Inborn errors of metabolism in newcomer and refugee populations in Ontario, CA

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ABSTRACT

Inborn errors of metabolism (IEM) are a heterogeneous group of rare, inherited disorders that impair the biochemical processes involved in metabolism. Many are treated with various restrictive diets in early infancy, prior to the appearance of symptoms to improve the overall outcomes of the affected individuals. Identification of individuals at a risk of developing metabolic disorders through newborn screening (NBS) programs and the subsequent early diagnosis and treatment are an invaluable aspect of healthcare in Canada. Incorporation of Canada's expanding population of refugees and new immigrants presents with potential challenges and changes. Without the availability of NBS programs in many countries contributing to the refugee influx in Canada, it may be difficult to identify patients who are affected with these rare conditions. This article discusses: 1) the utility of newborn screening and diagnosis of metabolic diseases in immigrant and refugee populations, with complex medical presentations, and 2) a recent diagnosis of succinic semialdehyde dehydrogenase deficiency (an IEM) in a refugee child past the age limit of NBS. An increasingly complicated and diverse refugee population requires a need for revision of existing healthcare practices pertaining to the diagnosis of rare diseases.

Keywords: inborn errors of metabolism, succinic semialdehyde dehydrogenase deficiency; newborn screening; refugee; rare diseases

INTRODUCTION

Inborn errors of metabolism (IEM) are rare, inheritable disorders that impair biochemical processes in the body through alteration of cellular transport and enzyme activities such as mitochondrial bioenergetics.¹ IEMs are often characterized as monogenic autosomal recessive inherited conditions with specific causative enzyme deficiencies. Newborns and infants are affected as proper metabolic function is integral in normal growth and development. Left untreated, these disorders may be fatal, cause developmental delay or irreversibly decrease the quality of life, impair functionality, and affect overall lifespan.²

Advances in technology and knowledge have substantially improved the prognosis of many IEMs; particularly the development and implementation of newborn screening (NBS) programs around the world.³ NBS programs are population-based and aim to detect conditions in asymptomatic newborns where specific treatment or management can improve the disease outcome.³ In Canada, the list of diseases screened in newborns is decided by individual provinces

and may be influenced by prevalence, scientific assessment, and input from stakeholders including patients and families.³ Components of screening programs consist of initial screening, follow-up assessment, diagnosis, treatment, and evaluation of outcomes.^{3,4} NBS Ontario screens 29 different conditions including: metabolic and endocrine diseases, sickle cell disease, cystic fibrosis, and severe combined immunodeficiency.^{3,5,6}

It is important to note that not all IEMs fit the criteria for screening. A few reasons for exclusion include unavailability of an accurate biochemical screening test, costs to benefits ratio, and lower prevalence of disease in a specific population. A rare autosomal recessive metabolic disorder that is not covered by NBS is succinic semialdehyde dehydrogenase (SSADH) deficiency. The incidence of this condition is unknown.⁷ SSADH is a nuclear-encoded mitochondrial enzyme involved in the degradation of gamma-aminobutyric acid (GABA).⁸ GABA is a major inhibitory neurotransmitter that controls movements and integral for proper neurotransmitter signaling.⁹ Biallelic pathogenic variants in the gene *ALDH5A1* result in production of SSADH with aberrant function, disrupting the conversion of succinic semialdehyde to succinic acid. Increasing levels of succinic acid are converted back to GABA and gamma-hydroxybutyrate (GHB), a related molecule.⁹ The accumulation of GABA and GHB leads to the various clinical findings of this condition including a variety of neurological, neuromuscular, and psychiatric problems such as global developmental delay, ataxia, seizures, and aggression.¹⁰ The following section will expand upon a recently diagnosed case of SSADHD in a refugee child in the Medical Genetics program at London Health Sciences Center.

A CASE OF SSADHD

The patient, currently a 13-year-old female, is originally from Syria. She was born at term via spontaneous vaginal delivery and was discharged from the hospital immediately. Around age two, parents noticed that she was not meeting developmental milestones and sought medical advice. At this time, she was diagnosed with cerebral palsy. Her entire family arrived in Canada as Syrian refugees in 2015. Parents are first cousins with a family history significant for consanguinity. When seen by Pediatric Neurology in 2017, she presented with axial hypotonia, appendicular ataxia, and was profoundly neurodevelopmentally compromised. Interestingly, she did not demonstrate the typical upper motor neuron findings in cerebral palsy such as spasticity or dystonia. Her unusual clinical findings and the knowledge of familial consanguinity prompted reinvestigation of her condition, with a differential diagnosis of a metabolic disorder. A full metabolic workup demonstrated elevated

levels of 4-hydroxybutyric acid in urine, raising the suspicion of SSADHD. Subsequently, genetic testing confirmed a homozygous frameshift mutation (p.Phe462LysfsTer53) in the *ALDH5A1* gene.

The treatment of SSADHD is supportive, requiring more personnel to be involved in the care of a patient, including broad spectrum antiepileptics for seizure management, medications for neuropsychiatric symptoms, and occupational and physiotherapy to address other concerns.¹⁰ Home and school classroom modifications may be required for some of these affected children.

