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Relevance of tandem mass spectrometry-based newborn blood spot screening for 3-methylcrotonyl-CoA carboxylase deficiency (3-MCC).)

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SUMMARY

Relevance of tandem mass spectrometry-based newborn blood spot screening for 3-methylcrotonyl-CoA carboxylase deficiency (3-MCC).

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 3-methylcrotonyl-CoA carboxylase deficiency (3-MCC).

3-MCC is an inborn error in the metabolism of organic acids that result from leucine degradation and is transmitted in an autosomal recessive manner. It is the organic aciduria most frequently observed in Germany, Australia and the Faroe Islands. In Ontario, the birth prevalence has been estimated at 1 case per 50,000 births. In Québec, it is reported to be 1 case per 138,320 participants, based on neonatal urinary screening. The clinical presentation and course are variable, ranging from an asymptomatic state in adulthood to neonatal manifestations with severe neurological involvement that sometimes lead to death. The most frequently reported symptoms are muscle hypotonia, psychomotor delay, hypoglycemia and seizures. Other neurological manifestations have also been described, as has failure to thrive.

The age at onset of symptoms varies greatly from the neonatal period to adulthood. Of 131 3-MCC patients identified by neonatal screening in 9 studies, 21 (16%) were asymptomatic. Of 13 patients in a series of clinically reported cases, 2 (15%) were diagnosed before 28 days of age, while 11 patients were diagnosed after the neonatal period.

Neonatal 3-MCC screening is based primarily on the measurement of C5-OH by MS/MS, a marker used to identify other IEMs as well. The sensitivity of the screening test was estimated at 100%, and its specificity varied from 99.974% to 99.997% in the studies retrieved to evaluate the performance of MS/MS-based screening. However, because of the small number of patients diagnosed with 3-MCC, the sensitivity estimates are imprecise. The referral rate varied from 6.7 to 32.2 newborns per 100,000 screening participants, and the detection rate varied from 1 case per 16,115 to 1 case per 164,000 newborns. Of the patients referred for diagnostic work-up, 37% to 96% did not, in the

