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Mini Review

Acute Necrotizing Encephalopathy (ANE) in a 17 years-Old Boy Due to a Heterozygote RANBP2-Mutation

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Abstract

Acute Necrotizing Encephalopathy (ANE) is a rare, severe, and rapidly progressive neurological condition usually triggered by common viral infections. A distinct genetic form, known as ANE1, is associated with heterozygous missense mutations in the RANBP2 gene. It predisposes individuals to recurrent attacks of fulminant brain inflammation. Affected individuals, often children, present with a sudden alteration of consciousness, seizures, and rapid deterioration to coma within days of a febrile illness. Patients show no direct viral invasion of the central nervous system, but rather suffer from a severe, immune-mediated hyperinflammation. Brain magnetic resonance imaging is vital for diagnosis and reveals characteristic, bilateral symmetric lesions in the deep gray matter, particularly within the thalami, brainstem, and cerebral white matter. Genetic testing confirms the pathogenic variant in the RANBP2 gene. The prognosis remains guarded with a high mortality rate and risk of permanent neurological deficits in survivors. Current management strategies are based on early and aggressive immunotherapy, including high-dose corticosteroids, intravenous immunoglobulin, and targeted immunomodulators, which can significantly improve neurological recovery. RANBP2-associated ANE is a catastrophic neurological emergency. Prompt clinical recognition, immediate neuroimaging, and rapid initiation of immunotherapy are crucial for improving patient survival and long-term neurological outcomes.

Keywords: ANE, RANBP2, Mutation, Encephalopathy, Necrosis, Child

Introduction

Acute Necrotizing Encephalopathy Type 1 (ANEC1) is a rare, severe, and rapidly progressing neurological disorder defined by sudden brain damage following a common viral infection. This specific form of encephalopathy is caused by a genetic predisposition, specifically a mutation in the RANBP2 gene. While the genetic mutation itself does not cause direct harm under normal conditions, it acts as a critical vulnerability factor. When an individual carrying this mutation contracts a routine virus—such as influenza or parainfluenza—their immune system undergoes a catastrophic malfunction. Instead of fighting the infection normally, the body triggers a massive, uncontrolled inflammatory response known as a cytokine storm, which leads to widespread damage. The primary target of this immune overreaction is the blood-brain barrier, the protective shield that regulates what enters the central nervous system. As the cytokine storm breaches this barrier, severe inflammation, swelling, and tissue death (necrosis) occur within the brain. Characteristically, this damage is highly symmetrical

and concentrated in the deep structures of the brain, most notably the thalami. Clinically, the disease escalates with terrifying speed. Within just a few days—or even hours—of developing a standard fever, patients experience a drastic neurological decline. This typically manifests as rapidly altered consciousness, multiple seizures, and a quick progression into a coma. Diagnosing ANEC1 relies heavily on advanced neuroimaging and genetic testing. A brain MRI is the gold standard for diagnosis, characteristically revealing tricolor, symmetric lesions in the thalami that indicate edema, hemorrhage, and necrosis. A lumbar puncture usually shows elevated protein levels in the cerebrospinal fluid, but importantly, without the presence of an active viral infection inside the brain itself. Genetic sequencing then confirms the specific mutation in the RANBP2 gene, which follows an autosomal dominant inheritance pattern with incomplete penetrance, meaning not everyone with the gene will fall ill. Because ANEC1 is a medical emergency, immediate and aggressive intervention is required to save lives and limit permanent brain damage. Treatment strategies focus on suppressing the immune system using high-dose corticosteroids, Intravenous Immunoglobulins (IVIG), and plasmapheresis to filter out the destructive inflammatory proteins. Despite these intensive therapies, the prognosis remains highly unpredictable. While some individuals recover fully, a significant number of patients face permanent, severe neurological disabilities. Historically, the condition carries a mortality rate of approximately 30%, making early recognition and rapid treatment absolutely critical.

