Letters to the editor

Valproate induced carnitine deficiency and hyperammonaemia

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Editor – I read with interest the article by Yu E et al., and the earlier case by Camilleri et al. Hyperammonaemia is a recognised complication of treatment with valproic acid (VPA) or its sodium salt (sodium valproate) and although the mechanism is not fully understood, secondary carnitine deficiency is believed to play a significant role.

Primary carnitine deficiency is an autosomal recessive inherited metabolic disorder (IMD) affecting the SLC22A5 gene and OCTN2 transporter. Secondary deficiencies are also seen in other IMDs (eg organic acidurias and primary disorders of fatty acid oxidation) or acquired through inadequate dietary intake, renal failure, malabsorption states or are drug induced (eg VPA).

VPA (and sodium valproate) is a widely used anti-epileptic drug (AED) and depletes carnitine stores, especially during long-term or high-dose therapy, through various synergistic mechanisms (including impaired renal tubular reabsorption). It has three pathways for metabolism: primarily glucuronidation, β-oxidation and, to a lesser extent, ω-oxidation. Carnitine is essential for β-oxidation and in the depleted state, ω-oxidation of VPA is favoured leading to elevated levels of 4-en-VPA, which can inhibit carbamoyl phosphate synthetase (CPS) and impair the urea cycle with resultant hyperammonaemia.

Risks factors for carnitine depletion include age <24 months, the presence of concomitant neurologic or metabolic disorders, and receipt of multiple AEDs (including VPA and sodium valproate). Measurement of carnitine levels is indicated in patients who are at risk for deficiency in order to identify those who would benefit from supplementation. In the acute setting, measurement of carnitine levels may not be useful (due to availability and turnaround time) and treatment should be initiated promptly where acquired carnitine deficiency is suspected, particularly in the presence of life threatening hyperammonaemia (e.g. valproate-induced hyperammonemic encephalopathy).

The British Inherited Metabolic Disease Group (BIMDG) formulary recommends levocarnitine (L-carnitine) 100–200 mg/kg/day, orally, in two to four divided doses, maximum of 3 grams a day for the treatment of adults with secondary carnitine deficiency. Furthermore, the development of life-threatening hyperammonaemia should raise concerns about the potential unmasking of an undiagnosed IMD (eg ornithine transcarbamylase OTC deficiency (particularly heterozygote female carriers) or another IMD).

References


Early applications of ChatGPT in medical practice, education and research

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Editor – ChatGPT is back, after the lifting of the temporary ban in Italy due to data breaches which were detected for ChatGPT also having been accused of not verifying user age. The opinion article by Sedaghat, which tackles a topic that is currently highly pertinent to the medical community and merits discussion, caught my attention. I would like to express my point of view on the rapidly evolving field of AI-driven large language models and in specific ChatGP.

Undoubtedly, one notable advantage of utilising AI tools is the ability to expedite research and publication processes. Consequently, researchers can allocate more time to conducting actual studies rather than solely focusing on writing up the findings. However, considering the current academic tenure system that relies on metrics like the H index, which is based on the number of citations an author receives, if AI-generated content were used extensively for the purpose of publication, it could potentially overwhelm journal editors and lead to an overflow of content in databases such as PubMed. This content would be primarily created by AI with minimal human input. The long-term impact of this trend on future research remains uncertain at this time.

In the article, the author discusses ChatGPT’s capability to successfully pass all three stages of the United States Medical Licensing Exam (USMLE). This seems obvious as it entails...
resolving clinical issues by understanding key terms and utilising AI-based reasoning. Moreover, AI does not possess the limitations observed in humans, as it can effortlessly store and retrieve vast amounts of information. Conversely, I believe that ChatGPT could potentially assist educators in developing medical school and residency programme assessments, presenting a safer application of this technology.

Furthermore, in Italy, it is legally required for medical students to defend a thesis before graduating as a physician (MD). However, considering the increasing use of LLM technologies in completing a significant portion of the work, it is worth reconsidering the purpose of writing a dissertation in the future. While various measures can be implemented to minimise the potential for cheating, it is crucial to cultivate a culture of trust and integrity within the educational community to encourage ethical conduct and responsible learning practices.

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