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Review article

Genetic Acute Necrotizing Encephalopathy Associated with RANBP2: Clinical and Therapeutic Implications in Pediatrics

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ABSTRACT

Genetic (also known as familial) acute necrotizing encephalopathy (ANE1) is a rare disease presenting with encephalopathy often following preceding viral febrile illness in patients with a genetic predisposition resulting from a missense mutation in the gene encoding RAN Binding Protein 2 (RANBP2). The acute episode is characterized by deterioration in consciousness, often with focal neurologic deficits and seizures. Additionally, symmetric multifocal brain lesions are seen in the bilateral thalami as well as other characteristic regions, involving both gray and white matter. Prognosis is variable, with a high mortality rate and most surviving patients having persistent neurologic deficits. Early treatment with high dose steroids is associated with a more favorable outcome, however the diagnosis is often overlooked resulting in delayed treatment. The RANBP2 mutation associated with ANE1 causes an incompletely penetrant predisposition to encephalopathy in the setting of febrile illness through a mechanism that remains elusive. There are several non-mutually exclusive hypotheses suggesting possible etiologies for this phenotype based on the many functions of RANBP2 within the cell. These include dysfunctions in nucleocytoplasmic trafficking and intracellular metabolic regulation, as well as cytokine storm, and abnormal distribution of mitochondria. This narrative review explores these key concepts of the RANBP2 mutation and its clinical and therapeutic implications in pediatric populations.

1. Introduction

RAN Binding Protein 2 (RANBP2) is a nuclear pore protein expressed in all tissues, with a wide range of intracellular functions. A missense mutation in the gene encoding RANBP2 (most commonly c.1880C > T: p.Thr585met) is associated with familial acute necrotizing encephalopathy (ANE1) (Neilson et al., 2009). Despite finding this clear relationship, the mechanism by which a mutation in RANBP2 predisposes a patient to ANE1 remains elusive. This may be due to several features of this protein and the resultant disease, including the many intracellular functions of RANBP2 and the rarity of ANE1. Here, the authors present a narrative review of the clinical phenotype previously described cases of RANBP2 associated ANE1 and its implications on therapeutic response and prognosis.

2. Clinical Disease Course

Though the condition is rare, the clinical and radiographic presentation of acute necrotizing encephalopathy (ANE) is highly conserved. From a phenotypic standpoint, most reported cases of ANE progress through three stages: prodromal, acute, and recovery. The prodromal stage is often characterized by a febrile viral illness, classically with upper respiratory infectious symptoms, but can be gastrointestinal or otitis media (Mizuguchi et al., 1995, Neilson et al., 2003). Preceding infection is noted in most but not all cases. The acute phase of the illness consists of acute encephalopathy presenting 1-3 days following the onset of the prodromal stage, without resolution of the inciting infection. This phase includes deteriorating consciousness, with rapid progression to coma, and can be accompanied by seizures and focal neurologic deficits (Mizuguchi et al., 1995, Neilson et al., 2003, Singh et al., 2015). A summary of the clinical spectrum of the disorder from pooled studies is presented in Table 1. The latter two findings are often dependent on the location and burden of lesions. These neurologic symptoms can be associated with systemic symptoms as well (Akiyoshi et al., 2006, Mizuguchi et al., 2007). Across two studies with a total of 18 children with ANE approximately 62% were found to have

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Table 1
Pooled cases of ANE/ANE1 in children

