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THE INFLUENCE OF RANBP2 MUTATION IN DEVELOPMENT OF INFLUENZA ASSOCIATED WITH ACUTE NECROTIZING ENCEPHALOPATHY IN CHILDREN. CURRENT KNOWLEDGE, AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Acute necrotizing encephalopathy (ANE) is amongst the infection related brain complications in which previously healthy children develop rapidly progressive neurological disease within a week following respiratory viral illness. It is a common knowledge that, most ANE are sporadic. However, familial autosomal dominant ANE due to mutations in the RANBP2 gene has been recently reported (ANE1 or infection-induced acute encephalopathy-3 (IIAE3)). Currently, the vast majority of available data are the case report and case series. This comprehensive review adds to the current knowledge of the pathogenesis, influence and the phenotype of ANE caused by mutations in RANBP2 gene.

KEYWORDS:

INTRODUCTION

Neurological manifestations of influenza virus infection can be meningitis, encephalitis, or encephalopathy. Encephalopathy is characterized by absence of inflammation in the brain and composed of several subtypes such as acute necrotizing encephalopathy (ANE), Reye's syndrome, and hemorrhagic shock and encephalopathy. Acute necrotizing encephalopathy (ANE) is amongst the infection related brain complications in which previously healthy children develop rapidly progressive neurological disease within a week following respiratory viral illness. Most common viral cause of ANE is influenza A followed by Influenza B, other respiratory viral infections such as, parainfluenza, H1N1 and HHV6 have been reported. Affect children are those who are apparently having normal growth and development. In 1995, Mizuguchi,[1-3] reported the first case in Japan and later on described in other parts of the world.[4] Brain Magnetic Resonance Imaging (MRI) is the most reliable imaging scan, demonstrating symmetrical lesions in the thalami, brainstem tegmentum, cerebellum, and periventricular white matter.[2] Many of the reported cases are sporadic and the disease is typically monophasic. There have been reports of multiple cases of ANE in the same family that has drawn attention of researchers leading to identification of a genetic locus on chromosome 2q,[5,6] with subsequent identification of causative mutations in the gene RANBP2 (OMIM 601181). Thus, in addition to the sporadic ANE, a genetic form of the disorder, ANE1, has been recognized.[7]

An Overview of Acute Necrotizing Encephalopathy in General

Epidemiological reports of ANE show that Asia is leading in reported cases with no gender predisposition. ANE is clinically characterized by rapidly deteriorating febrile illness associated with multifocal, symmetric brain lesions affecting bilateral thalami, brainstem tegmentum, periventricular white matter, and posterolateral putamen that are preceded by 3.5 days of airway viral infections.[4] Influenza A virus is the most common agent associated with this, but other agents including influenza B had been reported.[8] Although brain MRI might be similar between Reye's syndrome and acute disseminated encephalomyelitis (ADEM), some distinct features do exist in ANE. In Reye's syndrome, neurologic manifestations are usually delayed from the onset of respiratory symptoms. Other prominent metabolic changes seen in Reye's syndrome such as hyperammonemia, hypoglycemia, and massive brain edema. On the other hand, ADEM typically presents with asymmetric distribution of lesions in the brain as well as CSF pleocytosis.[9] The precise pathogenesis of ANE is still elusive. Presence of elevated IL-6 and TNF-alpha in CSF of the affected patients has been linked with the theory that possibly cause subsequent widespread damage to the vascular endothelial cells.[10]

Recurrent or familial forms of ANE

Acute necrotizing encephalopathy (ANE) typically affects children who are young and previously healthy, progressing to severe form and usually is triggered by

