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Short Communication

Outcome of the glutaric aciduria type 1 (GA1) newborn screening program in Manitoba: 1980–2020

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ABSTRACT

Glutaric aciduria type 1 (GA1) is a severe inherited neurometabolic disorder whose clinical outcome has improved after implementation of newborn screening (NBS) programs and prompt beginning of guideline-directed presymptomatic metabolic treatment. We report the outcome of our 40-year experience with the diagnosis and management of GA1 which has improved but remains suboptimal.

1. Introduction

GA1 is overrepresented in the Indigenous communities of northeastern Manitoba and northwestern Ontario, two adjacent provinces in Canada [7]. A single homozygous founder variant in glutaryl-CoA-dehydrogenase (*GCDH*) IVS-1 + 5 g → t was identified in this population with a carrier frequency of 1 in 10 individuals; [3,5]. DNA-based NBS for the IVS-1 + 5 g → t variant began in these communities in May 1998 to provide presymptomatic detection and treatment to prevent encephalopathic crises characteristic of most patients with GA1 [8,9]. In 2011 tandem mass spectrometry (MS/MS) was introduced in Manitoba for universal NBS which included the detection of GA1.

Worldwide, before implementation of NBS for GA1 by MS/MS, 90% of affected patients presented with acute encephalopathic crises with severe striatal injury and irreversible brain damage, including our patients with the founder mutation [2,12]). After the introduction of NBS for GA1 by MS/MS, the incidence of acute encephalopathic crises fell worldwide to 10–20% [8,10,11,13] but remained unchanged for our cohort at 90% [4]). Despite newborn screening in our population and presymptomatic management as recommended, this world-wide experience with reduction in the incidence of encephalopathic crises has not yet been achieved in our population. We now report updated outcome results of NBS for GA1 in our population, cumulatively over 40 years.

2. Materials and methods

Our study population is detailed in Table 1: Cohort 1 (20 patients) ascertained between 1980 and 2000 and cohort 2 (19 patients) ascertained between 2000 and 2019. Between 2000 and 2020, we ascertained 20 newborns on DNA-based and/or MS/MS NBS. The patients in both cohorts followed the same recommended management guidelines (24/7 access to metabolic consultants with rapid institution of the emergency treatment) except for the use of the lysine-free analog formula after the year 2000 versus protein-reduced formula between 1980 and 2000 [6,8]. Since the year 2000 we began using the recommended lysine-free analog formula. Appendix 1 contains representative individualized emergency management protocol. All patients were on carnitine supplements with a mean free serum carnitine level of 50 umol/L. The carnitine dose was doubled during any febrile illness.

3. Results

The prevalence of acute encephalopathic crises has fallen to 60% over the last 20 years versus 90% in the previous 20 years 1980–2000 (Table 1). Proportions with encephalopathy in each era were compared by Fisher Exact Test assuming a hypergeometric distribution. The odds ratio was 0.19 (0.02–1.2, $p = 0.06$). Although we note a trend of improvement in prevention of CNS damage from 10% to 40%, this is not statistically significant and is different from the observed outcome in the affected non-Indigenous patients followed at our tertiary center, and in patients worldwide. Insidious onset in GA1 patients without an acute precipitating event manifesting as truncal hypotonia from early infancy progressing to global developmental delay and gross motor dysfunction is noted in 2 and 3 patients before and after the year 2000 respectively (Table 1). Four patients remain asymptomatic at ages

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Table 1
GA1 newborn screening outcome updates.

Ascertained before 2000	AEC	Insidious onset	Normal
Total of patients	19	2	0
Age range	6–12 months	Birth	0
Sex	10 F/9 M	2 F	0

Deceased	Alive	Total number
17	4	21
2–40 years	26–48 years	
9 F/8 M	3 F/1 M	

Ascertained after 2000	AEC	Insidious onset	Normal
Total of patients	12	3	4
Age range	6–12 months	Birth	8–12 years
Sex	8 F/4 M	3 M	3 F/1 M

Deceased	Alive	Total number
8	11	19
2–11 years	9 months – 20 years	
5 F/3 M	6 F/5 M	

Acute encephalopathic crisis (AEC).
Females (F).
Males (M).

ranging from 8 years to 12 years in the cohort ascertained after the year 2000.

