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Case Report

Pediatric Influenza-Associated Encephalopathy: A Case Report

Pediatrik İnfluenza ile İlişkili Ensefalopati: Bir Olgu Sunumu

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ABSTRACT

Influenza-Associated Encephalopathy (IAE) is a rare but highly fatal neurological complication of influenza infection, especially prevalent in the pediatric age group. The condition is characterized by an abrupt onset of neurological symptoms and a risk of severe, irreversible damage. IAE is primarily understood to be a non-infectious complication triggered by a massive systemic inflammatory response, or cytokine storm, rather than direct viral invasion of the central nervous system. A severe manifestation of this syndrome is known as Acute Necrotizing Encephalopathy (ANE). In this report, we present two pediatric cases of Influenza-Associated Encephalopathy to highlight the variability in clinical presentation and the importance of early recognition and supportive management.

Keywords: *influenza-associated encephalopathy, acute necrotizing encephalopathy, pediatric neurology, cytokine storm*

ÖZET

İnfluenza ile İlişkili Ensefalopati (IAE), çocuklarda nadir görülen ancak yüksek mortaliteye sahip bir nörolojik komplikasyondur. Ani başlayan nörolojik belirtilerle seyreder ve ciddi, geri dönüşsüz hasar riski taşır. IAE, merkezi sinir sistemine doğrudan viral invazyon yerine sistemik inflamatuvar yanıt veya sitokin fırtınasıyla oluşan enfeksiyöz olmayan bir komplikasyondur. Bu sendromun şiddetli formu Akut Nekrotizan Ensefalopati (ANE) olarak bilinir. Bu çalışmada, pediatrik yaş grubunda iki IAE olgusu sunularak klinik sunumdaki farklılıklar vurgulanmakta ve erken tanı ile destekleyici yönetimin önemi gösterilmektedir.

Keywords: *İnfluenza ile ilişkili ensefalopati, akut nekrotizan ensefalopati, pediatrik nöroloji, sitokin fırtınası*

INTRODUCTION

Pediatric IAE is a rare but serious complication of influenza infection, typically presenting with acute-onset neurological symptoms including seizures, altered consciousness, and coma [1, 2]. Unlike direct viral invasion, this condition is primarily mediated by immune mechanisms, particularly the cytokine storm, leading to widespread brain damage [3]. With mortality rates ranging from 9-40% and permanent neurological sequelae in up to 56% of cases, early recognition and aggressive supportive treatment are crucial [4].

The pathophysiology of IAE involves an excessive host immune response characterized by a cytokine storm rather than direct viral neuroinvasion. This hyperinflammatory state, driven by proinflammatory cytokines such as interleukin-6 and tumor necrosis

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factor-alpha, disrupts the blood-brain barrier and leads to widespread cerebral edema and ischemic damage [5, 6]. The absence or minimal presence of cerebrospinal fluid pleocytosis supports this immune-mediated mechanism.

During influenza seasons, clinicians must maintain a high suspicion for neurological conditions in children who present with symptoms following a fever and respiratory illness. Early Brain MRI, especially diffusion-weighted sequences, is crucial for diagnosis, often revealing characteristic signs like corpus callosum involvement and periventricular white matter lesions. The most severe form, ANE, is typically marked by bilateral symmetric thalamic lesions. Management is centered on prompt antiviral therapy and aggressive supportive care in intensive settings, but no consensus guidelines currently exist. By presenting these cases, we aim to highlight the significance of early diagnosis and neuroimaging in children with influenza presenting with neurological symptoms, and to contribute to the understanding and clinical management of pediatric IAE.

CASE REPORT

Case 1

A 12-year-old girl (29 kg) presented to an outside facility with weakness, blurred vision, disorientation, and behavioral changes. Within 30 minutes of emergency department admission, she developed recurrent generalized tonic-clonic seizures and desaturation, necessitating transfer to the pediatric intensive care unit. Her medical history included sore throat for the past 2 days. A nasopharyngeal swab tested positive for Influenza A on the day of admission.

Physical examination showed moderate general condition with fever and tachycardia (158 bpm). Pupils were bilaterally reactive, and the Glasgow Coma Scale (GCS) score was 15. No meningeal signs were detected. Lumbar puncture was performed, showing no cells on direct microscopy. Respiratory panel confirmed Influenza A. Electroencephalography (EEG) showed rare isolated spike-wave discharges from central regions, indicating focal epileptic activity.

The cranial MRI revealed marked T2 signal and diffusion restriction in the entire corpus callosum, with minor foci in the periventricular white matter. No enhancement or susceptibility artifact was seen. These results were interpreted as cytotoxic callosal lesions, requiring clinical correlation for encephalitis or metabolic causes.

Upon intensive care admission, empirical therapy was initiated, including midazolam, acyclovir, oseltamivir, levetiracetam, and cefotaxime. Following consultations, antibiotics were discontinued, while antiviral and anticonvulsant therapy continued. The patient remained hemodynamically and neurologically stable throughout the intensive care course. After confirming Influenza A positivity and the absence of meningitis findings on CSF, the patient was prepared for discharge with outpatient follow-up recommendations.

Case 2

A 7-year-old male (23 kg) was referred from an outside facility due to persistent fever, lethargy, and feeding difficulties. He had no underlying chronic disease. Upon initial admission, he was placed under intensive care monitoring with suspected meningitis or encephalitis. Physical examination revealed lethargy, with fluctuating consciousness (GCS score 12-13). Kernig sign was positive.