viral infections. When there is a pattern of recurrence or familial forms of ANE, the condition is called ANE1. These patients are increasingly reported to have the missense mutations (c.1880C > T mutation) in the gene encoding the nuclear pore protein called RAN binding protein 2 (*RANBP2*).[7,11-16] The following features inform the practicing clinicians to always consider ANE1 as differential diagnosis in any patient presenting with ANE: (a) family history of neurological symptoms, occurring during an infection; (b) recurrent encephalopathy following fever, with or without findings of ANE; (c) MRI changes of ANE with additional lesions in any of the following areas: medial temporal lobe, insular cortices, claustrum, external capsule, amygdale, hippocampi, mammillary bodies, spinal cord.[3,4,7] Some cases of ANE have brain lesions in the thalami bilaterally, putamen, deep periventricular white matter, cerebellum, and brainstem,[17,18] while in ANE1 the MRI changes are seen in the external capsules, claustrum, limbic structure, or temporal lobes.[7] Reports from Asian patients with ANE, have shown that hepatic involvement is common, but not in ANE1.[7] Differential diagnosis of ANE includes mitochondrial disorders, especially Leigh/Alpers syndrome,[19] inflammatory, demyelinating brain diseases, acute disseminating encephalomyelitis (ADEM).[20]

RANBP2 mutation and association with acute necrotizing encephalopathy in General

The RAN binding protein-2 (RANBP2) is a large, mosaic protein,[21] whose pleiotropic functions are reflected by its interaction with a set of well-defined partners implicated in a wide variety of biological processes, such as nucleocytoplasmic.[22-28] and cytoplasmic.[29-31] trafficking, protein modification through sumoylation,[32-35] protein turnover and biogenesis.[21,36-39] and energy homeostasis.[40] Evidence supports the view that RANBP2 is significantly involved during cell proliferation and death.[7,30] These physiological activities are affected by some stressors like infections through modulating RANBP2.[7,11]

In a study of 29 Japanese patients with AESD or ANE, a higher frequency of several single nucleotide polymorphisms in the carnitine palmitoyl transferase II gene was found compared with healthy controls.[41] Another study identified an association between AESD and a genetic variant of the adenosine A2A receptor (ADORA2A) which may alter cyclic AMP signaling.[42] Moreover, the missense mutations in the gene encoding Ran binding protein 2 (RANBP2) have been identified in a Taiwanese family in which 16 family members were diagnosed ANE.[7]

To elucidate the genetic propensity or find out other clinically plausible host factors, genomic typing of human leukocyte antigen (HLA) using PCR-sequence-specific oligonucleotide probes/sequence specific primers technique with gel immune-electrophoresis was done in 3 children, mitochondrial DNA studies were screened in 6 children and direct sequencing and next generation sequencing of entire coding regions of RANBP2 gene were conducted for a child and her parents suspicious of having ANE1.

The RANBP2/Nup358 is a only found in vertebrate as multipurpose protein.[21,43-45] Several roles of RANBP2 have emerged that implicate RANBP2 in nucleocytoplasmic trafficking,[22,44] protein biogenesis,[36,37] the formation of the mitotic spindle, assembly of the nuclear envelope.[46]

Common viral infections in ANE

Influenza A (H3N2) or Influenza A (H1N1), are the most common types of respiratory viral infections that provoke the CNS complications in about a week post such infection. Others include influenza B, parainfluenza, H1N1 and HHV6

Patient Clinical characteristics

Acute encephalopathy following a viral febrile disease is characterized by rapid deterioration in the level of consciousness and convulsions. The CSF lacks pleocytosis while the liver enzymes (serum aminotransferases) derangement vary considerably. No increase in blood ammonia.

Differential diagnosis from clinical viewpoints

Various severe disease can mimic ANE, and the following are such examples; overwhelming bacterial and viral infections, fulminant hepatitis; toxic shock, hemolytic uremic syndrome and other toxin-induced diseases such as Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.

Differential diagnosis from radiological viewpoints

ANE is not a unique entity causing brain lesions, either gross or specific foci in the brain. Other metabolic disorders and diseases related mitochondrial myopathies may also mimic the ANE. Such conditions include ; glutaric acidemia, methylmalonic acidemia, Wernicke encephalopathy, acute disseminated encephalomyelitis, and acute hemorrhagic leucoencephalitis, Normally there is defect in the blood-brain barrier surported by the brain neural imaging findings in the thalamus showing changes with vasogenic edema, representing hemorrhage and necrosis,[12,18] and hypercytokinemia and cytokine storm proposed in various studies.[3] CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brain stem tegmentum and cerebellar medulla. No involvement of other CNS regions.