Study (n cases)	Age	Gender (F:M)	Febrile illness (%)	Seizure (n, %)	FND (n, %)	Encephalopathy (n, %)	CSF (n, %)	Radiologic findings (n)
Singh et al., 2014 (summary of cases 2003-2014) (59) (Singh et al., 2015)	5 mo-36y	28:31	30/40 (75%)	34/37 (92%)	2/12 (17%) (Neilson et al. 2003)	54/59 (92%)	EP: 44/47 (94%) Pl: 2/12 (17%)	Bilateral thalami (33/42) Basal ganglia (1/42) Temporal lobe (33/42) Brainstem (32/42) Cerebellum (2/15) Spinal Cord (4/27)
McSwiney et al., 2014 (1) (McSwiney et al., 2014)	3y	1:0	1/1 (100%)	0/1 (0%)	1/1 (100%)	1/1 (100%)	Pl: 1/1 (100%)	Bilateral thalami (1/1) Extreme capsules (1/1) Hippocampi (1/1) Mammillary bodies (1/1) Hypothalamus (1/1) Brainstem (1/1) Cerebellum (1/1)
Bloch et al., 2015 (2) (Bloch et al., 2015)	10y, 40y	1:1	2/2 (100%)	1/2 (50%)	0/2 (0%)	2/2 (100%)	EP: 2/2 (100%) Pl: 1/2 (50%)	Bilateral thalami (2/2) Brainstem (2/2) Hippocampi (2/2)
Anand et al., 2015 (1) (Anand et al., 2015)	28 mo	1:0	1/1 (100%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	EP: 1/1 (100%) Pl: 1/1 (100%)	Bilateral thalami (1/1) Bilateral claustrum (1/1)
Nishimura et al., 2016 (2) (Nishimura et al., 2016)	3y 5 mo, 4y 8 mo	0:2	2/2 (100%)	1/2 (50%)	0/2 (0%)	2/2 (100%)	EP: 0/2 (0%) Pl: 0/2 (0%)	Bilateral thalami (2/2) Basal ganglia (2/2)
Sell et al., 2016 (2) (Sell et al., 2016)	10 mo, 19 mo	0:2	2/2 (100%)	2/2 (100%)	1/2 (50%)	2/2 (100%)	EP: 1/2 (50%) Pl: 2/2 (100%)	Bilateral thalami (2/2) Capsula externa (1/2) Brainstem (2/2) Temporal lobe (1/2)
Sondhi et al., 2016 (1) (Sondhi et al., 2016)	3.5y	1:0	1/1 (100%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	EP: 1/1 (100%) Pl: 0/1 (0%)	Bilateral thalami (1/1) Brainstem (1/1) Cerebellum (1/1) Temporal lobe (1/1)
Isikay et al., 2018 (1) (Isikay and Sahin, 2019)	12y (2^{nd} event at 14y)	0:1	1/1 (100%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	EP: 0/1 (0%) Pl: 0/1 (0%)	Bilateral thalami (1/1) Insular cortices (1/1) Basal ganglia (1/1)
Soriano-Ramos et al., 2018 (1) (Soriano-Ramos et al., 2018)	10y (first event at 7 mo)	0:1	1/1 (100%)	-	-	1/1 (100%)	EP: 1/1 (100%) Pl: 0/1 (0%)	Bilateral thalami (1/1) Temporal lobe (1/1) Occipital cortices (1/1) External capsule (1/1) Brainstem (1/1)
Howard et al., 2018 (2) (Howard et al., 2018)	17 mo, 5y	1:1	2/2 (100%)	2/2 (100%)	0/2 (0%)	2/2 (100%)	Pl: 0/1 (0%)	External capsules (2/2) Temporal lobe (2/2) Brainstem (1/2) Bilateral thalami (1/2) Parietal lobe (1/2)
Kelly et al., 2019 (1) (Kelly et al., 2019)	22y (1^{st} event at 15 mo)	1:0	1/1 (100%)	0/1 (0%)	1/1 (100%)	1/1 (100%)	EP: 1/1 (100%) Pl: 0/1 (0%)	Bilateral thalami (1/1) Brainstem (1/1) Hippocampi (1/1)
Lee et al., 2019 (12) (Lee et al., 2019)	Range 6-93 mo	7:5	12/12 (100%)	8/12 (67%)	3/12 (25%)	7/12 (58%)	EP: 4/12 (33%) Pl: 1/12 (8%)	Bilateral thalami (12/12) Brainstem (8/12) Cerebellum (5/12) Basal ganglia (4/12) White matter (4/12) Mammillary body (1/12)

(*continued on next page*)

Table 1 (*continued*)

Study (n cases)	Age	Gender (F:M)	Febrile illness (%)	Seizure (n, %)	FND (n, %)	Encephalopathy (n, %)	CSF (n, %)	Radiologic findings (n)
Pooled Totals: N = 87	**Range: 5 mo-36y**	**41:44**	**56/66 (85%)**	**49/62 (79%)**	**8/37 (22%)**	**75/85 (88%)**	**EP: 55/70 (79%)** **PI: 8/37 (22%)**	**Thalami: 58/68 (85%)** **Temporal Lobe: 38/48 (79%)** **Brainstem: 49/64 (77%)** **Cerebellum: 9/29 (31%)** **Basal Ganglia: 8/57 (14%)**

Legend: EP: elevated CSF protein; PI: pleocytosis in CSF

elevated transaminases and 12% with findings suggestive of disseminated intravascular coagulation (DIC) (Lee et al., 2019, Seo et al., 2010). In patients with liver dysfunction, transaminitis is seen in the absence of hyperammonemia (Lee et al., 2019, Seo et al., 2010).

ANE1 is a subtype of ANE that is distinguished by its genetic origins and potentially relapsing disease course and is the focus of this study. Compared to ANE, ANE1 involves a positive family history and/or personal history, as recurrent episodes are common in this disease (Neilson et al., 2003). In fact, half of patients with ANE1 will have at least one additional episode (Neilson et al., 2014). Positive family history can include affected relatives beyond first-degree relatives. Often, prior episodes of encephalopathy with preceding illness in the patient or family members may not have been diagnosed as ANE. Specifically, other personal or familial episodes may be labeled as acute disseminated encephalomyelitis (ADEM), cerebellitis, primary angiitis of the central nervous system, aseptic meningitis, viral encephalitis, or 'non-classic' Leigh syndrome (Neilson, 2010). Interestingly, patients with ANE1 have not been reported to have transaminitis or DIC as is commonly observed in patients with ANE (Neilson et al., 2009). There have been no studies assessing the association of ANE1 episodes with myelin oligodendrocyte glycoprotein (MOG) antibodies although this could potentially be a close mimic as well, especially in young children (Baumann et al., 2015).

