



Acute Necrotizing Encephalopathy: 2 Case Reports on *RANBP2* Mutation

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Abstract

Infection-induced acute encephalopathy 3 (IIAE3) is an autosomal dominant disease resulting from a pathogenic variant in the *RANBP2* gene. IIAE3 results in the susceptibility to the recurrence of acute necrotizing encephalopathy (ANE1) which presents as bilateral symmetric thalamic, midbrain and/or hindbrain lesions that typically develops within 1-4 days post-acute viral infection, commonly occurring before age 6.¹⁻⁶ These case reports highlight a retrospective analysis of clinical data and radiographic studies on 2 ANE1 cases from our institution. The novel p.Leu450Phe variant of the *RANBP2* gene was analyzed using in silico algorithms (PolyPhen-2, SIFT, Mutationtaster) which suggests the p.Leu450Phe variant is probably deleterious.⁷ An expansion of documented ANE1 case presentations and clinically significant *RANBP2* gene mutations has the potential to improve long term outcomes if more informed therapeutic decision making can be achieved.

Keywords

seizure, status epilepticus, pediatrics, genetics, *RANBP2* mutation, neuroimaging, EEG

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Introduction

Infection-induced acute encephalopathy 3 (IIAE3, MIM # 608033) is an autosomal dominant disease with reduced penetrance resulting from a pathogenic variant in the *RANBP2* gene. IIAE3 results in the susceptibility to the recurrence of acute necrotizing encephalopathy (ANE1) which presents as bilateral symmetric thalamic, midbrain and/or hindbrain lesions that typically develops within 1-4 days post-acute viral infection, commonly occurring before age 6.¹⁻⁶ Most cases progress through a characteristic prodromal, acute and recovery stage.⁶ The prodromal stage often presents with a nonspecific febrile viral-like illness lasting up to 5 days.⁷ An acute phase follows where the inciting infection progresses into deteriorating consciousness, seizure, focal neurological deficits and coma.^{5,8} The final recovery stage is variable and can result in a full resolution of brain lesions, atrophy, the deposition of hemosiderin or the development of white matter cysts.⁹ This case series is a presentation of 2 patients from our institution, one with a pathogenic *RANBP2* gene variant and one with a variant of unknown significance in the *RANBP2* gene highlighting similarities and differences in the patient presentations and disease course.

Case Presentation

Case 1

A 9-month-old previously healthy female presented with a seizure and a 4-day history of fever. Her family history was significant for an aunt who passed away of infection leading to encephalitis at age 30. She had no additional seizures, but developed weakness and spasticity in her left side, and developmental regression. An infectious study was positive for Human herpesvirus 6 (HHV-6). Her CSF results showed glucose of 66 mg/dL (reference range: 60-80 mg/dL) and protein of 43 mg/dL (reference range: 15-45 mg/dL), concerning for

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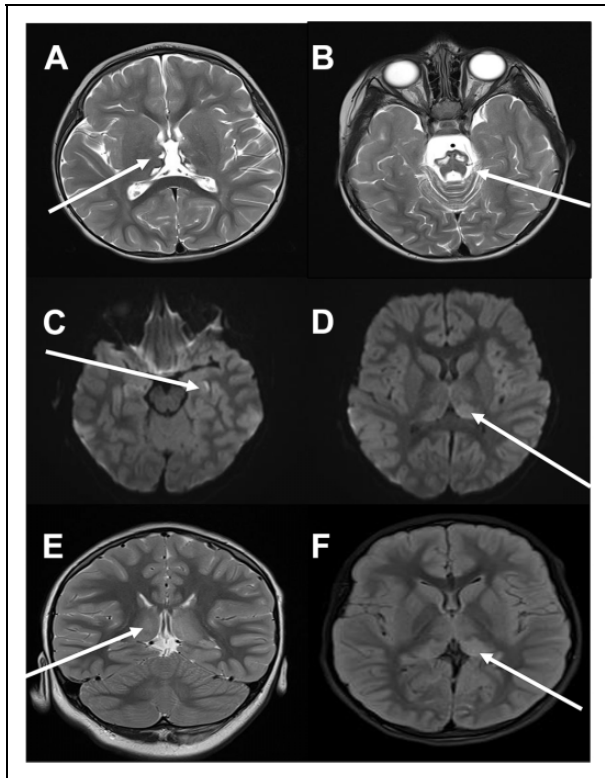


