by intravenous immunoglobulin (IVIG). On day four, diffusion-weighted MRI revealed significant periventricular diffusion restriction. Genetic analysis showed several mitochondrial DNA variants of uncertain significance (VUS). Immunomodulatory and metabolic treatments were administered, leading to a gradual neurological recovery over the following weeks and months. Although ALERD is typically observed in younger children, clinicians should be aware that it may rarely occur in adolescents. Emergency physicians should maintain a high index of suspicion for ALERD in patients with unexplained encephalopathy, especially when initial imaging is normal but symptoms progress. Prompt diagnosis and immunotherapy may prevent long-term neurological sequelae.

Keywords: Adolescent, diffuse encephalopathy; emergency service, hospital mitochondrial diseases, leukoencephalopathy

Introduction

Acute encephalopathy refers to sudden damage to the brain and is characterized by seizures, altered consciousness, and other neurological disturbances. Acute encephalopathy frequently develops as a complication of viral infections (rarely bacterial infections) and often affects children. This condition can result in severe neurological sequelae and even death. Accurate diagnosis and early treatment are crucial (1). The etiologies of acute encephalopathy are diverse and include infectious causes (e.g.,viral meningoencephalitis, bacterial meningitis, tuberculosis meningitis, cerebral malaria, acute disseminated encephalomyelitis (ADEM), systemic disorders (such as electrolyte imbalances, hepatic or renal failure, sepsis), hypoxic-ischemic encephalopathy, toxic exposures, traumatic brain injury, stroke, and other causes. Additionally, autoimmune encephalitis should be considered as a cause of acute encephalopathy. Over the past two decades, new conditions that cause acute encephalopathy in children have been described. These include ADEM, acute necrotizing encephalitis (ANE), fever-induced refractory epilepsy syndrome (FIRES), and mild encephalopathy with reversible splenial lesion (MERS) (2,3). Recently, a new condition called acute encephalopathy with biphasic seizures and restricted diffusion (AESD) has been identified. AESD typically follows a biphasic course, beginning with febrile seizures and temporary recovery, followed by recurrent seizures and the appearance of restricted diffusion areas on MRI in the second phase (4). Acute leukoencephalopathy with restricted diffusion (ALERD) is a newly recognized syndrome characterized by acute encephalopathy, seizures, and evolving radiological findings. It is typically preceded by a febrile illness and may initially show normal MRI findings. However, follow-up diffusion-weighted imaging (DWI) reveals restricted diffusion in both gray and white matter regions, especially in the periventricular white matter. The underlying pathogenesis is thought to involve excitotoxic injury and cytokine-mediated inflammation rather than direct infectious invasion. Unlike AESD, ALERD does not follow a biphasic clinical course. Due to the high risk of long-term neurological

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sequelae, early diagnosis and immunomodulatory treatment are crucial (4, 5,6). Although ALERD has predominantly been reported in children under the age of six, particularly between 36 and 48 months, emerging evidence suggests that it may occasionally occur in older age groups. A limited number of case reports and small series have described ALERD in older children and adolescents, often with atypical presentations or underlying metabolic susceptibility (4, 5, 7). Our case, involving a 17-year-old patient, expands the known age range and emphasizes the need for clinicians to consider ALERD even in adolescent patients presenting with unexplained encephalopathy.

Recognizing ALERD in its early stages is particularly critical in the emergency setting, where initial imaging may be misleading, and the clinical picture may mimic other causes of encephalopathy. Because delayed treatment may lead to permanent neurological deficits, emergency physicians should maintain a high index of suspicion in cases presenting with acute encephalopathy and evolving radiological findings. Prompt initiation of immunomodulatory therapy can significantly improve outcomes.

