Quinolinic acid

Quinolinic acid is a naturally occurring compound that belongs to the class of organic compounds known as quinolines. It is a derivative of quinoline and is an intermediate in the metabolism of the amino acid tryptophan. Quinolinic acid is also considered an excitotoxic neurotoxin due to its ability to overstimulate certain receptors in the brain, leading to neuronal damage or death.

Here are some key points about quinolinic acid:

Biosynthesis: Quinolinic acid is produced in the body as part of the kynurenine pathway, which is responsible for the metabolism of tryptophan. In this pathway, tryptophan is converted into various intermediate compounds, including quinolinic acid.

Role in neurodegenerative diseases: Quinolinic acid has been implicated in the pathogenesis of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). Elevated levels of quinolinic acid have been observed in the brains of individuals with these conditions, and it is believed to contribute to neuroinflammation and neuronal damage.

Excitotoxicity: Quinolinic acid acts as an agonist for the N-methyl-D-aspartate (NMDA) receptor, a type of glutamate receptor in the brain. Overactivation of the NMDA receptor by quinolinic acid can lead to an excessive influx of calcium ions into neurons, triggering a cascade of events that can result in oxidative stress, inflammation, and ultimately neuronal death.

Research and therapeutic implications: Due to its involvement in neurodegenerative diseases, quinolinic acid has been a subject of research aimed at understanding its mechanisms of action and developing potential therapeutic strategies. Various compounds have been investigated as potential quinolinic acid synthesis inhibitors or NMDA receptor antagonists to mitigate their neurotoxic effects.

Dale et al. measured CSF neopterin, quinolinic acid, kynurenine, and kynurenine/tryptophan ratio using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) system. The CSF of 18 children with ITES was compared with acute encephalitis (n = 20), and three control groups, namely epilepsy (n = 20), status epilepticus (n = 18), and neurogenetic controls (n = 20).

The main ITES phenotypes in 18 patients were acute encephalopathy with biphasic seizures and late restricted diffusion (AESD, n = 4), febrile infection-related epilepsy syndrome (FIRES n = 4), and other ITES phenotypes. Influenza A was the most common infectious trigger (n = 5), and 50% of patients had a prior notable neurodevelopmental or family history. CSF neopterin, quinolinic acid, and kynurenine were elevated in the ITES group compared to the three control groups (all $p < 0.0002$). The ROC (area under the curve) for CSF neopterin (99.3%, CI 98.1-100) was significantly better than CSF pleocytosis (87.3% CI 76.4-98.2) ($p = 0.028$). Elevated CSF neopterin could discriminate ITES from other causes of seizures, status epilepticus, and febrile status epilepticus (all $p < 0.0002$). The high CSF metabolites normalized during longitudinal testing in two patients with FIRES.

CSF neopterin and quinolinic acid are neuroinflammatory and excitotoxic metabolites. This CSF metabolomics inflammatory panel can discriminate ITES from other causes of new-onset seizures or status epilepticus, and rapid results (4 h) may facilitate early immune modulatory therapy [1)]

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Dale RC, Thomas T, Patel S, Han VX, Kothur K, Troedson C, Gupta S, Gill D, Malone S, Waak M, Calvert S, Subramanian G, Andrews PI, Kandula T, Menezes MP, Ardern-Holmes S, Mohammad S, Bandodkar S, Yan J. CSF neopterin and quinolinic acid are biomarkers of neuroinflammation and neurotoxicity in FIRES and other infection-triggered encephalopathy syndromes. Ann Clin Transl Neurol. 2023 Jun 20. doi: 10.1002/acn3.51832. Epub ahead of print. PMID: 37340737.