Hyperglycemic hyperosmolar state

CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

PROTOCOL

Principal investigators

Paul MacDaragh Ryan, MB, BCh, BAO, PhD, Paediatrics Resident, Department of Paediatrics, University of Toronto, The Hospital for Sick Children

Jill Hamilton, MD, MSc, FRCPC, Head of Division of Endocrinology, Department of Paediatrics, University of Toronto, The Hospital for Sick Children

Co-investigators

Shazhan Amed, MD, MSc, FRCPC, Head of Division of Paediatric Endocrinology, University of British Columbia, BC Children's Hospital

Elizabeth Sellers, MD, MSc, FRCPC, Paediatric Endocrinologist, University of Manitoba, The Children's Hospital of Winnipeg

Collaborators

Ereny Bassilious, MD, FRCPC, MHPE, Paediatric Endocrinologist, McMaster Children's Hospital

Tracey Bridger, MD, FRCPC, Paediatric Endocrinologist, Eastern Health Newfoundland and Labrador

Stasia Hadjiyannakis, MD, FRCPC, Paediatric Endocrinologist, Children's Hospital of Eastern Ontario

Andrea M. Haqq, MD, MHS, FRCPC, FAAP, Paediatric Endocrinologist, Walter C. Mackenzie Health Sciences Centre

Andrew Helmers, MDCS, MSc, FRCPC, Department of Critical Care, University of Toronto, The Hospital for Sick Children

Josephine Ho, MD, MSc, FRCPC, Paediatric Endocrinologist, Alberta Children's Hospital

Mona Jabbour, MD, MEd, FRCPC, Paediatric Emergency Medicine Physician, Associate Professor and Vice Chief/Chair, Department of Paediatrics, Children's Hospital of Eastern Ontario

Munier Nour, MD, MSc, FRCPC, Head, Division of Paediatric Endocrinology, Jim Pattison Children's Hospital

Mona Patel, MD, Department of Critical Care Medicine, University of British Columbia, BC Children's Hospital

Teresa Pinto, MD, Paediatric Endocrinologist, IWK Health Centre

Background

Rates of obesity in children and adolescents continue to increase globally[1] and despite encouraging trends, over a quarter of children in Canada were overweight or obese in 2013.[2] In parallel, paediatricians continue to treat greater numbers of adolescents presenting with obesity-related type 2 diabetes (T2D).[3] Indeed, the SEARCH for Diabetes in Youth Study revealed a concerning 4.8% increase in paediatric T2D incidence between 2002 and 2015. Similarly, a recent provincial report from Manitoba revealed a more than 20% increase in the incidence of children with T2D from 2009/2010 to 2017/2018.[4] As a result, paediatricians are now increasingly challenged with the acute complications and chronic sequelae of both obesity and T2D.

One important acute complication of T2D is hyperglycemic hyperosmolar state (HHS), formally known as hyperosmolar hyperglycemic non-ketotic coma (HONK). HHS stems from a relative deficiency in insulin, either as a result of insufficient insulin or a physiological stressor (e.g., infection, trauma), and an increase in counter-regulatory hormones, such as glucagon, catecholamines, and cortisol. Despite profound dehydration, the exceedingly high serum glucose levels create an osmotic gradient which draws water from intracellular compartments and acts to maintain intravascular volume, until an ultimate decompensation which can be swift and dramatic if left untreated. The mortality rate in HHS is striking, with one review of the literature in 2006 uncovering 18 case reports, of which 13 (72%) were fatal.[5] Even considering substantial publication bias, if we consider the most modest of reported mortality estimates (2.7%),[6] HHS is 5 to 10 times more fatal than diabetic ketoacidosis (DKA) in children (0.38%).[7]

As presentations of HHS and DKA have certain key similarities and DKA can often display a hyperosmolar element (i.e., hyperosmolar DKA), HHS is often misdiagnosed due to its comparative rareness and relatively recent recognition in children. Although there is considerable crossover in the therapeutic management in both acute complications, there are key differences in pathophysiology and optimal care which have clinically important implications if the incorrect diagnosis is presumed. Most notably, children in HHS require considerably greater volumes of fluid rehydration, are far more likely to present with concerning neurological deficits, and are more likely to experience potentially fatal complications, including thrombosis and renal failure.

