INESSS
LE SAVOIR PREND FORME

SEPTEMBER 2019

Relevance of tandem mass spectrometry-based newborn blood spot screening for propionic acidemia (PA)

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Direction des services de santé et de l'évaluation des technologies

Québec

Le présent rapport a été présenté au Comité d'excellence clinique en dépistage des maladies chroniques de l'Institut national d'excellence en santé et en services sociaux (INESSS) à sa réunion du 24 janvier 2019.

Le contenu de cette publication a été rédigé et édité par l'INESSS.

Membres de l'équipe de projet

Auteures
Valérie Turcot, Dt.P., Ph. D.
Ingeborg Blancquaert, Ph. D.
Julie Brunet, Ph. D.
Maryse St-Louis, Ph. D.

Coordonnatrice scientifique
Mélanie Martin, Ph. D.

Directrice
Michèle de Guise, MD, FRCPC

Repérage d'information scientifique
Lysane St-Amour, M.B.S.I.
Flavie Jouandon, *tech. doc.*

Soutien administratif
Jacinthe Clusiau

Équipe de l'édition

Patricia Labelle
Denis Santerre
Hélène St-Hilaire

Sous la coordination de
Renée Latulippe, M.A.

Avec la collaboration de
Littera Plus, révision linguistique
Mark Wickens, traduction

Dépôt légal

Bibliothèque et Archives nationales du Québec, 2019
Bibliothèque et Archives Canada, 2019
ISSN 1915-3104 INESSS (PDF) ISBN 978-2-550-84965-0 (PDF)

Pour citer ce document : Institut national d'excellence en santé et en services sociaux (INESSS). Évaluation de la pertinence du dépistage néonatal sanguin par spectrométrie de masse en tandem de l'acidémie propionique (PA). Rapport rédigé par Valérie Turcot, Ingeborg Blancquaert, Julie Brunet et Maryse St-Louis. Québec, Qc : INESSS; 2019. 68 p.

L'Institut remercie les membres de son personnel qui ont contribué à l'élaboration du présent document.

SUMMARY

Relevance of tandem mass spectrometry-based newborn blood spot screening for propionic acidemia (PA)

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 propionic acidemia (PA).

PA is an autosomal recessive disease caused by a defect in the enzyme propionyl-CoA carboxylase. In Québec, PA affected close to one in 100,000 participants in neonatal urinary screening, according to data collected between 2000 and 2006, and 10 patients were enrolled in the Programme alimentaire québécois pour le traitement de maladies métaboliques héréditaires in 2016-2017. Patients can present with a neonatal or late-onset form and with variable acute or chronic symptoms that include metabolic decompensations, encephalopathy, hypotonia, developmental delay, motor disorders, seizures and cardiac manifestations.

According to a European registry study, the median age at onset of symptoms in clinically identified patients is reportedly 4 days for the early-onset form and 195 days for the late-onset form compared to 6 days for patients identified by neonatal screening. Between 65% and 85% of patients identified clinically become symptomatic during their first week of life, while approximately 60% to 70% of patients identified by neonatal screening would become symptomatic before the test results are obtained.

Newborn screening for PA is performed by MS/MS on dried blood samples obtained during the first few days of life. The main marker is an elevated C3-carnitine level, which can be associated with other abnormal markers. Certain strategies have been proposed to reduce the number of false positives associated with PA screening and the simultaneous discovery of other IEMs, such as methylmalonic acidemia (MMA).

The evaluation of the performance of the MS/MS-based screening test for PA revealed that protocols vary in terms of the choice of targeted markers and the threshold values

leading to retesting, second-tier testing or diagnostic procedures. The screening test's sensitivity was estimated at 100%, and its specificity ranged from 99.917% to 99.997%. The positive predictive value varied from 0% to 11%, and patients with MMA accounted for 0% to 63% of false positive results. Overall, the performance indicators met the standards established by the MSSS [2018]. However, methods are proposed in the literature to reduce the number of false positive results associated with screening for PA. In a study using a second-tier test, the number of patients referred to specialized services for diagnostic procedures decreased significantly, thereby reducing the number of false positive results [Lim et al., 2014].

The diagnosis of PA can be based on typical biochemical abnormalities in the urine and plasma and can be confirmed by enzymatic studies or genetic analysis.

