Micronutrient deficiencies and autism spectrum disorder

CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

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Background

In addition to impairments in both verbal and non-verbal communication, autism spectrum disorder (ASD) is characterized by restricted and repetitive behaviours. These can manifest as insistence on sameness and may result in food selectivity as well as limited food repertoire. Children with ASD may therefore be at increased risk of nutritional deficiencies. Some evidence suggests there may be a higher rate of iron deficiency in the ASD population relative to their typically-developing peers.[1,2] In the scientific literature, there are also numerous case reports of children with ASD and restricted diet who have developed micronutrient deficiencies such as vitamin A deficiency,[3-12] scurvy (vitamin C deficiency),[13-24] and nutritional rickets (vitamin D deficiency).[4,25] At The Hospital for Sick Children, for example, there have been at least five recent cases of scurvy and four recent cases of vitamin A deficiency in children with ASD.[12,23,24,26] It is unclear whether additional cases have been identified across the country, and the incidence of micronutrient deficiencies in Canadian children with ASD is unknown.

Micronutrient deficiencies can result in significant morbidity, which may be compounded by prolonged admissions, invasive investigations, and delayed diagnosis, given the perceived rarity of these conditions. Study results will be used to increase awareness of risk of micronutrient deficiencies in children and youth with ASD, to inform the need for clinical guidelines addressing anticipatory guidance and prevention in this population, and to guide future research.

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Methods

Via the established methodology of the CPSP, over 2,800 paediatricians and paediatric subspecialists will be actively surveyed on a monthly basis for cases of serious micronutrient deficiencies in Canadian children with ASD. Participants who identify cases through the monthly reporting form will be asked to complete a detailed questionnaire.

For the purposes of this study, the population of interest is Canadian children and youth with ASD. To ensure that a reported case meets the case definition, it will be confirmed through the detailed questionnaire that the child and youth in question has been diagnosed with ASD by a general paediatrician, developmental paediatrician, psychiatrist, or psychologist.

Objectives

1) Understand the burden of serious micronutrient deficiencies in Canadian children and youth with ASD to better inform anticipatory guidance, screening, and prevention strategies in this population.
2) Ascertain the minimum incidence of specific micronutrient deficiencies in Canadian children and youth with ASD.
3) Obtain demographic and clinical information to better understand factors associated with micronutrient deficiency in children and youth with ASD.
4) Determine the use of health care services in children and youth with ASD and micronutrient deficiency.
5) Assess significant health complications of micronutrient deficiency in children and youth with ASD.

Case definition

Report all children and youth less than 18 years of age (up to their 18th birthday) with autism spectrum disorder **AND** a new diagnosis of one or more of the following micronutrient deficiencies:

- Vitamin A deficiency/xerophthalmia
- Scurvy
- Severe, symptomatic vitamin D deficiency
- Severe iron-deficiency anemia

The patient's autism spectrum disorder must have been diagnosed by a general paediatrician, developmental paediatrician, psychiatrist, or psychologist.

Definitions for the micronutrient deficiencies and laboratory reference ranges can be found in Appendix 1.

Duration

January 2020 to December 2022

Micronutrient deficiencies and autism spectrum disorder (continued)

Expected number of cases

Based on a literature review, the best estimate (with incidence of xerophthalmia/vitamin A deficiency and scurvy being particularly difficult to hypothesize) of the maximum number of new cases over the two-year study period is as follows:

- <35 cases of vitamin A deficiency/xerophthalmia
- <35 cases of scurvy
- <55 cases of severe, symptomatic vitamin D deficiency
- <35 cases of severe iron-deficiency anemia

The anticipated total is therefore 160 new cases over the two-year study period.

Study limitations

As with any voluntary reporting system, the CPSP recognizes that reporting on minimum incidence rates can have limitations, including under-representation of the disease in the population. It is possible that some groups of children will be missed, for example, those who live in rural and remote areas as they may be less likely to receive timely specialist care. Case-level data is extracted from patient charts following the clinical encounter. Data elements not collected at the point of care may be absent from the surveillance totals. Surveillance still serves a very important purpose and provides rich clinical data that will allow us to better understand micronutrient deficiencies in Canadian children and youth with ASD.