There are limited high quality data available to discern the incidence rate of HHS in children. Case reports and case series represented the sole published data until an analysis of the Kids' Inpatient Database in the United States (US) demonstrated an estimated incidence of ~3.2 per million in 2009.[6] There is evidence that certain minority communities may be at greater risk of HHS when compared to the general population in the US.[8] In Canada, T2D disproportionately affects Indigenous, Black, and South Asian children and adolescents,[9] but the incidence of HHS is not yet known. It is important to establish whether certain populations are at elevated risk to raise awareness of this condition amongst practitioners and inform the safest and most effective approach to treatment.

Methods

Using the established Canadian Paediatric Surveillance Program (CPSP) methodology, approximately 2,800 paediatricians and paediatric subspecialists will be surveyed monthly and asked to report all new cases of HHS in children and youth up to 18 years of age diagnosed in the previous month. Paediatricians who identify cases will be asked to complete a detailed questionnaire to better understand the gravity of the disorder in terms of disability, morbidity, and mortality, as well as the necessity for paediatric subspecialist input and management.

Case definition

Report any patient less than 18 years of age (up to the 18th birthday), with or without a prior diagnosis of diabetes, presenting to hospital with hyperglycemic hyperosmolar state (HHS), defined as:

- Serum glucose concentration of >33 mmol/L
- Serum osmolality of >320 mOsm/kg
- Absence of significant acidosis:
  - Serum bicarbonate concentration of >15 mEq/L
  - Arterial/capillary pH of >7.30 or venous pH of >7.25

This case definition aligns with the current Diabetes Canada *diagnostic criteria[10] for HHS with one important amendment: ketosis is* ***NOT*** *an exclusion factor. The rationale for including ketosis is that the original HHS definition was based on adult presentation, and it is well demonstrated that more than 40% of children and adolescents with type 2 diabetes present with ketones (even if not acidotic).*

Objectives

1) Estimate the minimum annual incidence of HHS in Canadian children
2) Determine the populations most at risk for and precipitating factors of HHS in childhood
3) Determine the morbidity and mortality associated with HHS in Canadian children
4) Determine the relative contributions of the different types of diabetes to HHS cases in Canadian children
5) Assess current standard practice in terms of paediatric HHS management across Canada
6) Determine how frequently HHS represents first presentation of T1D or T2D in Canadian children

Duration

June 2023 to May 2025

Expected number of cases

With a Canadian paediatric population of 8 million, approximately 25 cases are expected across the nation in one year if the 2009 US estimates noted above are applicable. Preliminary analysis of the CPSP study on the "Incidence trends of

type 2 diabetes, medication induced diabetes, and monogenic diabetes in Canadian children" found seven cases of unconfirmed HHS among children with non-type 1 diabetes (unpublished; previous iteration available[9]). However, in the context of rising diabetes rates,[11] this figure is likely a significant underestimation of true incidence and there is some evidence that children with type 1 diabetes are also susceptible to HHS,[12] with up to 70% of cases occurring in such children in some studies.[6] Additionally, HHS is considered an under-recognised and under-reported hyperglycemic emergency in children as a result of its relative rarity. With all of this in mind, it is estimated that there will be 10 to 25 paediatric HHS presentations per year across Canadian hospitals during the proposed study period.

Study limitations

As with any voluntary surveillance system, CPSP relies on participants to report cases to generate data. Resulting rate estimations must therefore be considered minimum incidence rates. Additionally, it is likely that not all data points will be available for every patient and therefore exploration of several predisposing factors may be limited depending on data completeness and reporting rates. Finally, access to tertiary care is an important limitation, as a portion of the population may not have access to specialist paediatric input and therefore these cases would be unlikely to be captured. However, given the severity of such presentations, it is likely that most, if not all, cases will ultimately require transfer to tertiary or quaternary centres.

Ethical approval

- Health Canada and Public Health Agency of Canada Research Ethics Board
- The Hospital for Sick Children Research Ethics Board

Funding

Partial funding provided by:

- Internal research funds of Dr. Jill Hamilton, Division of Endocrinology, The Hospital for Sick Children
- University of Toronto, Elizabeth Arbuthnot Dyson Fellowship awarded to Dr. Paul MacDaragh Ryan

Analysis

Study data will be compiled and analysed at six-month intervals. Study data will be used to estimate minimum incidence rates of HHS in children across Canada and provincially (reported as cases per 100,000 children under 18 years of age per year). Additionally, predisposing and precipitating factors associated with the condition will be analyzed. Finally, the rates of a range of known complications of HHS in children will be explored and reported. Importantly, as ketosis has been removed as an exclusion factor in this case definition of HHS, each of the above parameters will be examined in cases of ketotic and non-ketotic HHS, independently.