The lumbar puncture showed no abnormal findings.Respiratory panel later tested positive for Influenza A virus. Initial laboratory values showed metabolic acidosis and mild hyponatremia.

Empirical antibiotics were discontinued after meningitis was excluded clinically and via CSF analysis.Pediatric neurology reported normal brain MRI, while imaging showed ethmoid and maxillary sinusitis. The patient was discharged in good condition with azithromycin and outpatient follow-up.

Table 1. Clinical course of Case 1

Day / Time	Findings	Intervention	Result
D1	Presentation with fever, seizures, and confusion	Emergency admission, intensive care transfer; intubation; sedation with Dormicum	Seizure control achieved
D2	MRI and CSF analysis	Initiation of antiviral (acyclovir, oseltamivir) and antibiotic therapy; loading dose of antiepileptic (levetiracetam)	Consciousness partially regained, stable course
D7	Follow-up	Antibiotic discontinued; antiviral and antiepileptic continued; rehabilitation recommended	Discharge planned

Table 2. Clinical course of Case 2

Day / Time	Findings	Intervention	Result
D1	Persistent fever, loss of appetite, Kernig's sign (+)	Emergency admission, intensive care transfer	Stable follow-up
D2	CSF analysis and laboratory investigations	Empirical antibiotic (ceftriaxone + vancomycin), oseltamivir initiated	Fever control achieved
D3-4	Respiratory panel showed Influenza A (+)	Antibiotics discontinued, cefotaxime continued, vitamin K administered	Improvement in general condition
D7	Follow-up MRI showed no parenchymal pathology, sinusitis findings present	Oral azithromycin treatment planned	Discharge recommended

DISCUSSION

These two pediatric cases illustrate the clinical spectrum of IAE, a rare but devastating complication with high morbidity and mortality rates. Both patients initially presented with typical flu-like illness that rapidly progressed to acute neurological manifestations. Case 1 showed recurrent seizures and altered consciousness, while Case 2 presented with persistent fever and fluctuating mental status, demonstrating the varied neurological presentations.

The pathophysiology of IAE is primarily linked to an excessive host immune response or cytokine storm, rather than direct viral neuroinvasion [5, 6]. This hyperevolutionary immune response releases proinflammatory cytokines (IL-6, TNF-), which disrupt the blood-brain barrier, causing cerebral edema and ischemic damageAlthough markers like IL-6 or ferritin were unavailable, the clinical course without CSF pleocytosis aligns with cytokine-mediated pathology reported in prior cases. Brain MRI is the most valuable imaging modality for diagnosis and prognosis. Typical ANE findings include bilateral symmetric thalamic hyperintense lesions [8, 9].

In Case 1, diffusion restriction involving the corpus callosum with periventricular white matter foci suggested cytotoxic callosal lesions within the IAE/ANE spectrum. The absence of contrast enhancement helped differentiate from infectious meningoencephalitis, and the lack of hemorrhagic component excluded the hemorrhagic variant of ANE. Case 2 showed no parenchymal pathology on MRI, reflecting the variable neuroimaging presentation across the IAE spectrum. Normal MRI in Case 2 may reflect the early stage of IAE, before cytokine-mediated changes develop.

Diagnosis relies on clinical suspicion and exclusion of other etiologies (meningitis, Reye syndrome, metabolic encephalopathies). Both cases underwent thorough evaluation, including lumbar puncture, demonstrating the appropriate clinical approach.

No evidence-based international standard treatment protocol exists for IAE. However, aggressive early treatment is suggested. Neuraminidase inhibitors like oseltamivir should be initiated within 48 hours of flu-like symptoms to reduce viral replication [11]. High-dose pulse methylprednisolone and intravenous immunoglobulin (IVIG) are widely used to suppress the cytokine storm Despite recommendations for

methylprednisolone or IVIG in severe cases [12-14], our patients' early diagnosis and stable course did not require immunomodulatory therapy. Intensive care monitoring, respiratory support, seizure control, and intracranial pressure management form the foundation of supportive treatment.

This condition occupies an important place in pediatric practice due to a high mortality rate and the potential for severe neurological sequelae (epilepsy, cognitive impairment) in of cases [15]. Intensive care admission and seizures in our cases indicate a severe disease form, suggesting the need for long-term physical therapy and rehabilitation.

Our cases align with characteristic features described in the literature. They demonstrate the importance of maintaining high clinical suspicion during influenza season, performing early neuroimaging for diagnosis and prognostication, initiating prompt antiviral therapy, and ensuring multidisciplinary follow-up. Annual influenza vaccination should be encouraged as the most effective prevention method.

CONCLUSION

Pediatric IAE, though rare, can progress rapidly and be life-threatening . These cases underscore that early neurological symptoms following Influenza A infection warrant prompt evaluation. Diffusion-weighted MRI may reveal cytotoxic lesions even when standard imaging appears normal, aiding diagnosis and management. CSF findings in both patients supported a cytokine-mediated mechanism rather than direct viral invasion. Early antiviral therapy and supportive care contributed to favorable short-term outcomes, while immunomodulatory treatment is reserved for severe presentations. Raising clinical awareness during influenza season is crucial to reduce morbidity and mortality in children.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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