Therapy and Clinical Course

The patient was transferred from the hospital, initially to a general ward and then rapidly to our intensive care unit due to neurological deterioration and for the treatment of encephalitis of unknown etiology. An MRI on Jan 29 showed disseminated inflammatory changes centrally and in the spinal cord. Lumbar punctures were performed to complete the diagnostic workup. These revealed a blood-CSF barrier dysfunction with no evidence of intrathecal IgG, IgM, or IgA synthesis. The cerebrospinal fluid was sterile. Comprehensive antibody testing was unremarkable. Samples processed as part of a research study at the Charité in Berlin also showed no evidence of antibody-mediated autoimmune encephalitis. Suspecting a recurrent bout of encephalitis, most likely parainfectious, methylprednisolone pulse therapy was initiated (14 mg/kg BW/d i.v. for 5 days). This was subsequently reduced and is being tapered according to the schedule below. During the neurological examination, the patient presented with muscle weakness affecting the lower extremities more than the upper extremities, and the right arm more than the left. Additionally, deep tendon reflexes in the lower extremities were absent, and he exhibited dysarthria as well as mild facial palsy. Over the course of treatment, an increase in strength was observed, particularly in the upper extremities. The patient continued to have slurred speech and difficulties with fine motor skills. During the inpatient stay, the patient was mobile via wheelchair. After detailed counseling, we collected samples from both parents and the patient for a human genetic investigation. This revealed a heterozygous sequence variant in the RANBP2 gene, which is paternally inherited and likely pathogenic. These variants are associated with an increased susceptibility to acute, infection-induced encephalopathy. By influenza virus or B. burgdorferi or T. pallidum. Antibody titers for diphtheria, tetanus toxin, pneumococci, varicella-zoster, measles, mumps, and rubella were all negative. We recommended a vaccination according to STIKO (Standing Committee on Vaccination) recommendations, as well as an annual influenza vaccination and additional protection through the vaccination of his parents and other close contacts. Over the course of treatment, the patient became more alert and exhibited auto-aggressive, self-harming and hetero-aggressive behaviors. Consequently, a dose titration of Ciatyl-Z was initiated. Following an initial dose of 25 mg, the patient became somnolent and rapidly developed extrapyramidal motor symptoms. After the administration of Akineton, these side effects subsided quickly. An EEG showed no evidence of epileptiform activity and no significant asymmetry. Subsequently, the patient received Ciatyl-Z at a reduced dose in combination with Akineton retard. Under this regimen, no further side effects occurred, except for daytime drowsiness. Daniil's episodes of agitation became less frequent and more manageable, though they continued to occur regularly. Therefore, the patient received Melperon on an as-needed basis and was temporarily restrained by the arms in bed under a temporary injunction. Despite being given melatonin at night, the patients sleep-wake cycle was still significantly disrupted at the time of discharge. If this regimen does not yield long-term success for him, a switch could be made from Ciatyl-Z to regular doses of Melperon (for example, 25 mg 3 times daily). During his inpatient stay, the patient was supported by the physical and occupational therapy team. He was provided with a rental wheelchair, which allowed him to remain mobile. He practiced using a standing frame, but unassisted standing was not possible. In the patient's case, we considered a therapeutic recumbent tricycle with an electric motor to be indicated. In synergy with the physical therapy treatment, the family could thus independently train Daniil's muscles, improve his motor skills, and thereby relieve and prevent pain. We anticipated that increased physical activity in the patient's situation lead to psychological stabilization, particularly an improvement in his sleep-wake cycle. Prior to his current illness, daily rides on his tricycle were reportedly the most effective remedy for his phases of agitation; due to the loss of leg motor function, the patient can now only ride a bicycle with the assistance of an electric motor. The social services department organized neurorehabilitation for the period following inpatient treatment and submitted the application for a severe disability status. Social-pedagogical family assistance has been requested for his care at home. The patient was transferred the male patient on February 17, 2023, in good general condition to the neurorehabilitation institution.