3. Neurodiagnostic Studies

MRI of the brain is more sensitive than CT for the diagnosis of ANE1, specifically T2-weighted and fluid attenuated inversion recovery (FLAIR)-weighted MRI, which classically shows symmetric hyperintense T2 signal prolongation in the bilateral thalami and brainstem, with thalamic lesions being the most distinctive feature of this disease (Figures 1-2) (Wu et al., 2015). Lesions are most commonly also hypointense on T1 and presence of restricted diffusion, often profound, has been reported (Carmo et al., 2019). Albayram et al. (Albayram et al., 2004) reported that in patients with ANE (not specifically ANE1) with restricted diffusion on neuroimaging can develop a ring pattern of high apparent diffusion coefficient (ADC) observed on the perimeter of lesions (reflecting vasogenic edema) with low ADC in the peri-core (indicating cytotoxic edema), and high ADC in the core representing hemorrhage and/or necrosis (Figure 3). A distinguishing neuroradiographic finding amongst patients with ANE1, as demonstrated in the figures, is that there is a higher predilection for lesions in the bilateral thalami and pons as opposed to more diffuse findings (Wu et al., 2015, Carmo et al., 2019). Less frequently lesions can be found in the cervical spinal cord, cerebellum, medial temporal lobes or insular cortex, and other subcortical regions including mammillary bodies, hippocampus, amygdala, claustrum, and external capsule. These multifocal lesions are typically symmetric, but can be asymmetric (Neilson, 2010, Wu et al., 2015). Further, lesions may evolve over the course of the disease, progressing from edema, to petechial hemorrhage, to necrosis. Following clinical recovery, lesions may fully resolve or result in atrophy, hemosiderin deposition, or development of white matter cysts (Wu et al., 2015).

Of note, there can be significant overlay between the neuroradiographic signatures of viral encephalitides (specifically influenza virus) and ANE/ANE1 (Khandaker et al., 2012, Ishida et al., 2015, Britton et al., 2017). Several larger studies investigating influenza infection have noted a small percentage of cases meet criteria for ANE (3-5.7%) although detailed genetic testing for RANBP2 mutation is infrequent in these studies (Ishida et al., 2015, Britton et al., 2017). This finding is notable in that influenza triggered encephalitides may have nearly identical neuroimaging findings but different clinical courses, highlighting the complexities of the gene-environment interface. For this reason, even if influenza is identified as the causative agent for ANE, additional genetic testing for RANBP2 is warranted.

Additional neurodiagnostic studies are of limited utility in ANE1.

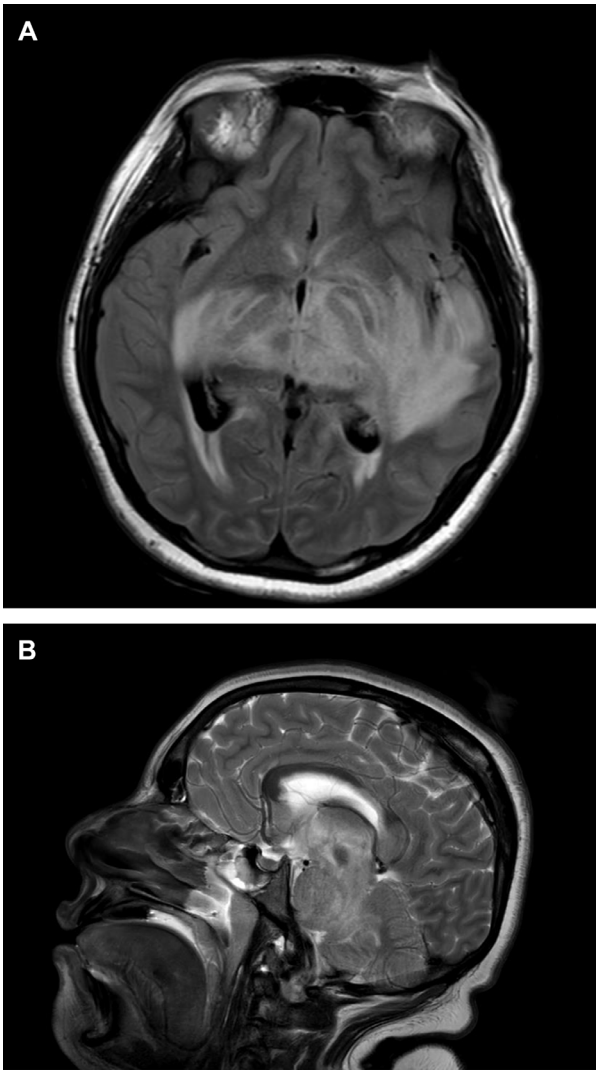

Figure 1. A) 12-year-old female with a diagnosis of ANE1. Axial FLAIR demonstrating bi-thalamic involvement and left temporal lobe edema. B) Same 12-year-old female with ANE1. Sagital T2 demonstrating thalamic and brainstem hypertintensities with sparing of the cortical structures

EEG done in these patients has shown patterns classic of diffuse cerebral dysfunction with global slowing although asymmetry based on lesion location can be observed (Soriano-Ramos et al., 2018, Marco et al., 2010). CSF studies in patients with ANE1 have been reported to demonstrate elevated CSF protein in the absence of pleocytosis in as many as 94% of patients (Singh et al., 2015, Neilson, 2010, Wu et al., 2015). There are no specific CSF biomarkers for the diagnosis of ANE1 at this time although testing for influenza in the CSF is reasonable given the association between influenza as a trigger for ANE1.