This case provides an example of a rare metabolic disorder being diagnosed past the newborn period. SSADH is not included in NBS. However, keeping a strong index of suspicion of IEM in this scenario provided the correct diagnosis, which was beneficial for the patient and her family. Knowledge about the condition will aid in obtaining the support needed for the child and will help family in making informed decisions about future pregnancies. Genetic counselling was provided for the family. This case demonstrates the importance of keeping metabolic disorders as part of the differential diagnosis when patients demonstrate unusual findings within the setting of neurological deficits and when there is a family history of consanguinity.

REFUGEE AND NEWCOMER POPULATIONS IN ONTARIO

Recent statistics showed that 1 212 075 new immigrants gained permanent residency between 2011 and 2016.¹¹ Interestingly, twenty four percent of immigrants admitted into the country in 2016 occupied refugee status.¹¹ Many identified Syria as their country of origin, a direct result of the geopolitical landscape at present.¹¹ Like other vulnerable populations in Canada, refugees and newcomers present unique challenges as a result of their specific medical needs and cultural differences.¹² Increased and continual cultural education will enable healthcare providers and stakeholders to remain cognizant of any cultural beliefs or practices that influence information shared, traditional medicine preferences, and how to discuss medical information with family members.¹³

IEMS IN REFUGEE POPULATIONS

Though the collective incidence of IEMs is approximately 1 in 800 births globally, it varies greatly across populations.¹ As these disorders are often inherited in an autosomal recessive manner, populations with a higher frequency of consanguineous unions tend to share common mutations, resulting in a higher prevalence of IEMs. A study from Denmark found ethnic minorities, primarily of Pakistani, Turkish, Afghan, and Arab origin, had a 30-50-fold increase in frequency of IEM compared to Danish children.¹⁴ Another study in the United Arab Emirates also showed a significantly larger presence of homozygous mutations resulting in IEMs than compound heterozygotes, implicating traditional practices of cousin marriage as a contributory factor.¹⁵

Though no exhaustive list of Syrian-specific IEMs exists, there is a consensus that in Syria, disorders like organic acidemias and PKU are often misdiagnosed or undiagnosed due to lack of resources—no NBS program, few trained specialists, expensive diagnostic tests, and low public awareness.¹⁵ Thus, it is not surprising that an influx of individuals older than one year who

are affected with an IEM will likely face a prolonged diagnostic odyssey as they have not been through the existing NBS program. NBS test ranges and confirmatory diagnostic tests are designed with reference ranges relevant to infants less than a year old. Many refugee children and young adults are not eligible for these tests based on age. Modifications to assay methods will ensure quicker diagnostic outcomes.

As mentioned previously, not all IEMs are diagnosed during the NBS period. Appropriate and adequate evaluation of medical conditions in refugee individuals might be a challenge given the vast differences in the resources allocated to each person in their respective home countries. Recognition of this disparity is of importance in the Canadian healthcare context as it emphasizes the need for increased index of suspicion and evaluation as was given in the SSADHD case described above.

DIAGNOSIS AND MANAGEMENT OF IEMS IN NEWCOMER/ REFUGEE POPULATIONS

Ontario has five referral centers (Toronto, Kingston, London, Ottawa, and Hamilton) that participate in the NBS program. Each center has a multidisciplinary team, including a primary metabolic physician, laboratory director, dietitian, genetic counsellor, and a social worker, who together manage the affected infants following their detection through NBS.

Treatment goals are often focused on the prevention of severe and irreversible sequelae such as neurodegeneration, development delay, and death. There are many disorders, such as SSADHD, where treatment remains suboptimal or only supportive. However, there are IEMs screened through NBS in Canada and other developed countries such as phenylketonuria (PKU), biotinidase deficiency, and maple syrup urine disease (MSUD) that can be effectively treated with stringent dietary management, given that treatment requires initiation in a very early period of life and is often the only way to mitigate or reduce disease progression.¹⁶⁻¹⁸ The clinical heterogeneity of IEMs remains a genuine challenge in designing effective healthcare interventions.

CONCLUSION

As Canada continues to have an expanding newcomer population, it becomes imperative to learn about the different cultural and medical backgrounds of the incoming individuals to improve existing healthcare support offered. Refugee patients diagnosed with rare metabolic diseases present a challenge to the existing infrastructure, processes, and services of our healthcare system. Medically complex clinical manifestations require multidisciplinary teams to ensure best outcomes. However, given the cultural differences between healthcare professionals and refugee patients, it is important to incorporate a bilateral flow of knowledge, acceptance, and modifications. Though screening and diagnostic programs for IEM have been successful thus far, there is a great need to revise and augment our healthcare services given the noticeable influx of individuals with specialized needs in the context of migration.

ACKNOWLEDGEMENTS

We would like to thank the staff in the Department of Medical Genetics for providing us with valuable information. We would like to thank Dr. Tony Rupar, PhD, FCCMG Biochemical Laboratory Director for his helpful comments.

ABBREVIATIONS

Inborn errors of metabolism (IEM); phenylketonuria (PKU); medium-chain acyl-CoA dehydrogenase deficiency (MCADD); newborn screening (NBS); succinic semialdehyde dehydrogenase deficiency (SSADHD)

ELECTRONIC DATABASE INFORMATION.

URLs used in preparation of this article are:

Locus Link. National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 1999. World Wide Web URL: <http://www.ncbi.nlm.nih.org/LocusLink>

Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 1999. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>

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