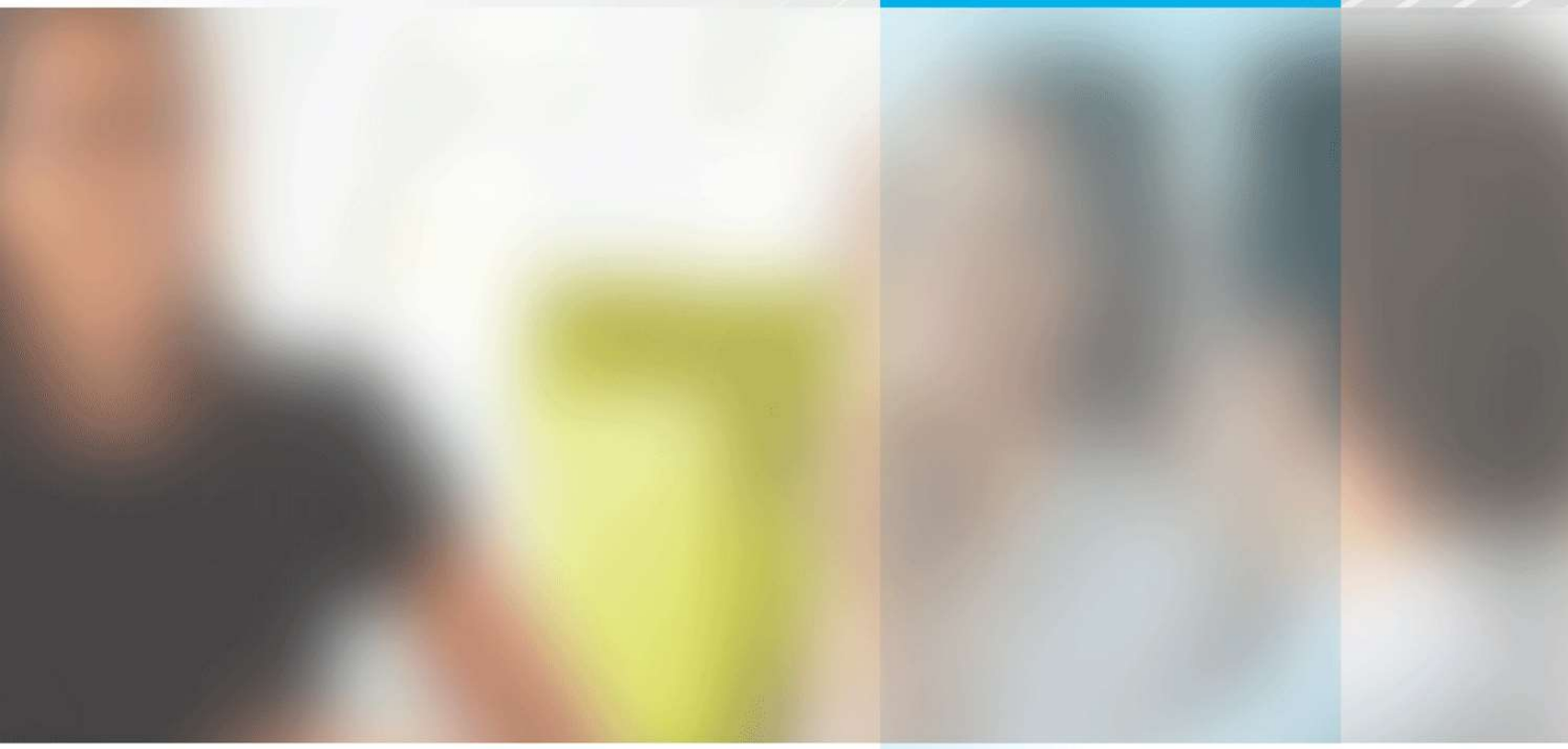
end, have 3-MCC. In one study, all the false positive results were related to abnormal metabolites from placental transfer of maternal metabolites, while such observations were not found, or only rarely, in other studies. Other IEMs (multiple carboxylase deficiency, beta-ketothiolase deficiency and 3-hydroxy-3-methylglutaryl-CoA lyase deficiency) accounted for 0 to 4.5% of the false positive results.

The usual diagnostic procedures include the analysis of urinary organic acids and plasma acylcarnitines. Diagnostic confirmation is increasingly being carried out by enzymatic or genetic tests. However, clinicians cannot predict which children with 3-MCC will develop severe sequelae, since there is no known correlation between the genotype and phenotype.

No study has conducted a prospective comparative analysis of clinical outcomes in 3-MCC patients identified by neonatal screening versus those identified following clinical manifestations. A retrospective study reported data for patients identified clinically and by neonatal screening but did not perform a comparative analysis between the two groups. Mining of the available data revealed more clinical manifestations in the group identified clinically. However, it is not possible to determine whether this difference is explained by prompt management following neonatal screening or by differences in the severity profile of the disease. This greatly limits the significance of these results.

No comparative studies were identified with regard to the safety of neonatal 3-MCC screening. Some authors have called attention to the physical (protein deficiency), psychosocial (stress) and organizational (family management and treatment costs) risks. This disease also raises ethical issues relating to the identification of benign forms, with possible overtreatment, of healthy carriers and of maternal cases of 3-MCC.

Internationally, there seems to be no consensus on the relevance of MS/MS-based newborn blood spot screening for 3-MCC. A few reports do not recommend neonatal 3-MCC screening, mainly because of the benign nature of this condition, the concomitant detection of maternal cases, the risks associated with treating asymptomatic patients, and the lack of proven clinical benefit. Other reports recommend neonatal 3-MCC screening, primarily because of the potential health benefit associated with initiating treatment early.



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