3.1. Diagnostic criteria

The conserved clinical and neuroradiographic presentation of ANE1 detailed above has been compiled into diagnostic criteria for this disease. First described by Nielson et al. (Neilson, 2010) and elaborated upon by Singh et al. (Singh et al., 2015), these criteria enumerate the findings that should drive the clinician to do genetic testing for mutations in RANBP2 to achieve a genetic diagnosis of ANE1. However, these criteria are not specific for ANE1 and meeting them does not rule out other diseases such as encephalitis and ADEM. Table 1 summarizes the cases of ANE present in the literature and describes their clinical and radiologic features. While some of these cases have diagnosed ANE1 genetically, others lack differentiation between ANE and ANE1 or are limited by lack of genetic testing.

4. Outcomes, Risk-Modifiers and Prognosis

The outcome of ANE ranges from complete recovery (<10%), to recovery of the acute episode with persistent deficits, to death; with a mortality rate of 30%. Poor prognostic factors include age of presentation <1-year-old, symptoms of delirium associated with brainstem lesions, hemorrhage and tissue loss on MRI, and degree of elevation of aminotransferases and CSF protein (Wu et al., 2015, Skelton et al., 2008, San Millan et al., 2007, Ormitti et al., 2010, Aydin et al., 2010, Okumura et al., 2009). Better outcome is associated with unilateral thalamic lesions and reversal of lesions on imaging (Wu et al., 2015, Yoshikawa et al., 1999). Importantly, early treatment of ANE with high dose steroids is associated with improved outcomes, specifically in patients without brainstem lesions, but often the diagnosis is missed, resulting in delayed treatment (Okumura et al., 2009). However, in ANE1, brainstem lesions are less prognostic (Neilson, 2010). Notably, other treatments including IVIG, plasmapheresis, or antivirals have not shown efficacy, although these are limited to case series level data (Okumura et al., 2009, Bloch et al., 2015).

5. Pathophysiology

5.1. Immune Dysregulation and Antigenic Response

While the clinical presentation and neuroimaging features are predominantly consistent, other elements can be variable. A mutation in RANBP2 engenders a predisposition to ANE1, but becoming symptomatic requires an environmental trigger, which is often a febrile viral infection. Several viruses have been implicated in ANE1 including influenza A and B, parainfluenza, varicella, HHV6, HHV7, enterovirus, rotavirus, HSV, rubella, coxsackievirus A9, measles, with influenza A being most common (Neilson et al., 2009, Soriano-Ramos et al., 2018, Skelton et al., 2008, Tran et al., 2001, Sugaya, 2002, Sazgar et al., 2003, Oki et al., 1995, Ohsaka et al., 2006, Mastroyianni et al., 2003, Martin and Reade, 2010, Mariotti et al., 2010, Lyon et al., 2010, Huang et al., 2004). Recently, SARS-CoV2 (also referred to as COVID-19) has been associated with the onset of ANE, adding to the existing literature of viral trigger phenomenon observed in the disease (Poyiadji et al., 2020). While most cases are associated with preceding viral infection, some cases have also been reported secondary to mycoplasma pneumonia and the diphtheria-tetanus-whole cell pertussis vaccine (San Millan et al., 2007, Narita, 2002, Ashtekar et al., 2003). Interestingly, while the course and outcome of ANE1 vary, this variability does not depend on the inciting agent, indicating that a genetic predisposition to immune dysregulation is more likely the etiology than a specific antigenic trigger (Neilson, 2010).

RANBP2 has many functions within a cell that could potentially be affected by the mutation, resulting in this disease, including interactions with mitochondria, metabolism, and nuclear signaling, with potential effects on viral invasion directly. Many functions of RANBP2 are exerted through its interaction with Ran GTPase, though mitochondrial trafficking is Ran GTPase-independent (Patil et al., 2013). Figure 4 provides an image of the hypothetical interactions between the function of RANBP2 and downstream cascades. The roles of RANBP2 are consistent with the proposed hypotheses regarding the pathophysiology of ANE1, including cytokine storm and metabolic and mitochondrial dysfunction.

Unsurprisingly, in most cases of ANE1 evidence of infection and inflammatory cell infiltration are not found in the CSF, suggesting the symptoms in ANE1 are not a direct effect of the infectious process itself. However, cytokines such as TNF alpha and IL6 are found to be elevated in the serum and/or CSF of patients with ANE1 (Ichiyama et al., 2003,