Case Report

A 17-year-old 9-month-old female patient with a known history of anxiety disorder presented to the emergency department (ED) with acute-onset confusion, altered mental status, and fixed gaze after experiencing one week of diarrhea, three days of insomnia and hearing loss, and one day of disorientation. Upon triage in the ED, she was lethargic with a Glasgow Coma Scale (GCS) score of 12, absent light reflexes, and extensor Babinski sign, indicating central nervous system involvement. Immediate stabilization and etiological investigations were initiated, considering differential diagnoses such as infectious, autoimmune, metabolic, and toxic encephalopathy, and non-convulsive status epilepticus. These early ED findings prompted urgent imaging and lumbar puncture, as well as empirical antimicrobial and antiviral therapy. Laboratory tests revealed negative acute-phase reactants. Electrolyte imbalances and metabolic acidosis were absent; liver and kidney function tests, ammonia, and lactate were within normal limits. A brain CT scan, diffusion MRI, and contrast MRI were reported as normal. A toxicology panel for possible toxic pathology was negative. A comprehensive toxicology screen was conducted upon admission to the emergency department to rule out substance or drug intoxication. The results were negative for all commonly screened agents, including alcohol, illicit drugs, and prescribed medications. For the possibility of meningitis, a lumbar puncture was performed, and CSF parameters were normal. CSF-PCR did not show any growth. Empirical treatment with ceftriaxone and acyclovir was started for bacterial or viral meningitis, respectively, pending CSF culture results. Given the patient's fixed gaze and non-purposeful motor tonic contractions, generalized seizures could not be ruled out, so levetiracetam was administered for loading and maintenance. The patient's consciousness was monitored daily with EEG, which showed 2–3 Hz delta rhythm initially, with a gradual increase to theta and alpha rhythms over time. The EEG findings were consistent with encephalopathy. Non-convulsive status epilepticus was ruled out, and intravenous diazepam was administered during the EEG, with no changes in the background rhythm or traces. With no history of fever, normal CSF findings, and the clinical presentation, autoimmune encephalitis was suspected, and the patient was treated with 30 mg/kg pulse steroid therapy. When no clinical improvement was seen by the third day, 2 g/kg intravenous immunoglobulin (IVIG) was given. After 7 days, methylprednisolone was continued at a maintenance dose of 2 mg/kg/day. As CSF-PCR results were negative, ceftriaxone treatment was discontinued, but acyclovir was continued for 7 days due to a recent history of herpes simplex virus infection. On the fourth day of hospitalization, to rule out pathology, a diffusion MRI was planned, which showed significant diffusion restriction in the periventricular area (Figure-1). Since this finding could also be meaningful in mitochondrial storage diseases, a metabolic panel (urine-amino acid, urine organic acids, tandem mass spectrometry) was sent. Genetic analysis detected some variants in the mitochondrial DNA sequence. Specifically, m.7169T>C (VUS), m.1686A>G (VUS), m.3010G>A (VUS) and m.9923C>T (VUS) variants were detected in the MT-CO1, MT-CO3 and MT-RNR2 regions. Empirical treatment with carnitine, thiamine, biotin, coenzyme Q10, arginine, riboflavin, vitamin E, and vitamin C was started. A follow-up MRI 36 hours after the diffusion MRI showed significant improvement in the diffusion restriction. At this point, ALERD/MERS syndrome was suspected. By the 14th day of IVIG treatment, the patient began to open her eyes spontaneously, respond to sound, and show purposeful movements.

After increasing physical therapy support during and after the treatment, the patient became conscious and gained motor function skills to walk independently within 1 month,

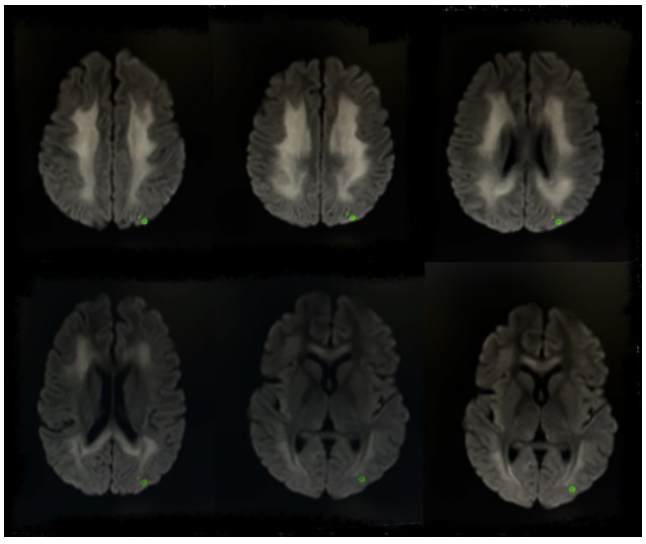

Figure 1. Diffusion MRI, which showed significant diffusion restriction in the periventricular area

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to speak within 3 months, and to follow commands when eye contact was established.

