

Metabolic Abnormalities in Tick-Borne Encephalitis: A Mini-Review

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ABSTRACT

Tick-borne encephalitis (TBE) is a debilitating, heterogeneous disease associated with myriad symptoms that vary depending on the infection subtype and duration. There are no known biomarkers for TBE, largely due to a lack of knowledge of its pathogenesis. Numerous studies have sought potential biomarkers for the disease. This mini review concisely outlines the current state of research on metabolic abnormalities in TBE, and may provide a foundation for further studies of the disease. Research progress in key areas such as the immune response and metabolites of dysregulation, is also described. The studies outlined here suggest potential biomarkers for TBE. Future research at multiple research centers should focus on firmly establishing these biomarkers. Whether the metabolic changes noted in this mini review are a cause or a consequence of TBE must also be verified.

Abbreviations: TBEV: Tick-Borne Encephalitis Virus; PLs: Phospholipids; DHA: Docosahexaenoic Acid; AA: Arachidonic Acid

Introduction

Tick-Borne Encephalitis (TBE) is a debilitating sudden-onset disease that affects the central nervous system. There are currently no definitive biomarkers for the disease and no therapeutic targets. TBE is usually treated with antipyretics and analgesics. This mini review outlines the progress made toward identifying potential metabolic biomarkers of TBE.

Immune Response and Metabolites Dysregulation

It is thought that Tick-Borne Encephalitis Virus (TBEV) infection activates the immune system. In humans, TBEV infection causes early immunological reactions that are initially pro-inflammatory, and then anti-inflammatory [1]. Numerous immune dysregulation phenotypes have been reported in patients infected with viruses, including TBEV [2,3]. After viral invasion, the body makes a series of adjustments to maintain homeostasis and health. Numerous biochemical compounds are released, leading to changes in amino acids, Phospholipids (PLs), sphingomyelins, and triglycerides.

Abnormalities in these metabolites may explain the typical findings of TBEV infection, i.e., fever, nausea, and encephalitis.

Many inflammatory and anti-inflammatory metabolites have been implicated in viral infection, including Arachidonic Acid (AA) and polyunsaturated fatty acids (PUFAs). AA, a potential biomarker for COVID-19, is involved in the passivation of enveloped viruses, such as influenza virus [4]. A relatively small study of 60 TBEV patients and 56 controls found that AA and PUFAs levels differed between the groups. Moreover, significant decreases in AA and Docosahexaenoic Acid (DHA) were observed, in contrast to another study [5]. Two of the most recent studies of AA provided conflicting results: one found decreased levels in herpes virus infection patients [6], while we found an increasing trend during the pyrogenic phase of coronavirus infection [7]. More recent studies have focused on the role of PLs in the pathogenesis of viral diseases, where PLs are potential therapeutic targets [8]. One recent study investigated the connection between PLs and disease severity and showed that lipid

species differed significantly in comparison to membranes from uninfected cells [9]. PLs dominate cell membranes and may disrupt cell homeostasis, thus causing physiological and pathological changes, and impairing barrier function [10].

Promising studies of immune dysregulation in TBE have implicated amino acids [11]. Amino acids initiate biochemical reactions and changes. Moreover, glutamate and aspartate are primary excitatory neurotransmitters, and may mediate the association between neurotropic viral infection and metabolite dysregulation [12]. There is some evidence that TBEV may affect, at least in part, energy metabolism. Studies of TBE have reported markers of energy metabolism dysfunction, such as abnormal acylcarnitine production and altered lipid metabolism, especially fatty acid β -oxidation. Changes in serum acylcarnitine levels suggest mitochondrial dysfunction, which is associated with altered fatty acid transport [13]. As well as showing significant differences between TBE patients and healthy controls, abnormal acylcarnitine metabolism was seen in HIV-exposed uninfected newborns [14].

Metabolomics

Few comprehensive metabolomic studies of TBE have been performed. One study assessed metabolites in enrichment pathways in the serum of 59 patients and 30 healthy controls. The results supported the hypothesis of a disordered metabolic state in TBE. The pathways in which metabolite levels were abnormal varied, with some being associated with the immune response. The authors suggested that a distinct metabolic response to viral infection occurs in TBE patients and concluded that serum metabolomics could be used to identify biomarkers of TBEV disease. However, the results were based on a small number of samples.

Conclusion

The pathogenesis of TBE remains elusive despite efforts to identify biomarkers of the disease. The studies outlined here identified potential biomarkers of TBE, including LPs, fatty acids, amino acids, and energy metabolites. The conflicting results, i.e., lack of reproducibility, make identifying biomarkers difficult. To clarify the mechanisms of the disease, further research into the pathology of TBE, and the role of TBEV, must be conducted at multiple centers to build create foundation for further research [2].

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Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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