Recurrent acute necrotizing encephalopathy type-1 (ANE1) associated with a RANBP2 variant: a case report and brief review.

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Aim of the study: Acute necrotizing encephalopathy type-1 (ANE1) is a rare autosomal dominant disorder with incomplete penetrance, linked to RANBP2 gene variants [1,2]. Early recognition is crucial, particularly in pediatric patients with a personal or family history of encephalopathy, presenting with altered consciousness, seizures, or focal neurological signs 1–3 days after a febrile illness. Typical MRI findings include bilateral, symmetric lesions in the thalami, external capsules, brainstem, insula, and medial temporal lobes [1,3]. Awareness of ANE1 has only recently grown, and the disease may present atypically or mimic other inflammatory CNS disorders, highlighting the need for heightened clinical suspicion even in non-classical scenarios.

Materials and methods: We describe the case of a female patient who experienced two episodes of encephalopathy over a nine-year period and was ultimately diagnosed with ANE1. A literature search was conducted using Medline and Scopus to identify relevant studies.

Discussion and results: A 23-year-old woman presented with a seizure followed by a traumatic fall, three days after a febrile episode accompanied by headache, vomiting, and drowsiness. At age 12 she was hospitalized for fever and coma, diagnosed as meningoencephalitis of unknown etiology, which resulted in residual intellectual disability and intentional/postural tremor. Neurological examination on admission revealed drowsiness and ataxia. Laboratory tests showed mild hyponatremia, cerebrospinal fluid (including autoimmune encephalitis autoantibody testing) was normal. Electroencephalography showed anterior slow-wave abnormalities. Brain MRI showed T2/FLAIR (Fig.1) and DWI (Fig.2) hyperintensities in the amygdala, hippocampus, thalamus, and external capsules bilaterally, along with pontine and cerebellar atrophy, and a mild subarachnoid hemorrhage. Genetic analysis revealed a heterozygous pathogenic RANBP2 c.1754C>T variant, the most frequently reported in ANE1. However, our case is notable for the presence of cerebellar atrophy (Fig.3), normal cerebrospinal fluid protein levels and a late-onset relapse (beyond the age of 20), which is also atypical [1,3]. The same variant was detected in her lifelong asymptomatic mother. Intravenous methylprednisolone treatment led to clinical and radiological improvement at one-month follow-up (Fig.4).

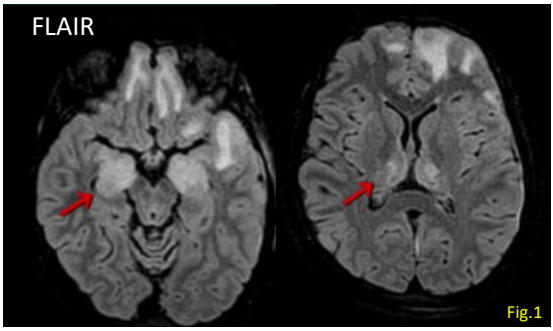
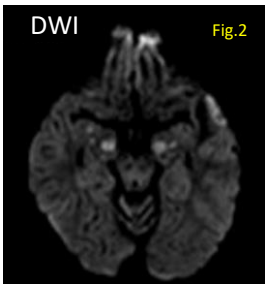


***Fig.1**: Axial FLAIR showing bilateral hyperintensities and swelling in the hippocampi and thalami.*



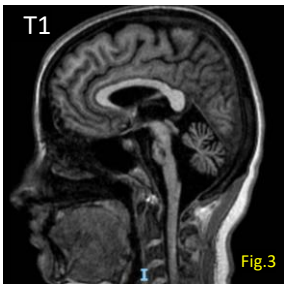


Fig.2: Axial DWI demonstrating symmetric hyperintensities in the hippocampi.
Fig.3: Sagittal T1-weighted sequence revealing severe cerebellar atrophy.

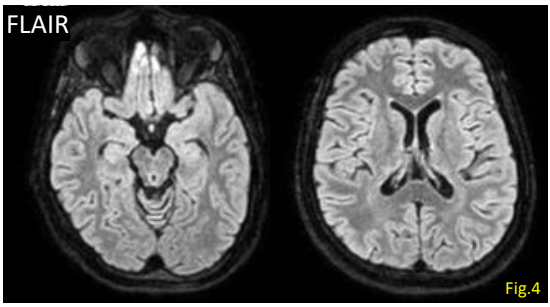


Fig. 4: Follow-up axial FLAIR showing marked reduction in hyperintensity and swelling in both hippocampi and thalami.

Conclusion: RANBP2 variants are thought to increase susceptibility to dysregulated inflammatory responses and mitochondrial dysfunction, leading to rapid energy depletion and neuronal necrosis [1-3]. Further studies are needed to expand the phenotypic spectrum and refine genotype-phenotype correlations.

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