
Persistently Increased Alloisoleucine in a Patient with Seizures

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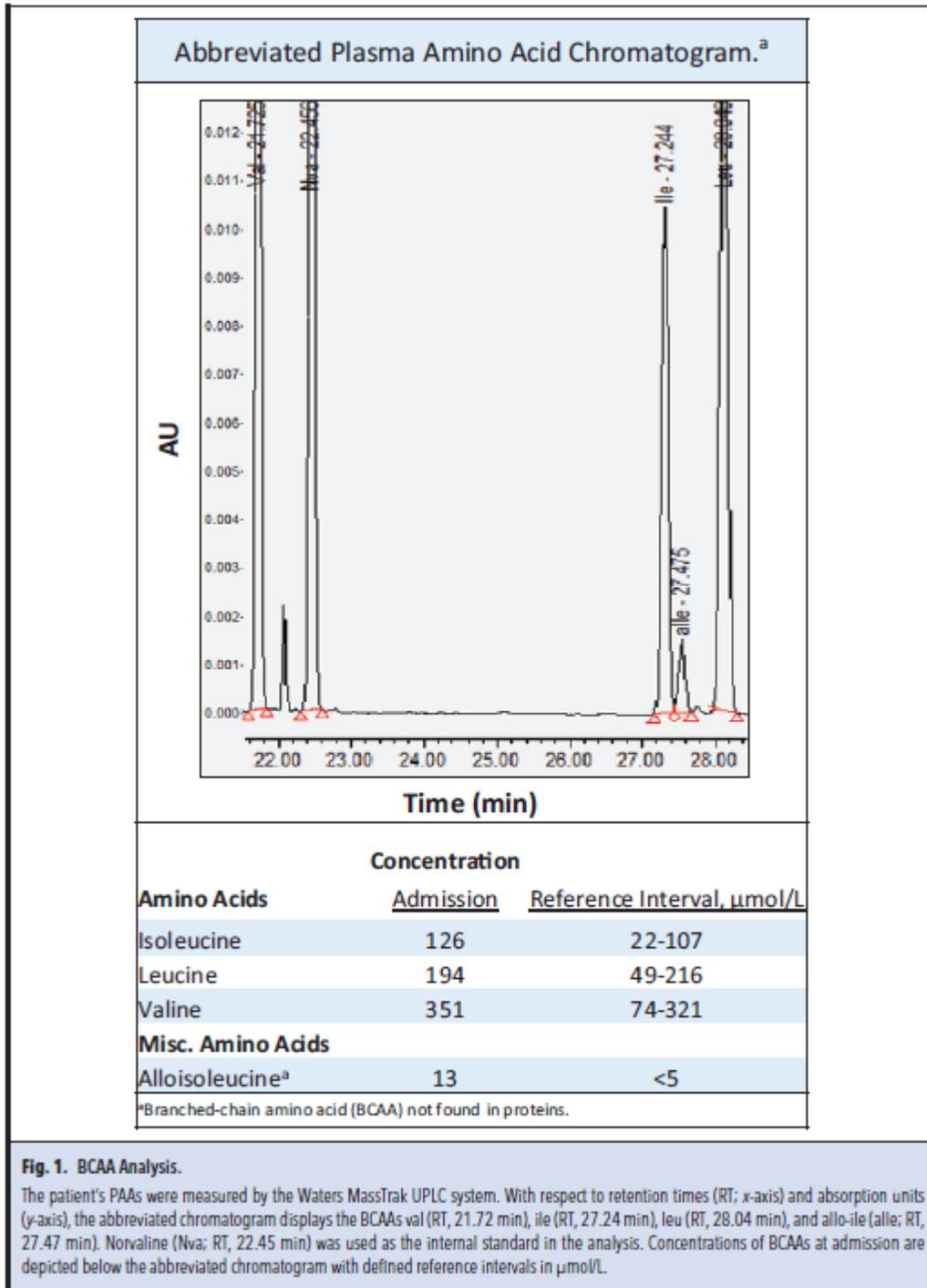
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CASE DESCRIPTION

A 3-year-old female presented to the emergency department with worsening myoclonic and atonic seizures. Several months before presentation, she was diagnosed with epilepsy and was treated with an antiepileptic medication (zonisamide, 10 g/L oral suspension, twice daily). While admitted, clinical laboratory testing for complete cell counts, comprehensive metabolic panel, and plasma lactate and ammonia were all within reference intervals (data not shown). However, nutritional assessment by plasma amino acid (PAA)⁶ analysis revealed that branched-chain amino acids (BCAAs) were increased for alloisoleucine (allo-ile), normal for leucine (leu), and mildly increased for valine (val) and isoleucine (ile; Fig. 1). Similar results were obtained following repeat PAA analysis despite a history of unremarkable newborn screening (NBS). Due to persistently increased allo-ile concentrations, the biochemical geneticist recommended urine organic acid (UOA) analysis and sequencing for a maple syrup urine disease (MSUD) panel [4 genes: branched chain keto acid dehydrogenase E1, alpha polypeptide (*BCKDHA*),⁷ branched chain keto acid dehydrogenase E1 subunit beta (*BCKDHB*), dihydrolipoamide branched chain transacylase E2 (*DBT*), and dihydrolipoamide dehydrogenase (*DLD*)]. The UOA analysis did not detect any compounds typically associated with MSUD and no previously-reported MSUD variants were identified through genetic testing. Perplexed by the inconsistent results, the geneticist reached out to the clinical laboratory.

6 Nonstandard abbreviations: PAA, plasma amino acid; BCAA, branched-chain amino acid; allo-ile, alloisoleucine; leu, leucine; ile, isoleucine; NBS, newborn screening; UOA, urine organic acid; MSUD, maple syrup urine disease; BCKD, branched-chain ketoacid dehydrogenase.

7 Human genes: BCKDHA, branched chain keto acid dehydrogenase E1, alpha polypeptide; BCKDHB, branched chain keto acid dehydrogenase E1 subunit beta; DBT, dihydrolipoamide dehydrogenase; DLD, dihydrolipoamide branched chain transacylase E2.



QUESTIONS TO CONSIDER
• What is the clinical significance of increased allo-ile concentrations in plasma?
• What methodologies are available for PAA analysis in the clinical laboratory?
• How do you explain the discrepancy between the PAA analysis and the UOA and genetic testing?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the October 2018 issue of *Clinical Chemistry*. To view the case and comments online, go to <http://www.clinchem.org/content/vol64/issue10> and follow the link to the Clinical Case Study and Commentaries.

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