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The Clinical Benefit of Newborn Screening for Patients with Maple Syrup Urine Disease

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Editor's Note: *Feria Ladha, MD, PhD (she/her/hers) is a resident physician in pediatrics at The Boston Combined Residency Program at Boston Children's Hospital and Boston Medical Center. She is an aspiring physician-scientist with research interests in cardiac genetics and developmental biology. -Rachel Y. Moon, MD, Associate Editor, Digital Media, Pediatrics*

Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolic disorder that results from a deficiency in the activity of an enzyme complex that is important in processing amino acids. Without proper activity of this enzyme complex, amino acid products can build up in the blood and can cause brain damage, seizures, and eventual death.

MSUD can range from severe or classic MSUD (cMSUD) due to less than 2% enzyme activity, to variant MSUD (vMSUD), with enzyme activity ranging from 2–30%. While cMSUD presents in the neonatal period with feeding problems or muscular hypertonia, vMSUD presents later in life, but there can be severe consequences, including coma, respiratory failure, and death, with both forms of MSUD.

Therefore, early treatment, which aims to normalize blood concentration of these amino acid breakdown products, is crucial, and delay can lead to brain damage and developmental disability.

Because of the severity of this disease and because early treatment with a low-protein diet and medications can prevent disease, in the US and many other countries, we now test for MSUD in newborn screening

(NBS) programs, but the clinical benefit of early diagnosis for patients has been inconsistently demonstrated.

In an article being early released in *Pediatrics* this week, Dr. Katharina Mengler at Heidelberg University and colleagues at 16 German institutions sought to evaluate the long-term outcomes of patients who had been diagnosed through NBS with MSUD (10.1542/peds.2023-064370).

The authors conducted a multicenter, observational study of 35 patients with confirmed cMSUD or vMSUD and found that:

- NBS identified 33 of these patients, while two were missed and identified later. All patients were started on treatment as soon as possible after diagnosis.
- The two patients not identified by NBS had intermittently normal amino acid levels. They were diagnosed with vMSUD and had normal development and IQ.
- All of the 33 patients who were diagnosed by NBS survived the neonatal period. One patient died at the age of 16 due to perforated appendicitis.

Consistent treatment was important. Although the overall IQ of patients with MSUD was on the lower end of the normal range, those who maintained lower concentration of amino acid products in their plasma had higher IQ values.

Limitations to consider include the small cohort size and variable cooperation of younger patients with IQ testing.

The NBS tests for diseases for which early diagnosis and treatment can improve survival and long-term outcomes, and this article uses the example of MSUD. Follow up on your patients' NBS results! For diseases such as MSUD, early treatment can make a significant impact in the future health of affected patients.