4. Discussion

Although we demonstrate a trend towards the prevention of acute encephalopathic crises since 2000, we remain below the desired outcome achieved worldwide in the prevention of the first metabolic decompensation in these patients with the ensuing devastating irreversible CNS damage. The reasons for this are likely multiple. In the largest international GA1 cohort published so far [8], neurologic outcome primarily depended on treatment quality: patients following guideline recommendations for both dietary and emergency treatment remained asymptomatic in over 90%. Patients with inadequate emergency treatment were at high risk for acute crisis and severe dystonia whereas patients with inadequate dietary treatment showed increased risk for developing insidious onset dystonia and minor neurologic deficits. Of note, neurologic long-term outcome is still unclear. Better understanding of the neurotoxic mechanisms underlying this devastating disorder is still needed to better understand the basis for the insidious and/or acute onset in patients and will help overall effective management and prevention of the neurologic damage. It is likely that there are unidentified genetic, non-genetic and epigenetic factors modifying the natural history of GA1 in our population even with presymptomatic identification and current treatment.

We have thus carefully evaluated what the reasons for the less than optimal outcome might be. From 1980 onward, we had introduced aggressive protocols for prompt presymptomatic management of intercurrent illnesses with well- and sick-day management protocols. Insertion of PICC lines and gastrostomy tube placements for rapid management of acute illnesses and attempts to relocate families with newly diagnosed infants from their home remote communities to be close to tertiary care during intercurrent illnesses have not had the positive effects intended. Well-day management with Xlys-Xtryp formulae were introduced in accordance with international guidelines [1,2].

The families involved are committed to the care of their children as are the primary care providers although timely implementation of emergency protocols for acutely ill patients may still not be as rigorous as is necessary and may be a factor in long-term outcome. Our approach to the care of patients with GA1 has always been one of community involvement and partnership. The results we present must be considered in the context of what is known about the overall health status of Indigenous people in our province. On multiple measures, the health of Indigenous peoples in Manitoba is considerably worse than non-Indigenous people (http://cfla-fcab.ca/wp-content/uploads/2017/04/Truth-and-Reconciliation-Committee-Report-and-Recommendations.pdf; http://mchp-appserv.cpe.umanitoba.ca/reference/FN_Report_web.pdf). Historical and social determinants of disease continue to disadvantage the health of Indigenous peoples today and thus it is not surprising that we also see widening disparities in outcome of NBS for GA1 in our Indigenous population.

Our current initiatives to overcome potential barriers to optimum care are multifaceted. Direct engagement of the communities involved and their leadership to ensure their voices are heard and adopting a more holistic approach encompassing traditional values and culture will facilitate the development and implementation of more culturally appropriate solutions and ultimately improve outcome for children with GA1. Such solutions will address the root cause of health disparities and equitable access to clinical services for which we advocate. In considering the social structure and family dynamics in the relevant communities, disease education will now consistently go beyond the focus on the mother and father: such education will include the extended family members and all potential care providers for the affected infant. Extensive education sessions will be conducted through virtual care to all the extended family members. Additionally, language-specific parental guides and onsite community based educational workshops are planned. To further facilitate the acute care of affected children early in the course of any intercurrent illness, we developed a simple algorithm protocol for the emergency management in these remote communities upon presentation of the infant to the local community health center until the infant's transfer to the tertiary center. We have engaged the health care providers in the local centers in the development of these emergency protocols to identify and overcome any potential gaps in care. Periodic scheduled teaching sessions for all health care providers in the local health centers are being conducted to keep an open educational forum and discuss any potential impediments to care. This continued education will ensure that any new staff attending the local health centers receive the required education about the disease management and hopefully improve outcomes in the future.

Authors statement

Mhanni A. and Rockman-Greenberg C: Conceptualization, Methodology, data collection, data analysis, writing - original draft preparation.

Aylward N: Data collection, writing - reviewing and editing the manuscript.

Boy N and Martin B: Writing - reviewing and editing the manuscript.

Sharma A: Statistical analysis, writing - reviewing and editing the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2020.100666.

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