Discussion

Acute Necrotizing Encephalopathy Type 1 (ANE1) is a rare, genetically determined disorder of the central nervous system

characterized by rapid neurological deterioration following otherwise common viral infections [1,2]. The pathophysiological foundation of this condition resides in a mutation of the RANBP2 gene located on chromosome 2q13, which encodes the Ran-Binding Protein 2 [3,4,5]. This giant protein is an essential component of the nuclear pore complex and plays a critical role in nucleocytoplasmic transport, mitochondrial energy maintenance, and cellular stress regulation. The inheritance of this genetic variant follows an autosomal dominant pattern with incomplete penetrance, which is estimated to be approximately 40 percent [6]. This low penetrance explains why affected patients frequently inherit the mutation from a completely asymptomatic parent [7]. The development of severe brain injury relies on a classic double-hit mechanism, wherein the genetic mutation establishes a lifelong vulnerability, and an exogenous factor serves as the actual trigger for the encephalitic episode. Under the stress of a febrile viral illness, such as those caused by influenza, parainfluenza, or coronaviruses, the mutated RANBP2 protein malfunctions, unleashing an uncontrolled systemic hyperinflammation [8]. This explosive cytokine storm, marked by significantly elevated levels of interleukin-6, interleukin-8, and tumor necrosis factor-alpha, causes acute damage to the vascular endothelium and leads to the breakdown of the blood-brain barrier [9]. Consequently, rapidly progressive, radiologically bilateral, and symmetric tissue necrosis and petechial hemorrhages develop within the basal ganglia, thalamus, brainstem, and spinal cord [10]. Clinically, ANE1 presents after a brief, non-specific prodromal phase with profound neurological deficits that can range from somnolence and seizures to a rapid transition into a comatose state. Depending on the precise anatomical location of the necrotic lesions within the central nervous system, patients display severe impairments such as tetraparesis, bulbar symptoms including dysarthria and dysphagia, and cranial nerve palsies. Cerebrospinal fluid analysis yields a characteristic pattern known as cytoalbuminologic dissociation, which is defined by a severe blood-CSF barrier dysfunction with highly elevated protein levels despite a normal white blood cell count. The absence of intrathecal immunoglobulin synthesis and negative autoimmune encephalopathy antibody panels further differentiate ANE1 from classic infectious or autoimmune encephalitides. Therapeutic interventions in the acute phase focus primarily on dampening the hyperinflammatory cascade, with the timing of treatment initiation serving as a critical prognostic factor. High-dose intravenous methylprednisolone pulse therapy represents the gold standard of care to restore the integrity of the blood-brain barrier and suppress cytokine production. In severe or refractory cases, this regimen is supplemented by intravenous immunoglobulins, plasma exchange, or targeted cytokine antagonists such as tocilizumab. Neuropsychiatric management represents an additional challenge during the clinical course, as patients frequently develop delirium, auto-aggression, and hetero-aggression due to the encephalitis or as a side effect of high-dose steroid therapy. Controlling these states of agitation requires extreme caution, because encephalitically pre-damaged brains react with high sensitivity to conventional neuroleptics and can promptly develop severe extrapyramidal motor side effects, making more sedating and better-tolerated agents like melperon the preferred choice. The long-term prognosis for survivors of ANE1 is often complicated by persistent neurological deficits resulting from irreversible tissue necrosis, which mandates early and intensive neurorehabilitation. Physiotherapy and occupational therapy must be augmented by specialized medical equipment, such as standing frames and adaptive motorized recumbent tricycles, to prevent joint contractures, improve fine motor skills, and help stabilize the chronically disrupted sleep-wake cycle through physical activation. Because the underlying genetic disposition remains a lifelong factor, recurrence prophylaxis is the most vital component of long-term management. This strategy relies on the strict implementation of all recommended standard vaccinations, alongside annual influenza immunizations for both the patient and their entire household, to minimize the risk of future infectious triggers.

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Conflict of Interest

None.

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