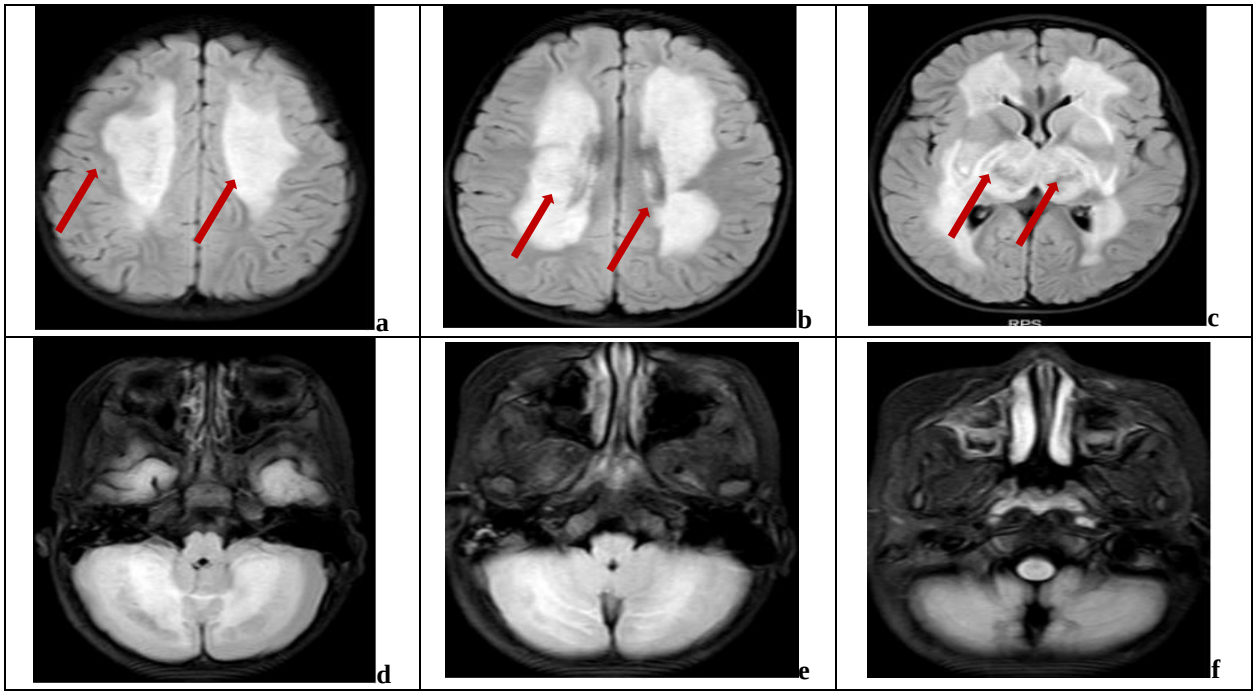

Fig. 1: CT/MRI T2 Weighted Set Cases (a - c) and (d - f). In a, b and c there are Symmetrical multiple abnormal signal shadows in the (a), cerebral white matter (b), and dorsal brainstem (c), considering encephalitis. In d, e, and f there are high signal within bilateral external capsules, left cerebellar gray matter and restricted diffusion against a background of increased diffusion involving both thalami, which are swollen, multiple hyperintense spots, consistent with multifocal necrosis in acute necrotizing encephalopathy.

CONCLUSION

RANBP2 mutations may lead to neurological presentations commonly known as ANE1, which is probably underdiagnosed. Clinicians should consider acute necrotizing encephalopathy in much older children, or those with recurrent neurological symptoms, or adults presenting with encephalopathy; genetic testing can confirm the diagnosis.

LIMITATIONS

The quality of the literature presented is limited as this review relies primarily on case reports, case series, and observational studies. The complications identified are also difficult to address in the context of severe systemic influenza infection as it is unclear if they are the consequence of the infection itself, systemic illness or shock in general, or an exacerbation of an otherwise underlying condition.

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