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Elevated Sialic Acid, Sphingomyelin, Tau and Low 2-MTHF are Inappropriate Biomarkers for Diagnosing Kearns-Sayre Syndrome

Josef Finsterer
MD, PhD, Neurology & Neurophysiology Center, Vienna, Austria, ORCID: 0000-0003-2839-7305

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LETTER TO THE EDITOR

We read with interest the article by Salvador, *et al*., on two patients with Kearns-Sayre syndrome (KSS), one of whom carried a 7kb single mtDNA deletion (m.6683-13659del) with a heteroplasmy rate of 25% (patient 1) while the other was diagnosed by the clinical presentation without genetic confirmation of the disease [Salvador, C. L. *et al*., 2023]. Cerebrospinal fluid (CSF) studies revealed that sialic acid, sphingomyelin C16:0, and tau were increased and that 5-methyl-tetra-hydro-folate (5-MTHF) was reduced [Salvador, C. L. *et al*., 2023]. It was concluded that elevated levels of sialic acid, sphingomyelin C16:0, and tau protein and low levels of 5-MTHF in the CSF could be used as biomarkers for the early diagnosis of KSS [Salvador, C. L. *et al*., 2023]. The study is excellent but has limitations that should be extensively discussed.

The major limitation of the study is that causes other than KSS for elevated sphingomyelin C16:0, sialic acid, and tau levels were not adequately ruled out. Sphingomyelin can also be elevated in sphingomyelinase deficiency (Niemann-Pick disease), or prodromal Alzheimer's disease [Kosicek, M. *et al*., 2023]. Sialic acid has been found to be elevated in patients with myocardial damage, particularly myocardial infarction [Govindarajan, S. *et al*., 2016]. Since KSS is often complicated by arrhythmias, conduction defects, and cardiomyopathy, it is conceivable that elevated sialic acid was caused by cardiac involvement in KSS. Sialic acid can also be elevated in sialidoses and sialic acid storage disease [www.sciencedirect.com].

A second limitation is that the conclusion that elevated free sialic acid, sphingomyelin C16:0, and tau protein as well as low 5-MTHF could serve as new biomarkers in the diagnosis of KSS is not supported by the results of the study [Salvador, C. L. *et al*., 2023]. Such a conclusion cannot be drawn from a group of only two patients. Multicentre studies need to be performed in a larger cohort of KSS patients to assess whether elevated levels of sialic acid, sphingomyelin C16:0 and tau and low levels of 5-MTHF really serve as biomarkers for the diagnosis of KSS.

A third limitation of the study is that the long-term course of sialic acid, sphingomyelin, tau, and 5-MTHF levels was not examined. In order to truly claim that these molecules can serve as biomarkers for the early diagnosis of KSS [Salvador, C. L. *et al*., 2023], they need to be identified at an early stage of the disease and their further progression in the disease process monitored by repeated determination.

A fourth limitation is that the family history was not provided and that first degree relatives were not evaluated clinically, biochemically, or genetically. Although mtDNA deletions are inherited through the maternal line in only 4% of cases [Poulton, J. *et al*., 2023], it is critical that first-degree relatives, particularly the mothers of the index cases, be thoroughly evaluated.

Overall, the interesting study has limitations which challenge the results and their interpretation. Addressing these limitations could further strengthen and reinforce the statement of the study. Assessing whether CSF sialic acid, sphingomyelin, tau, and 5-MTHF can truly serve as biomarkers for the diagnosis of KSS requires large cohort studies and long-term follow-up measurements of these molecules.

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***Corresponding Author:** Josef Finsterer

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studies with human participants or animals performed by any of the authors.

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