Discussion

Encephalitis refers to inflammation of the brain parenchyma. Acute encephalitis is a condition that is more commonly observed in children and young adults, and it tends to be more severe in young children (8,9). Although viruses are the primary cause, bacteria, fungi, parasites, and post-infectious or autoimmune processes can also contribute to its etiology (10,11). Autoimmune encephalitis, caused by antibodies targeting neural proteins, is increasingly recognized as a cause of encephalitis in children. In a retrospective single-center cohort of 164 children with acute encephalitis, autoimmune encephalitis accounted for 13% of cases, making it the second most common cause of non-infectious encephalitis (12). Autoimmune encephalitis typically presents with psychiatric symptoms, abnormal movements, seizures, autonomic instability, and hypoventilation (13). Steroids and intravenous immunoglobulin (IVIG) are used in the treatment, and the patient is simultaneously evaluated for the underlying etiology. In our case, since there was no significant seizure activity, anticonvulsant medication was initiated, but there was no notable improvement in the patient's clinical condition. Therefore, the diagnosis of epilepsy was reconsidered. Follow-up electroencephalograms (EEG) ruled out non-convulsive status epilepticus, but due to persistent encephalopathic background rhythms and continued epileptiform activity, a diffusion-weighted MRI was performed, which revealed significant diffusion restriction, leading to the exclusion of an encephalitis diagnosis. Furthermore, the autoimmune encephalitis panel was negative.

The term Acute Leukoencephalopathy with Restricted Diffusion (ALERD) is used to describe cases where seizures, encephalopathy symptoms, and restricted diffusion on MRI are observed in children. ALERD can be caused by various infections and does not follow a biphasic clinical pattern. In a case report published by Ranjan et al., a previously healthy one-year-old girl presented with fever, altered consciousness, and seizures. Following a diagnosis of Staphylococcus aureus-induced meningoencephalitis, the brain MRI revealed symmetric diffusion restriction in the periventricular white matter, leading to the diagnosis of ALERD (14). In a study by Lawrance and colleagues, 11 out of 78 children presenting with encephalopathy were diagnosed with ALERD. The children's ages ranged from 6 to 80 months, with a mean age of 34.9 months. Seizures were present in all but one case. Among these children, six experienced convulsive status epilepticus, one of whom also had non-convulsive status epilepticus. Seven children with shock and multiorgan failure included two with brainstem dysfunction, and one of these children died. At initial imaging, four children showed abnormal findings. In all of these children, abnormal MRI findings were detected between days 5 and 14 (median day 9), with seven children showing a diffuse type (63.6%) and four children showing a central-preserved type (36.3%) of ALERD (5). Similar to our case, viral etiology panels and metabolic screening were conducted in the studies in the literature (15). thAdditionally, Mild Encephalopathy with Reversible Splenial Lesion (MERS) is another clinical-radiological syndrome characterized by encephalopathy symptoms. The severity of symptoms can range from mild to severe and may include altered consciousness, irritability, delirium, occasional seizures, and fever. Diffusion MRI in MERS typically shows hyperintensities in the center of the corpus callosum (16). In our case, however, since there was no diffusion restriction observed in the corpus callosum on MRI, MERS was excluded from the differential diagnosis.

Mitochondrial DNA analysis is an important tool in understanding the genetic basis of neurological diseases (17,18). In the analysis performed on our patient, several VUS (Variation of Uncertain Significance) were detected, especially in the MT-CO1, MT-CO3 and MT-RNR2 regions. Although the clinical significance of these variants has not yet been clarified, some mitochondrial DNA changes are known to be associated with neurological diseases. In the literature, it has been suggested that the m.3010G>A (rs3928306) variant may be associated with Leber hereditary optic neuropathy (LHON). However, in light of current information, it is not possible to make a definitive comment on the contribution of these variants to the etiopathogenesis of the disease.

This case underscores the importance of early recognition and action in the ED setting, where ALERD may initially mimic more common etiologies of encephalopathy. Emergency physicians should be aware that initial imaging may be normal, and clinical deterioration should prompt reevaluation, including repeat MRI. A stepwise diagnostic approach, combined with early empirical immunotherapy in deteriorating cases, may be life-saving.

In conclusion, ALERD is a very rare syndrome and there is no case reported in the adolescent age group in the literature. Therefore, this case represents the first known instance of ALERD in an adolescent in the literature, to the best of our knowledge.

Conclusion

In ALERD, initial MRI findings can appear normal, but diffusion restriction in the periventricular regions frequently develops over time. Early diagnosis and treatment are essential because of the significant risk of long-term neurological sequelae. While more common in younger individuals, ALERD can also occur in older patients. Furthermore, the clinical significance of VUS in mitochondrial DNA remains unclear. Future studies with larger cohorts are necessary to clarify their role in neurological diseases, making long-term follow-up crucial for understanding their potential clinical implications.

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