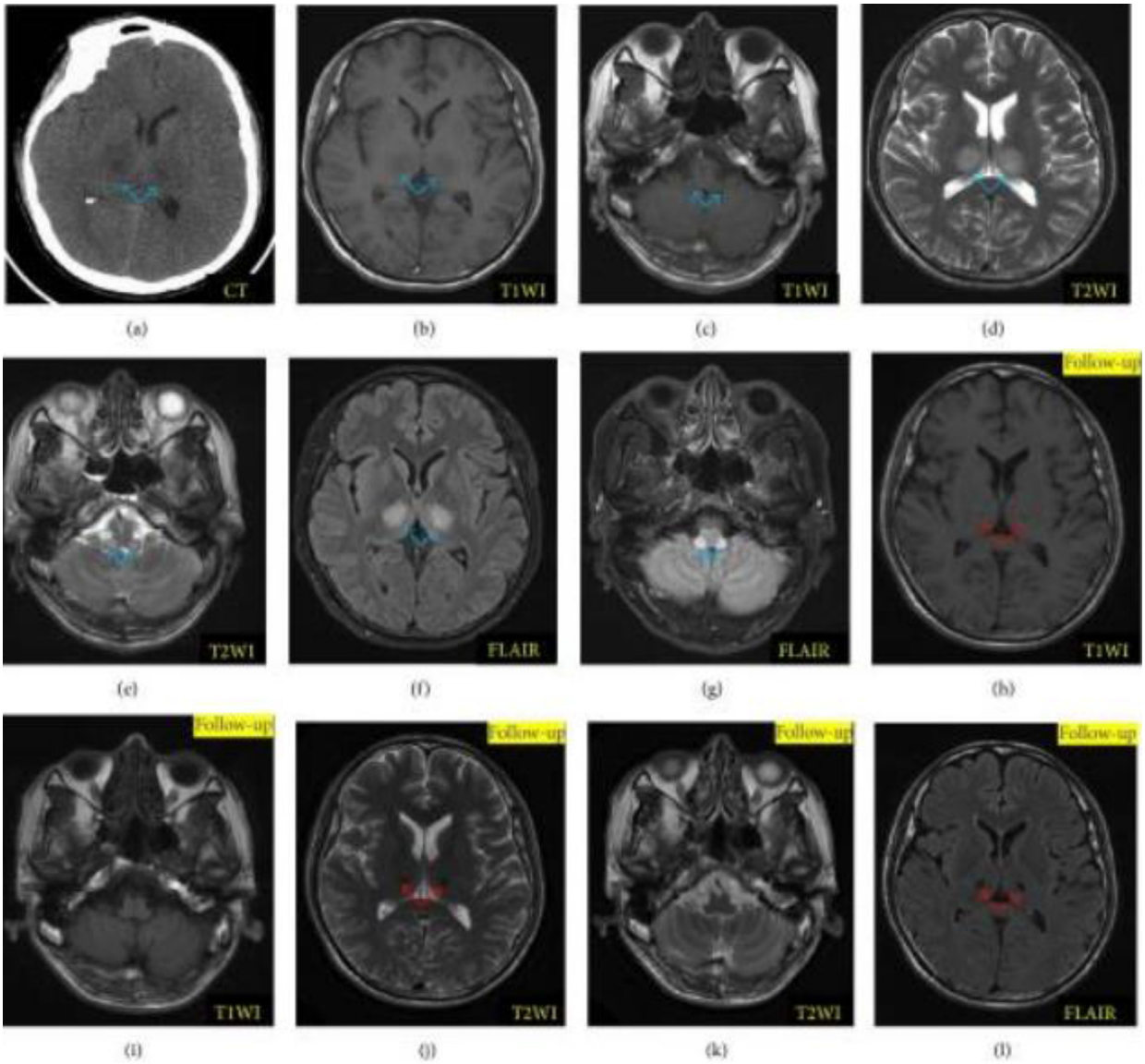

Figure 2. Dynamic changes of magnetic resonance imaging (MRI) of a patient with acute necrotizing encephalopathy (ANE). (a) was computerized tomography (CT) at onset; (b) and (c), (d) and (e), and (f) and (g) were, respectively, the T1-weighted image (T1WI), T2WI, and fluid attenuated inversion recovery (FLAIR) image at onset which showed lesions on bilateral thalamus and brain stem (blue arrow); (h) and (i), (g) and (k), and (l) were, respectively, the T1WI, T2WI, and FLAIR imaging of follow-up which revealed disappearance of the brain stem lesions and impressive regression of the thalamic lesions, just left hemosiderin deposition (red arrow). *Displayed with permission from Wu et al., 2015.*

Hosoya et al., 2005, Aiba et al., 2001). One prominent hypothesis of the etiology of ANE1 is that this encephalopathy is secondary to cytokine storm due to abnormal nuclear signaling, one of the important functions of RANBP2, with cytokines gaining access to the central nervous system as a result of disruption of the blood brain barrier (Mizuguchi et al., 2007). Consistent with this theory, in a motor neuron disease model with loss of RANBP2 in motor neurons, loss of this protein disrupts movement of nuclear transport receptors by the Ran GTPase, impacting proteostasis and nucleocytoplasmic trafficking, ultimately resulting in substrate accumulation and delocalization (Cho et al., 2017). RANBP2 is also found to regulate chemokine signaling by controlling the generation and regulation of components of the signaling pathway including, Stat3, Cxcr4 and its ligands Cxcl14/Cxcl12, as well as Metalloproteinase 28 (Cho et al., 2017). These are implicated in pro-inflammatory signaling, however there was no evidence of macroglia or microglia activation associated with this finding (Cho et al., 2017). Notably in ANE1, elevated CSF cytokines are not accompanied by elevations in inflammatory cells and, on autopsy the parenchymal changes appreciated are out of proportion to observed inflammation (Wu et al., 2015). Also important to note is that the same inflammatory cytokines are elevated in influenza-associated encephalopathy, resulting in a different phenotype, suggesting that this cannot be the only mechanism behind the pathogenesis of ANE1 (Neilson, 2010).