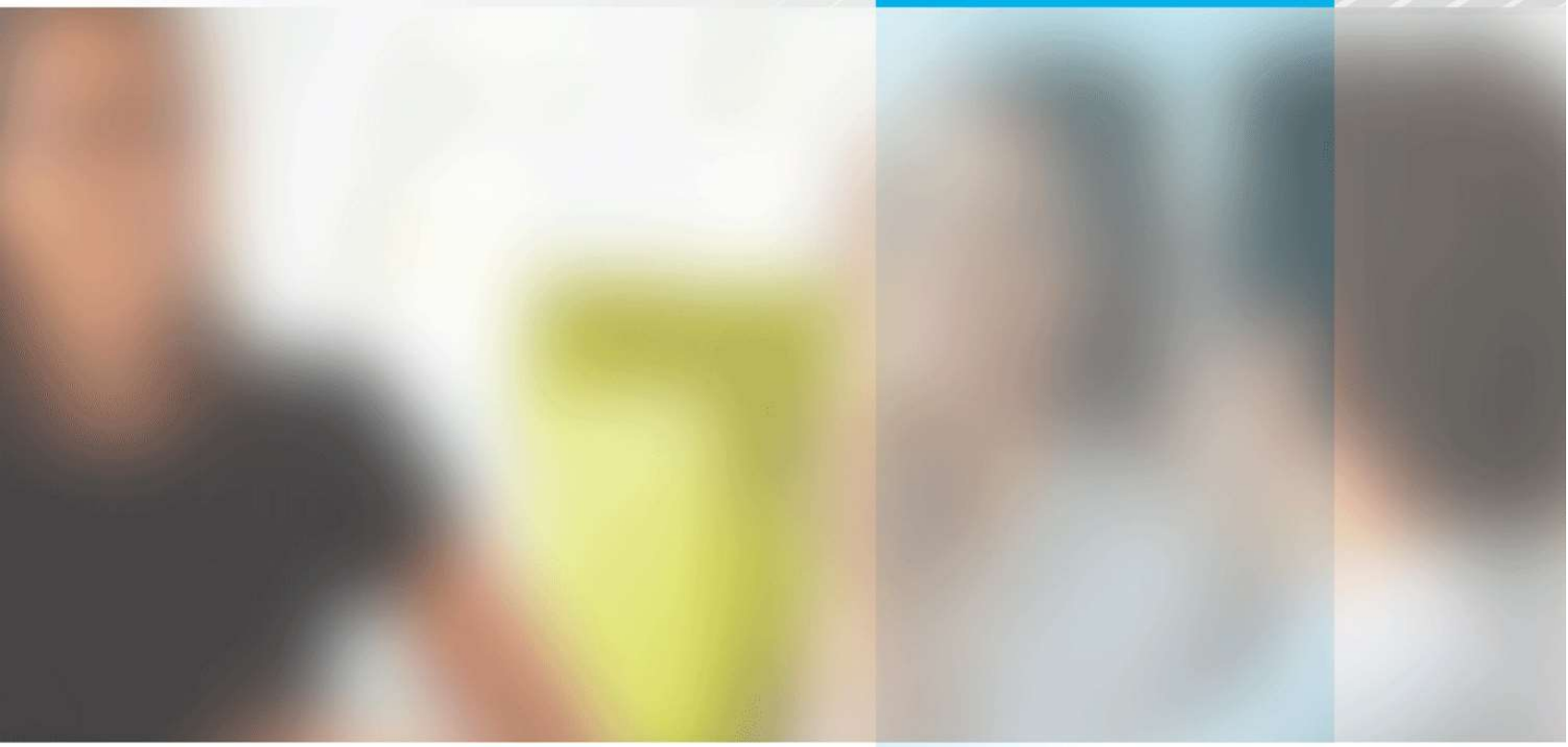
The long-term treatment of patients with PA generally consists in administering L-carnitine, vitamins and minerals, antibiotics and, if necessary, nitrogen-scavengers to normalize the blood ammonia level. A protein-restricted diet is recommended and is adjusted according to the patient's tolerance and needs. Liver transplantation may be an option when the metabolic stability is hard to achieve. Situations that can trigger a metabolic decompensation should be avoided or managed by ensuring, among other things, an adequate caloric intake. There are no guidelines for managing asymptomatic patients. The long-term survival of patients with PA has improved over the past 20 years. However, more than 50% of these patients exhibit cognitive delay.

As for the efficacy of neonatal PA screening, five studies were retrieved but several limitations complicated the interpretation of their results, including selection biases and differences in terms of methods used to assess clinical outcomes and therapeutic approaches. Only one study conducted comparative statistical analyses. No significant differences were reported with regard to movement disorders, delayed motor development or renal failure between the two groups of patients, while significantly more cardiac manifestations were reported in the patients identified clinically than in those identified by screening. The mortality rate varied from 0% to 22% in the patients identified by screening and from 0% to 33% for those identified clinically. A similar number of metabolic crises and hospitalizations as well as a similar IQ between the two groups were observed in one study. Two studies reported mild to severe cognitive delay in 0% and 40% of the patients identified by screening and in 33% and 78% of those identified clinically. None of the retrieved studies examined quality-of-life for patients identified by neonatal screening and for those identified clinically.

No comparative study provided data on safety of neonatal PA screening, whether in terms of the physical or psychosocial risks.

Internationally, there seems to be no consensus on the relevance of MS/MS-based newborn blood spot screening for PA. Some reports do not recommend such screening, particularly in light of secondary detection of other conditions, such as MMA, as well as of the uncertainties regarding the efficacy of screening and the treatment to be offered to

asymptomatic patients. However, other reports recommend screening for PA, mainly because of a possible health benefit associated with early treatment.



Siège social

2535, boulevard Laurier, 5e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563
inesss.qc.ca

Institut national d'excellence en santé et en services sociaux
Québec