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Correspondence

Letter to the Editors: Concerning "Hyperleucinosis during infections in maple syrup urine disease post-liver transplantation" by Guilder et al

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Dear Editors,

We read with interest the article by Guilder et al. that was published in Molecular Genetics and Metabolism Reports in 2021 [1]. This study included hearing-based and literature-based cohorts with maple syrup urine disease (MSUD) post liver transplantation (LT) and investigated the incidence of post-LT hyperleucinosis. Here, we would like to clarify that the incidence of symptomatic hyperleucinosis and asymptomatic mild leucine elevation should be separately addressed to avoid underestimating the preventive effect of LT against metabolic decompensation.

We previously reported a case of classical MSUD who underwent living-related LT [2]. The authors referred to our report as a case of hyperleucinosis and encephalopathy after living-related LT; however, this was incorrect because our patient did not develop neurological symptoms. Although she experienced a mild elevation of leucine (concentration $\leq$ 450 μmol/L) after 3 days of insufficient formula and oral intake due to respiratory syncytial virus infection, laboratory findings quickly improved to the normal range with intravenous dextrose and hydration. This episode indicated that LT, including living-related LT, could simplify sick day management compared to the period before LT. Our patient is currently maintaining leucine concentrations within the therapeutic target range on an unrestricted diet, has an intelligence quotient of 92 (WISC-IV) at 6 years of age, and is attending a normal elementary school. Another similar case from Japan referred to in the article by Guilder et al. as a case of hyperleucinosis was also asymptomatic, and the level of leucine elevation was mild at 340 μmol/L [3]. We propose that such cases should not be discussed in the same framework as severe hyperleucinosis with encephalopathy, as seen in a case reported by Al-Shamsi et al. [4], which was also referred to in Guilder et al.'s study [1].

We believe the presence of neurological symptoms and the duration of hyperleucinosis are critical factors in evaluating post-LT hyperleucinosis. However, it is challenging to distinguish between mild leucine elevations and acute metabolic crisis, since no clear-cut plasma leucine level is available to predict neurological damage. It remains unclear whether LT can fully restore brain amino acid balance, even if leucine is maintained within the recommended range. Imbalances in cerebral amino acids, such as glutamate or lactate, are likely contributing to the neuropsychiatric outcomes in patients with MSUD [5,6]. Therefore, investigating the balance of large neutral amino acids in the brain may help the discussion of post-LT hyperleucinosis. Furthermore, appropriate plasma biomarkers in MSUD that reflect a cerebral deficiency of neurotransmitters need to be identified.

To improve the long-term neurological prognosis of MSUD patients, it would be desirable to detect the asymptomatic hyperleucinosis that precedes encephalopathy as early as possible. Guilder et al. suggested that particular management should be considered after the first episode of unexplained encephalopathy or signs of acute hyperleucinosis. However, we recommend that the patients be closely monitored, even before the first symptomatic episode, under an appropriate medical system for the first few episodes of persistent fever or in cases of severe gastroenteric symptoms with poor oral intake after LT.

CRediT authorship contribution statement

Chika Takano: Conceptualization, Writing – original draft, Writing – review & editing. **Erika Ogawa:** Supervision, Writing – review & editing. **Natsuko Arai-Ichinoi:** Supervision. **Mika Ishige:** Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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