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Relevance of tandem mass spectrometry-based newborn blood spot screening for citrullinemia type II (CIT-II)

English summary

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SUMMARY

Relevance of tandem mass spectrometry-based newborn blood spot screening for citrullinemia type II (CIT-II)

The primary objective of population-based neonatal screening is to identify newborns with an inborn error of metabolism (IEM) at the asymptomatic stage and promptly initiate management in order to improve their prognosis.

Following previous work, the Ministère de la Santé et des Services sociaux (MSSS) plans to gradually transfer the screening of IEMs currently screened for on a urine sample to screening on dried blood spots, and will subsequently discontinue urine-based neonatal screening. However, the MSSS questions the relevance of tandem mass spectrometry (MS/MS)-based newborn blood spot screening for the seven IEMs for which urine-based screening is currently used. The Institut national d'excellence en santé et en services sociaux (INESSS) therefore assessed the relevance of newborn blood spot screening for these IEMs. The criteria that guided this assessment included test performance, the timeliness of newborn screening results, the effectiveness of neonatal screening, and the effectiveness of early treatment. This report examines the relevance of MS/MS-based newborn blood spot screening for citrullinemia type II (CIT-II).

CIT-II is a disorder of the urea cycle, which is responsible for nitrogen detoxification. The birth prevalence ranges from 1 case per 100,000 in Asia to 1 case per 2 million births in Western populations. This autosomal recessive disease is caused by pathogenic genetic variants in the *SLC25A13* gene. In Québec, five cases of CIT-II were detected by neonatal urinary screening between 1973 and 2009, and one patient was enrolled in the Programme alimentaire québécois pour le traitement de maladies métaboliques héréditaires, according to its 2016-2017 annual report.

The three clinical forms of the disease are characterized by different ages at onset of symptoms. The early-onset (or neonatal) form is observed in children under one year of age. It is generally benign. The main manifestations of the recently described intermediate form are liver disease and dyslipidemia. The adult-onset form is the most severe one and is characterized by metabolic decompensations. With the current state of knowledge, one cannot predict which individuals with the neonatal form will develop the intermediate or adult-onset form during their lifetime. This uncertainty raises ethical issues and may lead to psychosocial consequences and possible overdiagnosis and overtreatment.

According to the patient registry studies and case series that provide information on age at onset of symptoms, approximately 10% of cases had symptoms during the neonatal period. Thus, the result of the neonatal screening test appears to be obtained in a timely manner for about 90% of cases.

The prognosis for patients with the neonatal form is favourable, while that for the adult-onset form is poor in the absence of liver transplantation. The prognosis for the

intermediate form appears to be favourable, but since this form was only recently described, data are limited.