5.2. Metabolic and Mitochondrial Dysfunction

Several features of this condition suggest a metabolic or mitochondrial etiology. ANE1 clinically and histopathologically resemble other disorders of energy metabolism or defects in mitochondrial energy production such as Wernicke encephalopathy and Leigh encephalopathy, respectively (Neilson, 2010). Additionally, symmetric brain lesions are consistent with metabolic or mitochondrial disease which cause evenly distributed insults due to an energy failure state (Neilson, 2010). While many of the functions of RANBP2 are a result of its role in the Ran GTPase cycle, one if its Ran-GTP-independent

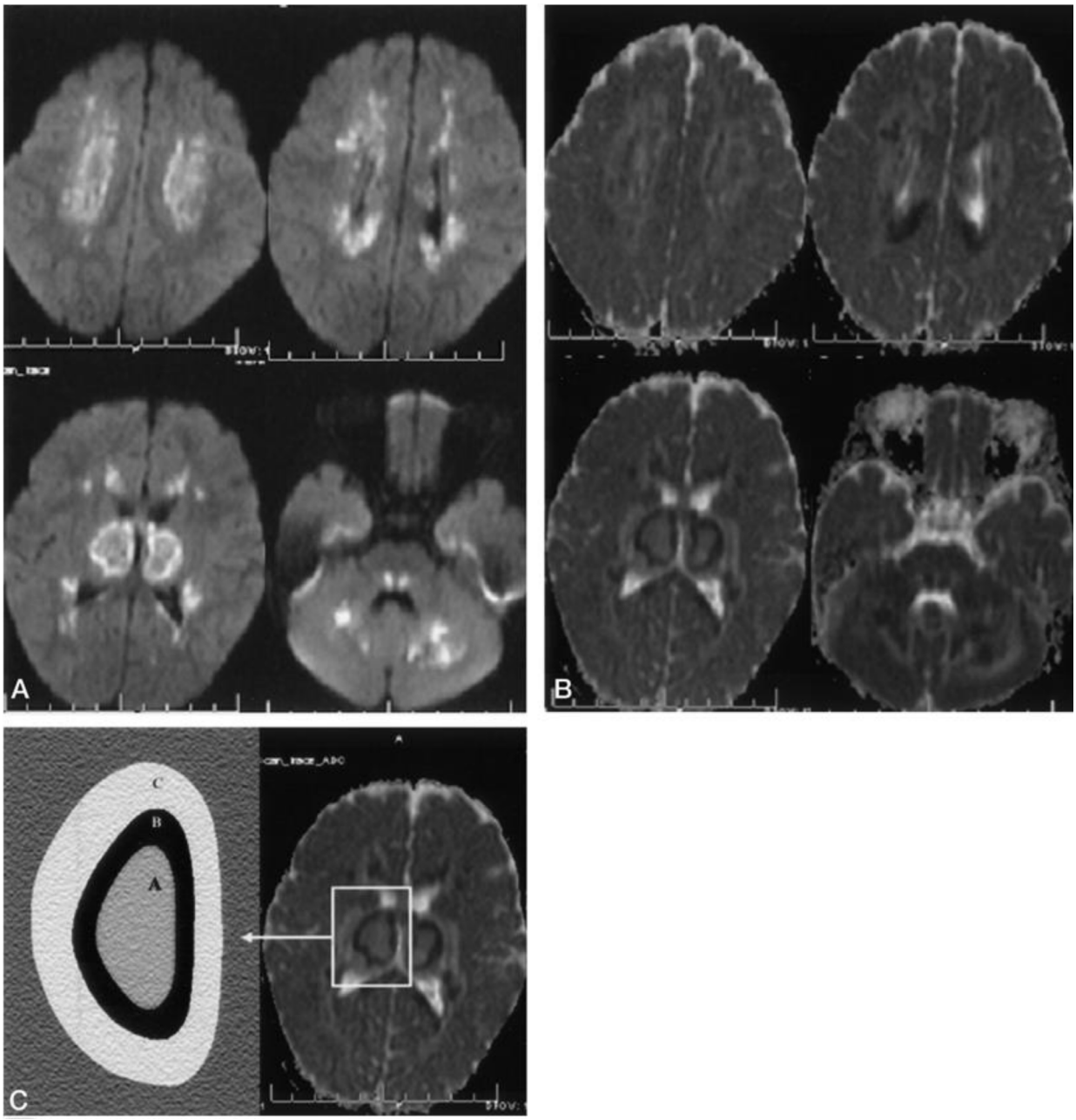

Figure 3. Diffusion findings in acute-stage ANE in a 2-year-old girl. A, Diffusion-weighted MR images (b = 1000) show bilateral symmetric diffuse hyperintense lesions in the cerebellar-cerebral white matter, thalami, and pontine tegmenta. B, The ADC map shows three different patterns of the thalamus and cerebral white matter. The center of the lesions shows higher ADC values than those of normal parenchyma, the peripheral portion of central lesions shows very low ADC values, and outside the thalamus and cerebral white matter are high ADC values, findings compatible with vasogenic edema. Note that the splenium of corpus callosum, pontine tegmanta, optic radiatia, and cerebellar white matter have low ADC values in the central portion and high ADC values in the peripheral portion. C, Mean ADC values and pattern on the right thalamus (A, center of thalamic lesions; B, periphery of the central thalamic lesions; C, outside portions of the thalamic lesions). *Displayed with permission from Albayram et al., 2004.*

