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Relevance of tandem mass spectrometry-based newborn blood spot screening for hyperargininemia (ARG1)

English summary

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SUMMARY

Relevance of tandem mass spectrometry-based newborn blood spot screening for hyperargininemia (ARG1)

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 hyperargininemia (ARG1).

This autosomal recessive disease is a disorder of the urea cycle, which is responsible for nitrogen detoxification. The birth prevalence is reportedly less than one case per million births. In Québec, four cases of ARG1 were identified by urinary neonatal screening between 1973 and 2006, and five patients were enrolled in the Programme alimentaire québécois pour le traitement de maladies métaboliques héréditaires, according to its 2016-2017 annual report. A recent review found 37 cases worldwide.

Hyperammonemia, which is characteristic for urea cycle disorders, is rarely present, although a few cases of recurrent hyperammonemia have been reported in patients with ARG1. The symptoms usually appear around the age of 2 to 4 years. Only a few cases with neonatal onset of symptoms have been described. According to the patient registry studies that provide information on age at onset of symptoms, approximately 5% of cases experienced symptoms before 15 days of age compared to nearly 80% during the post-neonatal period. The main symptoms included a slowing down of growth and cognitive development, and spastic diplegia.

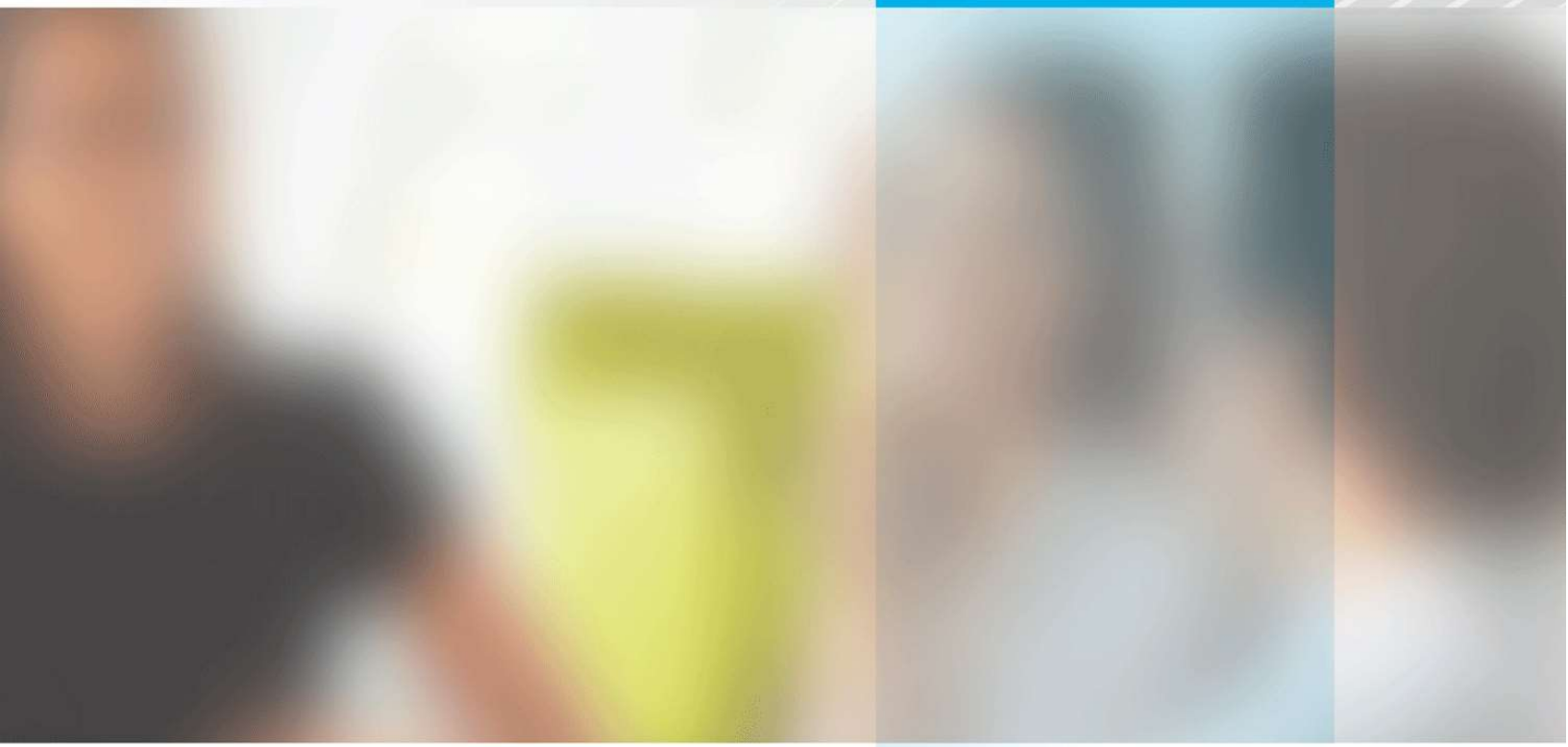
There is no consensus as to the natural history of the disorder or to the prognosis under therapy of affected individuals. A few early childhood deaths have been reported. Some authors argue that patients who are treated are generally asymptomatic, provided that strict dietary adherence is exercised, and that the arginine concentration is well controlled, while others maintain that stabilization or improvement of the neurological problems remains uncertain despite treatment.