Figure 1. First patient's follow-up MRI showing cystic encephalomalacia in bilateral medial thalamus (A) and pons (B). Second patient's DWI MRI showing subtle increased signal in bilateral hippocampus (C) and thalamus (D), and T2 coronal (E) and FLAIR axial showing increased signal in bilateral thalamus (F).

meningoencephalitis. EEG was consistent with encephalopathy. Brain MRI from an outside hospital reported extensive signal abnormalities and associated diffusion restriction and hemorrhage in the bilateral thalami, external capsules, medial temporal lobes, cerebral peduncles, pons, hypothalamus and mammillary bodies suggestive of possible acute viral encephalitis. Infectious and metabolic work up were negative. An epilepsy panel showed heterozygous mutation in *RANBP2* (c.1754C>T; p.Thr585Met) associated with susceptibility to recurrent acute necrotizing encephalopathy (ANE1). Parental testing was recommended, but not completed due to the family's socioeconomic situation. Patient was treated with high dose steroids and intravenous immunoglobulin (IVIG). She was discharged from the hospital with deficits including developmental delay, weakness, spasticity (left>right), and dysphagia and since then has been receiving IVIG every 2 months. She had recurrence of seizures 2 year later. Repeat MRI brain at our facility showed cystic encephalomalacia in above regions which is an expected change in *RANBP2* induced ANE1 (Figure 1).

Case 2

A 6-year-old female with no significant past medical history or family history presented in cardiac arrest likely secondary to

hypoxia from refractory status epilepticus. Patient was found to be febrile of unknown origin and duration in the emergency department. After admission she continued to have frequent electroclinical seizures. Infectious and metabolic workups were negative and the CSF had no pleocytosis with only mildly elevated protein of 76 mg/dL (reference range: 15-45 mg/dL) and glucose of 70 mg/dL (reference range: 60-80 mg/dL). Her EEG was markedly abnormal showing frequent high amplitude generalized spike and slow wave discharges alternating with short periods of suppression, likely suggestive of ictal-interictal continuum. The brain MRI was positive for symmetric T2 lesions in thalami and mild restricted diffusion in bilateral hippocampus likely representing features of viral or autoimmune encephalitis (Figure 1). An epilepsy panel showed a missense mutation (c.1350A>T; p.Leu450Phe) of uncertain significance in *RANBP2* gene (NM_006267.4). Although p.Leu450Phe is not a known variant of ANE1, her clinical presentation of acute encephalopathy with seizures, MRI and EEG findings, and negative autoimmune, metabolic, infectious and toxic workup support that p.Leu450Phe is likely another pathogenic variant of ANE1. Parental segregation analysis showed the patient's mother has the same variant of interest. During her hospital stay she was treated with several antiseizure medications, high dose steroids, IVIG, interleukin-1 inhibitor: Anakinra 100 mg subcutaneously, twice daily 5 days), and plasmapheresis. After a 42-day hospital stay, patient was discharged home where she has regained her ability to speak, feed herself and continues to improve.