mechanisms in the cell is to regulate the distribution of mitochondria by kinesin-1 activation (Patil et al., 2013). Additionally, loss of RANBP2 is associated with a shift toward fatty acid energy metabolism with concomitant decrease in both free fatty acids and phodphatidylcholine (Cho et al., 2017). Proposed mechanisms of the impact of RANBP2 deficits on stress-induced neurotoxicity include downregulation of hexokinase I activity and uncoupling of state IV of oxidative phosphorylation (Neilson et al., 2009, Neilson et al., 2003, Cho et al., 2012, Aslanukov et al., 2006). Errors in the metabolic functions of RANBP2 could potentially increase vulnerability to oxidative damage in the setting of infection, which itself may be associated with additive factors of fasting and catabolic stress (Cho et al., 2012).

5.3. Genetic Contributions

The inheritance of this mutation is autosomal dominant but carries a 40% rate of penetrance (Neilson et al., 2003). Even within a pair of identical twins who are both affected by recurrent ANE1, they are not always similarly affected by simultaneous infections (Neilson et al., 2009). Despite patients often having the same underlying mutation in the RANBP2 gene, presence and manifestations of the disease can be incongruent. For this reason, genetic testing of any patient presenting

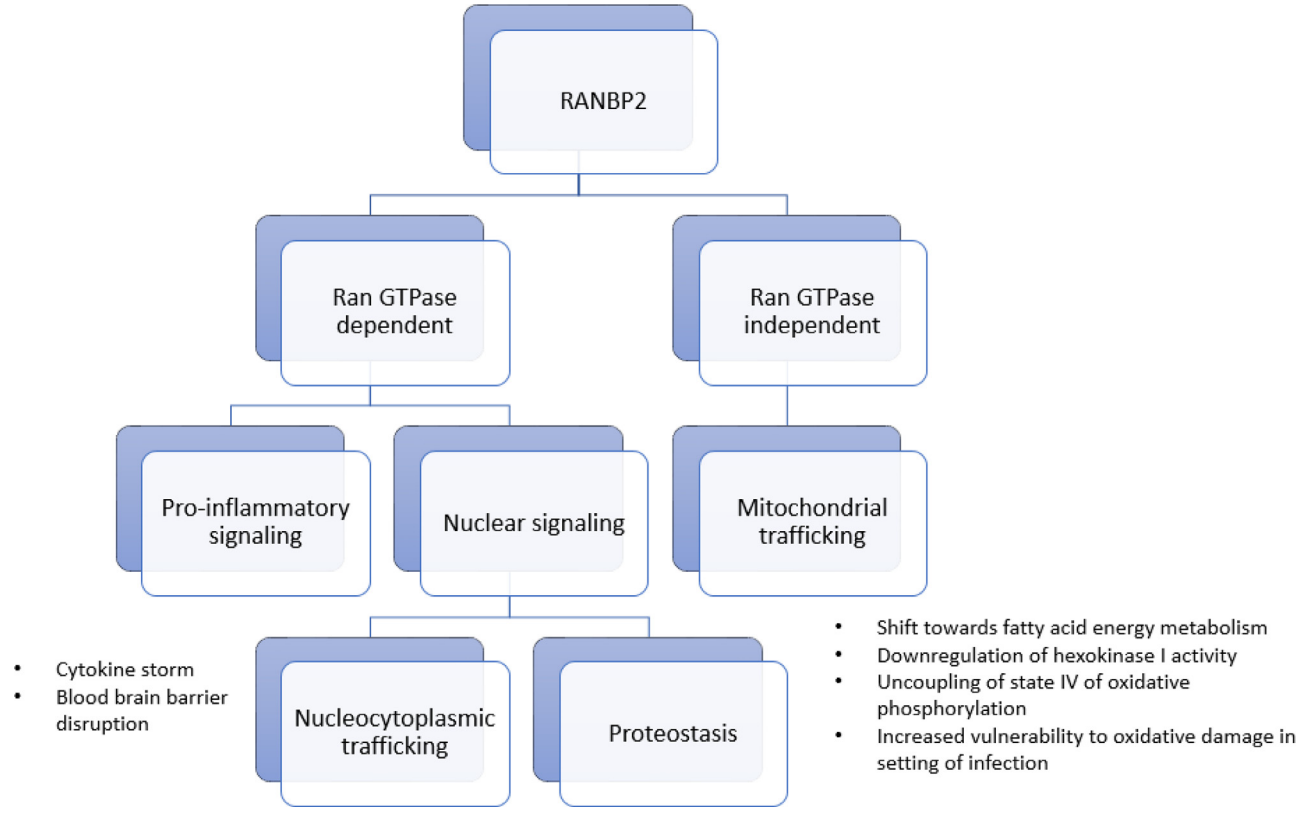

Figure 4. Roles of RANBP2 and effects of RANBP2 disruption

with ANE is reasonable as there is no one specific clinical or radiographic pattern observed in this population.