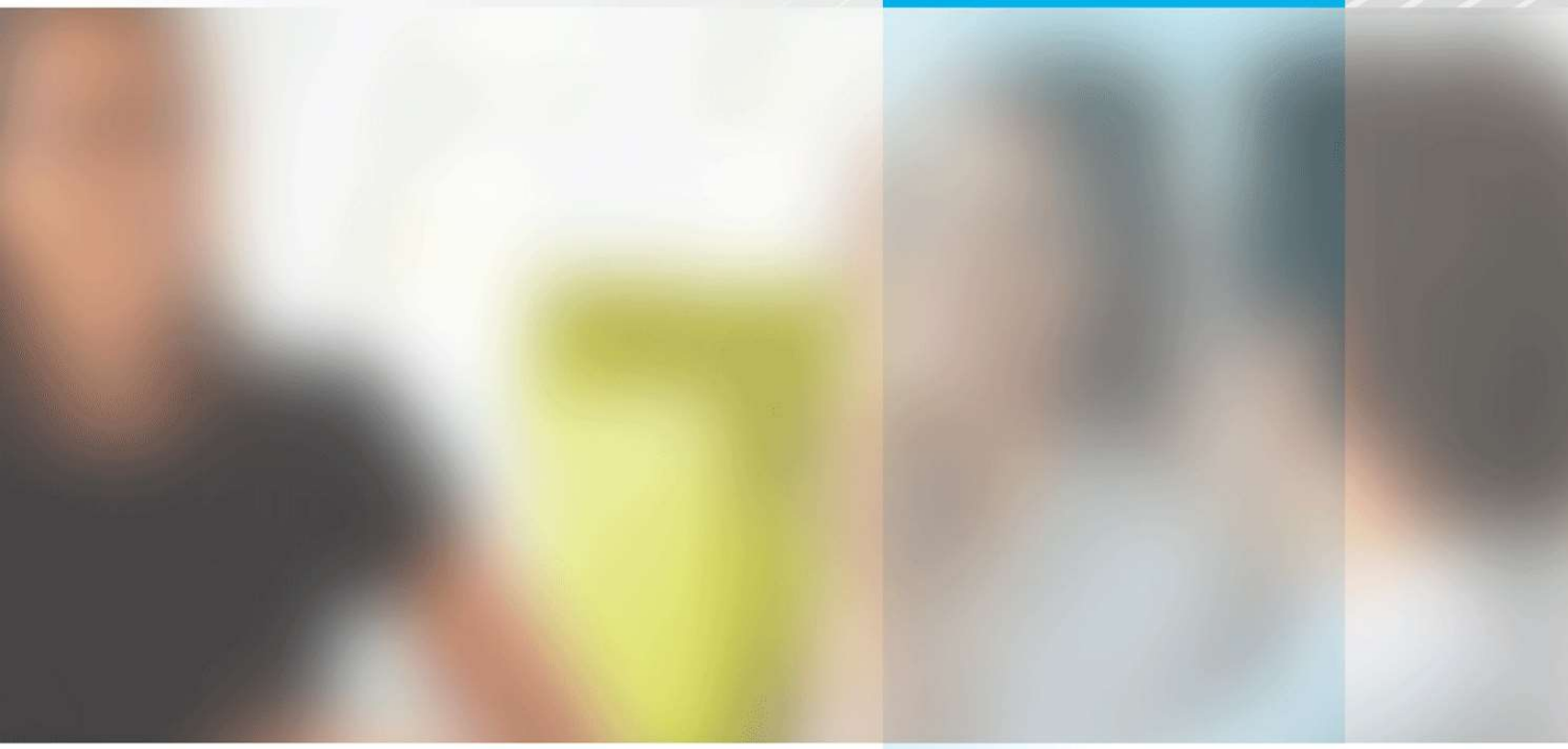
The studies retrieved in order to evaluate the performance of the CIT-II screening test involved approximately 46,700 to 592,700 newborns. Citrulline is the main marker for MS/MS-based neonatal screening. However, this marker is also associated with the detection of citrullinemia type I (CIT-I) and argininosuccinic acidemia (ASA). The screening test's sensitivity ranged from 25% to 100%, and its specificity was estimated between 99.985% and 100%. The positive predictive value ranged from 16.7% to 100%. There was significant imprecision around the sensitivity and positive predictive value estimates.

High concentrations of citrulline, several amino acids and galactose are among the results that point to a diagnosis of CIT-II. A differential diagnosis is required to discriminate between CIT-II and other IEMs. The diagnosis of CIT-II is generally confirmed by genetic analysis.

Treatment varies according to the form of the disease. A diet rich in protein and lipids is recommended in all cases. Guidelines have been developed for the management of urea cycle disorders, both for the acute treatment of hyperammonemia and for long-term treatment and follow-up. However, the recommended diet for urea cycle disorders should be avoided in CIT-II, since carbohydrates exacerbate the hyperammonemia. Periodic monitoring of the different biochemical markers, the anthropometric measurements and the serum lipid levels enables adjustment of the treatment plan, when necessary. Liver transplantation remains a recommended treatment for the adult-onset form.

None of the retrieved studies evaluated the clinical outcomes or the physical or psychosocial risks for patients identified by neonatal screening compared to patients identified following clinical manifestations.

Internationally, there appears to be no consensus regarding the relevance of offering neonatal screening for CIT-II. Some European countries, such as Spain and Iceland, have included this condition in their newborn screening programs, while Germany, the United Kingdom and France have not.



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