Discussion

RAN Binding Protein 2 (*RANBP2*) gene on chromosome 2q13 encodes for a nuclear pore protein that is expressed in all tissues and plays a role in regulation of proteostasis, chemokine signaling, intracellular metabolism, and mitochondrial distribution. Several varied hypotheses propose a number of explanations for phenotypic presentation based on *RANBP2*'s wide range of intracellular functions. The proposed cellular dysfunctions include problems with transport between the nucleus and the cytoplasm, error with intracellular metabolic regulation, abnormalities in mitochondrial distribution and erroneous elicitation of a cytokine storm.⁶

The pathophysiology of familial acute necrotizing encephalopathy (ANE1) is poorly understood due to the complexity and rarity of the disease. The leading hypothesis is that a trigger in genetically susceptible individuals with *RANBP2* mutations leads to abnormal nuclear signaling resulting in a cytokine storm that allows cytokines into the central nervous system, disrupting the blood brain barrier and causing encephalopathy.¹⁰ The triggering event is most commonly viral, such as influenza A and B, HHV6, HHV7, parainfluenza, varicella, enterovirus, rotavirus, herpes simplex virus, rubella, coxsackievirus A9, and measles.¹¹

A *RANBP2* c.1754C>T; p.Thr585Met missense mutation is most often associated with ANE1. Other mutations that have been identified in the literature include p.Thr653Ile,

Table 1. RANBP2 Gene Showing Conservation Across Species: Sequences Were Aligned Using COBALT (10) Using the RefSeqs of Homo Sapiens (NP_006258.3), Pan Troglodytes (XP_024210382.1), Macaca fascicularis (XP_005575292.1), Mus Musculus (NP_035370.2), Cricetulus Griseus (XP_027244142.1).^a

H. Sapiens	440	LGLQWNSLPALPGIRKWLKQ	459
P. Troglodytes	439	LGLQWNSLPALPGIRKWLKQ	458
M. Fascicularis	440	LGLQWNSLPALPAIRKWLKQ	459
M. musculus	440	LGLQWNSLSTLPAIRKWLKQ	459
C. Griseus	440	LGLQWNSLPTLPAIRKWLKQ	459

^aIn red, we have highlighted the leucine of interest.

p.Ile656Val and p.Trp681Cys.⁶ Four criteria have been proposed for RANBP2 testing including the presence of encephalopathy and polyfocal neurological deficits, supportive features, elevated CSF protein of greater than 0.45 g/L if no CSF pleocytosis is present and MRI findings of symmetric or asymmetric polyfocal lesions in the external capsule or brainstem.¹ The case 2 highlights clinical course of acute encephalopathy following a febrile illness, deterioration of consciousness, the supportive feature of seizures, brain imaging demonstrating symmetric bilateral thalamic lesions, CSF findings of increased protein and no pleocytosis as well as the exclusion of other infectious, toxic or autoimmune etiologies. Leucine at 450 position is located at the Leucine rich domain and is highly conserved through species. In silico algorithms suggest that this variant is probably deleterious (SIFT, Polyphen-2 (0.808), mutationtaster (Table 1)).^{12–15} The patient presentation meets the 4 clinical criteria and provides evidence that p.Leu450Phe is likely a clinically significant variant of ANE1.

Prior studies indicate there is no predilection to the gender and both males and females were approximately equally affected by ANE. Ages of impacted individuals ranged from 5 months to 36 years. Commonly presenting clinical features include encephalopathy, seizures and febrile illness.^{1–5} Less than 10% of individuals fully recover from the acute phase without deficits. Outcomes can include permanent neurologic deficit and death with a mortality rate of 30%.⁵ Poorer outcomes are associated with an onset of symptoms before the age of 1, delirium, hemorrhage or tissue loss on brain MRI and high levels of aminotransferase and CSF protein, while improved outcomes are associated with early treatment with high dose steroids and the lack of brainstem lesions.⁹

Conclusion

Above discussed cases highlights variability in presentation and genetic heterogeneity of ANE1 that resulted in very different outcomes. Patient 1 was treated with high dose steroids and IVIG and was discharged with significant neurological deficits, while patient 2 was treated with high dose steroids, IVIG, an interleukin-1 inhibitor and plasmapheresis and ultimately had minimal residual deficits. Broader recognition of the clinical presentation of ANE1 and the clinically significant mutations

of RANBP2 has the potential to improve long term outcomes with a more rapid and effective treatment course.

Author Contributions

All authors contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript, gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.


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Ethics and Informed consent

Our institution does not require ethical approval for reporting individual cases or case series. Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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