Ethics approval

- Research Ethics Board, The Hospital for Sick Children
- Health Canada and the Public Health Agency of Canada's Research Ethics Board

Analysis and publication

Study results will be disseminated through publication in appropriate peer-reviewed journals and presentations at national and international meetings. Findings will also be shared with ASD-focused organizations and groups.

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Appendix 1 — Micronutrient deficiency definitions with laboratory reference values

Vitamin A deficiency/xerophthalmia

Vitamin A level below normal for age **AND** one or more of the following:

- Visual symptoms including a sensation of dryness and night blindness
- Diagnosis of xerophthalmia by an ophthalmologist or optometrist
- Correction/resolution of vision symptoms with vitamin A supplementation

References ranges for serum vitamin A level[1]	Age	Range (µmol/L)
	<1 year	0.3 – 1.9
	1–10 years	1.0 –1.6
	11–15 years	0.9 –1.9
	16–19 years	1.0 – 2.6

[1] Based on reference ranges of the Department of Paediatric Laboratory Medicine at The Hospital for Sick Children

Scurvy

Classic signs and symptoms of scurvy including any of petechiae, ecchymosis, hyperkeratosis, corkscrew hairs, gingival disease, and joint pain **AND** one or more of the following:

- Vitamin C (ascorbic acid) level below normal for age
- Improvement/resolution in signs and symptoms of scurvy with vitamin C (ascorbic acid) supplementation

References range for serum vitamin C (ascorbic acid) level[2]	Age	Range (µmol/L)
	All	≥25

[2] Based on reference ranges of the Department of Paediatric Laboratory Medicine at The Hospital for Sick Children

Severe, symptomatic vitamin D deficiency

Serum 25-hydroxyvitamin D <25 nmol/L **AND** one or more of the following:

- Radiographic signs of rickets
- Symptoms consistent with vitamin D deficiency (seizures, hypocalcemia, inability to ambulate) without another identified cause[3]

[3] Based on definition used in previous CPSP study (https://www.cpsp.cps.ca/uploads/surveys/vitamin-d-deficiency-rickets-survey-results.pdf)

Severe iron-deficiency anemia

Hemoglobin <80 g/L **AND** low mean corpuscular volume **AND** one or more of the following[4]:

- Ferritin <12 µg/L[5]
- Iron below normal for age[6]
- Soluble transferrin receptor above normal for age[6]
- Transferrin above normal for age
- Correction of anemia with iron therapy

References ranges for mean corpuscular volume (MCV)[5]	Age	Range (fL)
	0–14 days	Male (M): 91.3–103.1 Female (F): 92.7–106.4
	15–30 days	M: 89.4–99.7 F: 90.1–103.0

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	31–60 days	M: 84.3–94.2 F: 83.4–96.4
	61–180 days	M: 74.1–87.5 F: 74.8–88.3
	6 months– <2 years	M: 69.5–81.7 F: 71.3–82.6
	2– <6 years	M: 71.3–84.0 F: 72.3–85.0
	>6– <12 years	M: 74.4–86.1 F: 75.9–87.6
	>12– <18 years	M: 76.7–89.2 F: 76.9–90.6
References ranges for iron	**Age**	**Range (µmol/L)**
	0–14 years	M: 4.8–25.3 F: 4.8–25.3
	14 – <19 years	M: 7.5–32.6 F: 5.5–31.5
References ranges for soluble transferrin receptor	**Age**	**Range (mg/L)**
	1–11 years	0.8–1.6
	12–19 years	0.7–1.5
References ranges for transferrin	**Age**	**Range (µmol/L)**
	0– <2 months	12.8–27.6
	2 months– <1 year	13.2–39.9
	1– <19 years	27.1–41.5

[4] Adapted from definition used in previous CPSP study (https://www.cpsp.cps.ca/uploads/studies/iron-deficiency-anemia-protocol.pdf)
[5] Based on recent consensus in the iron-deficiency literature
[6] Based on reference ranges of the Department of Paediatric Laboratory Medicine at The Hospital for Sick Children