The studies retrieved in order to evaluate the performance of the ARG1 screening test involved approximately 100,000 to 353,500 participating newborns. An increased arginine concentration was the main marker for MS/MS-based screening, but the threshold values varied. The arginine/ornithine ratio was used as a secondary marker. Overall, 6 true positives were identified among 69 newborns referred to specialized services for diagnostic workup out of a total of 1.3 million screened newborns. The test's sensitivity was estimated at 100%, and its specificity ranged from 99.965% to 100%. As for the referral rate, it varied from 0.32 to 37 newborns per 100,000 participants. The detection rate ranged from about 1 case in 50,000 to 1 case in 354,000 newborns. The positive predictive value ranged from 0% to 100%. There was significant imprecision around the sensitivity and positive predictive value estimates. In addition, in most studies, samples were collected at a later age than in Québec. In fact, it is possible that the arginine concentration in patients with ARG1 overlaps with the normal values at 2 to 3 days of age, while in Québec, more than 90% of blood samples are obtained between 24 and 48 hours of age.

The diagnostic markers for ARG1 are increased plasma arginine and urinary orotic acid levels. Genetic analyses and the measurement of erythrocyte arginase enzyme activity can be used to confirm the diagnosis.

The goal of treatment is to maintain the arginine concentration at a safe level by adjusting the diet and prescribing supplements and nitrogen scavengers. Guidelines have been developed for the management of urea cycle disorders, both for the treatment of acute hyperammonemia and for long-term treatment and follow-up. Periodically monitoring different biochemical markers and the child's physical and neurological development and school performance is recommended. Progressive spasticity could lead to injections of botulinum toxin or orthopedic surgery.

A registry data study suggests that children who are identified by neonatal screening may have a better prognosis in terms of mobility than affected children whose diagnosis was established following onset of symptoms, but these results are not statistically significant. The authors emphasize the importance of conducting larger studies with a longer follow-up. Therefore, the scientific evidence is insufficient for ruling on the efficacy and safety of MS/MS-based newborn blood spot screening for ARG1.Neonatal blood spot screening for ARG1 is performed by MS/MS in a few jurisdictions. In Canada, it is offered in Saskatchewan and Manitoba. Opinions seem to be divided regarding the relevance of neonatal ARG1 screening, as some countries, such as Denmark, removed ARG1 from their programs, while others seem to be considering adding it to their neonatal screening programs.



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