There are several possible contributors to the reduced penetrance seen in ANE1. These include differences in the environmental trigger associated with the episode, such as route of exposure and load of viral inoculum (Neilson et al., 2009). It has been speculated that RANBP2 gene mutation resulting in amino acid substitutions may cause the final protein to have increased temperature sensitivity, causing protein misfolding that may alter function (Neilson et al., 2009). Thus, severity and duration of fever, could potentially contribute to reduced penetrance although this has not been directly studied. One patient, who was not tested for RANBP2 gene mutation, was found to have a thermolabile phenotype of carnitine palmitoyltransferase II variants, resulting in vulnerability to temperature sensitive encephalopathy (Kumakura et al., 2011). Although difficult to extrapolate to patients with genetically confirmed ANE1, individual variability of fever between patients could play a role in the incomplete penetrance seen in this disease but more study is needed. Additionally, individual differences in immune system components may contribute to this feature (Neilson et al., 2009).

6. Therapeutic interventions and follow-up

Because ANE1 is a rare condition, studies investigating potential therapeutics are limited. Early treatment with steroids has been associated with improved outcomes, thought to be secondary to treating cytokine storm and metabolic dysfunction by decreasing inflammation (Okumura et al., 2009). In addition to anti-inflammatory effects, steroids may also provide protective regulatory effects on mitochondria, allowing for neuroprotection and synaptic plasticity (Cho et al., 2012). It is also possible that use of steroids, especially at high dose, can limit the extent of edema associated with neuroinflammation.

The same therapeutic effect has not been seen with IVIG, plasmapheresis, or antivirals (Okumura et al., 2009, Bloch et al., 2015). Treatment of inciting viral infection has been evaluated as the case report level and in non-familial ANE. Oseltamivir, at high doses and in combination with steroids, has been reported to have efficacy and tolerability (Alsolami and Shiley, 2017) although the mechanism of action of oseltamivir is not thought to impact the presumably pathologic cytokine cascade and immune dysregulation observed in ANE1. Similarly, the use of immunoglobulins or plasmapheresis would not address the presumed pathologic disturbances reported in ANE1, underscoring why these therapies have not been found to have therapeutic impact in such cases. Based on the pathophysiology of the disease, there may be a role for targeted therapies such as IL6 or TNF alpha inhibition, but studies on these targeted biologics are limited, with only one pediatric case series being reported to have benefit from the use of tocilizumab when administered with corticosteroids (Koh et al., 2019). In this study, it was proposed that the primary benefit of IL6 inhibition may come from both limiting downstream cytokine activation and prevention of secondary excitotoxic brain injury.

While it has not been rigorously studied, several case reports recommend continuing annual flu vaccination in these patients to limit future viral infections and have not seen any deleterious effects of the vaccine itself (Singh et al., 2015, Neilson et al., 2014, Soriano-Ramos et al., 2018, Kelly et al., 2019, McSwiney et al., 2014, Howard et al., 2018). However, avoidance of cellular pertussis in the DTaP immunization, which may hypothetically increase susceptibility to relapse, has been raised before although never studied in any scientific manner (Neilson et al., 2014). The authors would not advise holding any vaccinations without further study. The use of other vaccines has not been addressed in these patients.

7. Conclusion

ANE1 is a heterogenous clinical and genetic syndrome with high mortality due to lack of effective treatment options and frequently delayed treatment secondary to missed diagnosis. The diagnosis of

ANE1 is often overlooked because it lacks specific clinical characteristics and is very rare, with diagnosis often made in the setting of genetic test results revealing the common RANBP2 missense mutation. Increased awareness of ANE1 is critical and a low threshold for imaging in patients with acute encephalopathy following a viral syndrome to reveal the characteristic symmetric lesions in the bilateral thalami would be beneficial for appropriate and timely diagnosis and treatment. In patients meeting clinical or radiographic criteria for ANE, testing for RABNP2 mutation should be strongly considered.

RANBP2 is a nuclear pore protein that is expressed in all tissues and has numerous roles in the cell that may contribute to the pathogenesis of ANE1 including regulation of proteostasis, chemokine signaling, intracellular metabolism, and mitochondrial distribution (Patil et al., 2013, Cho et al., 2017, Cho et al., 2012, Aslanukov et al., 2006, Kumakura et al., 2011). Importantly, RANBP2 is known to have cell-type specific roles (Cho et al., 2010) and our understanding of its intracellular behaviors is incomplete and not limited to evidence from the neuronal and blood brain barrier components that may be implicated in ANE1. Increasing our understanding of the pathogenesis of ANE1 will elucidate potential treatment targets and ultimately improve outcomes in this disease that currently exhibits high morbidity and mortality.

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Declaration of competing interest

The authors declare no competing interests.

Supplementary materials

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