Knowledge translation

A CPSP Highlight article on HHS will be submitted for consideration to *Paediatrics & Child Health* to promote awareness of the condition and its management in children. In addition, the results of this study will be disseminated at institutional, national (e.g., Canadian Pediatric Endocrinology Group Annual Conference), and international platforms (e.g., International Society for Pediatric and Adolescent Diabetes Annual Conference). Finally, a manuscript will be submitted to a peer-reviewed journal.

Study data will also be disseminated at regular six-month intervals to stakeholders, including paediatric endocrinologists, diabetes nurse specialists, paediatric emergency physicians, paediatric intensivists, and general paediatricians. The results of this study will provide guidance on the incidence rates, the key predisposing or precipitating factors, and the common presenting features of HHS in children. In addition, the data will inform policy makers and professional clinical societies/associations on the current practise of HHS management by Canadian paediatricians and potentially identify ways to improve the care of children nationally.

It is anticipated that study results could inform guidelines on the presentation, management, and rates of complications of HHS in children. For example, if the majority of children experience a thrombotic event, then more broad application of thromboprophylaxis may be warranted and this information will steer future research. Additionally, if rates of HHS are found to be higher in certain populations, targeted interventions could be developed, and study results could provide evidence to support the pursuit of funding for such initiatives.

References

1. Abarca-Gómez L, Abdeen ZA, Hamid ZA, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *The Lancet*. 2017;390(10113):2627–42. doi:10.1016/S0140-6736(17)32129-3
2. Rodd C, Sharma AK. Prevalence of overweight and obesity in Canadian children, 2004 to 2013: Impact of socioeconomic determinants. *Paediatr Child Health*. Jun 2017;22(3):153–8. doi:10.1093/pch/pxx057
3. Nadeau K, Dabelea D. Epidemiology of type 2 diabetes in children and adolescents. *Endocr Res*. 2008;33(1-2):35–58. doi: 10.1080/07435800802080138
4. Ruth C, Sellers E, Chartrand C, et al. *Type 2 Diabetes in Manitoba*. 2020. Autumn 2020.
5. Cochran JB, Walters S, Losek JD. Pediatric hyperglycemic hyperosmolar syndrome: diagnostic difficulties and high mortality rate. *Am J Emerg Med*. May 2006;24(3):297–301. doi:10.1016/j.ajem.2005.10.007

6. Bagdure D, Rewers A, Campagna E, Sills MR. Epidemiology of hyperglycemic hyperosmolar syndrome in children hospitalized in USA. *Pediatr Diabetes*. Feb 2013;14(1):18–24. doi:10.1111/j.1399-5448.2012.00897.x

7. Ramphul K, Joynauth J. An Update on the Incidence and Burden of Diabetic Ketoacidosis in the U.S. *Diabetes Care*. Dec 2020;43(12):e196-e197. doi:10.2337/dc20-1258

8. Adeyinka A, Kondamudi NP. Hyperosmolar Hyperglycemic Nonketotic Coma. *StatPearls*. 2021.

9. Amed S, Dean HJ, Panagiotopoulos C, et al. Type 2 diabetes, medication-induced diabetes, and monogenic diabetes in Canadian children: a prospective national surveillance study. *Diabetes Care*. Apr 2010;33(4):786–91. doi:10.2337/dc09-1013

10. Goguen J, Gilbert J. Hyperglycemic Emergencies in Adults. *Can J Diabetes*. Apr 2018;42 Suppl 1:S109-S114. doi:10.1016/j.jcjd.2017.10.013

11. Cohen A, Mok E, Simard M, et al. Increasing incidence of type 1 and 2 diabetes among Canadian children. *Can J Diabetes*. 2021;ePubdoi:https://doi.org/10.1016/j.jcjd.2021.08.006

12. Rosenbloom AL. Hyperglycemic hyperosmolar state: an emerging pediatric problem. *J Pediatr*. Feb 2010;156(2):180–4. doi: 10.1016/j.jpeds.2009.11.057