The epidemiology and health system impact of medium-chain acyl-CoA dehydrogenase deficiency among affected children and those with false positive newborn screening results in Ontario, Canada

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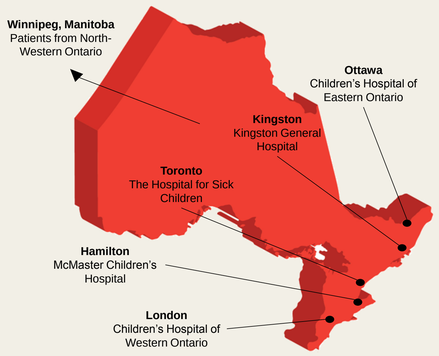
Background

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)

- A mitochondrial fatty acid oxidation disorder with an autosomal recessive inheritance pattern
- One of the most common inborn errors of metabolism: birth prevalence in Ontario estimated at 1 in 14,000 newborns (Kennedy et al., 2010, BMC Pediatrics)
- Characterized by the inability to form ketone bodies in the liver: essential alternative energy source in the fasting state and during intercurrent illness
- Clinical manifestations: risk of acute metabolic crisis during times of increased metabolic demands or reduced dietary intake
  - lethargy, vomiting, hypoketotic hypoglycemia, hypotonia – may progress to coma and death
- Pre-symptomatic diagnosis via newborn screening: early intervention to prevent metabolic crisis reduces morbidity and mortality (Wilcken et al., 2007, Lancet)



Newborn Bloodspot Screening in Ontario

- Received by nearly all babies born in Ontario: approx. 140,000 babies per year
- MCADD added to the panel of screened disorders in April 2006
- Tandem mass spectrometry (MS/MS) used to quantitatively assay acylcarnitine levels (primary marker for MCADD is octanoylcarnitine: C8)
- Babies with abnormal screening results are referred to one of five Newborn Screening Regional Treatment Centres (based at children's tertiary care hospitals – see map) for confirmatory diagnostic testing and follow-up care

Aim

- Limited research has been directed towards characterizing the health system impact of rare genetic disorders including MCADD
- Unique opportunity in Ontario to address this research gap:
  - Large population with universal health insurance
  - Newborn Screening Ontario data can be securely linked with health care administrative datasets: near complete population coverage for health services use (physician visits, emergency department care, hospitalizations)
- Using screening data linked with health services data, we aimed to describe patterns of health care services use for Ontario newborns diagnosed with MCADD and those with false positive newborn screening results over 4 years

Methods

- Study population: children who received newborn screening in Ontario from April 2006-March 2010, with a true positive or false positive result for MCADD
- Screening and confirmatory testing results securely linked at the individual level with health services administrative data from April 2006-March 2012 (linkage and analysis took place at the Institute for Clinical Evaluative Sciences):

Services Measures	Data Source
Physician visits (by specialty)	Ontario Health Insurance Program (OHIP) billing data
Emergency department care	National Ambulatory Care Reporting System (NACRS)
Hospitalizations	Canadian Institute for Health Information Discharge Abstracts Database (DAD)

- We calculated service use rates overall and by selected sociodemographic and geographic characteristics, accounting for different follow-up times

Study Participants

- Children with screen positive results for MCADD were identified and linked to health services databases
  - Less than 6 were lost to follow-up, deceased prior to diagnosis, or subsequently diagnosed with another disorder on the newborn screening panel. Thus, 83 children were included in the analysis.

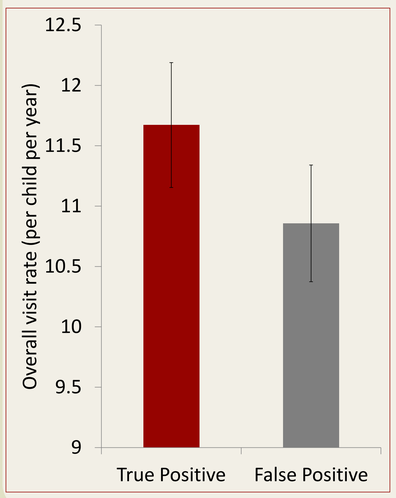
Characteristics of the study population

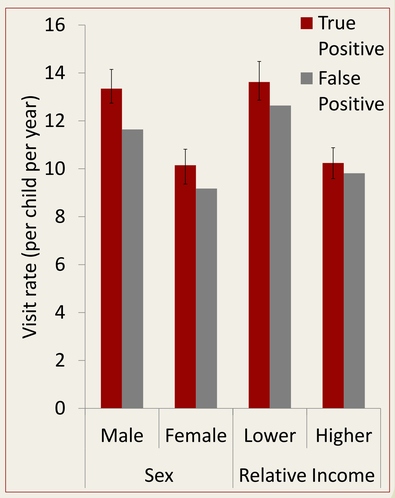
Characteristic	True Positives n = 40		False Positives n = 43	
	N	%	N	%
Total years of follow-up				
0 – 2	9	22.5	9	20.9
>2 – 4	19	47.5	22	51.2
> 4	12	30.0	12	27.9
Female	20	50.0	15	34.9
Pre-term birth (<37 weeks GA)	<6	NA	11	25.6
Treatment Centre				
Toronto	13	32.5	25	58.1
London	9	22.5	6	14.0
Hamilton	9	22.5	6	14.0
Ottawa/Kingston	9	22.5	6	14.0
Rural	6	15.0	<6	NA
Relative income (based on area of residence)				
Lower	16	40.0	21	48.8
Higher	24	60.0	21	48.8

Physician Visits

- True positive cohort (infants diagnosed with MCADD): total of 1956 recorded physician visits over the entire follow-up period, with an average rate of 11.7 physician visits per child per year (range: 2.6-41.6 visits per child per year)
  - Most common listed diagnoses: metabolic disorder, well baby care, respiratory infections
- False positive cohort (infants with false positive newborn screening results for MCADD): total of 1939 recorded physician visits, with an average rate of 10.9 visits per child per year (range: 0-49.4 visits per child per year)
  - Most common listed diagnoses: well baby care, diagnoses associated with prematurity or low birth weight, respiratory infections

Physician visit rates overall and by sex and relative income





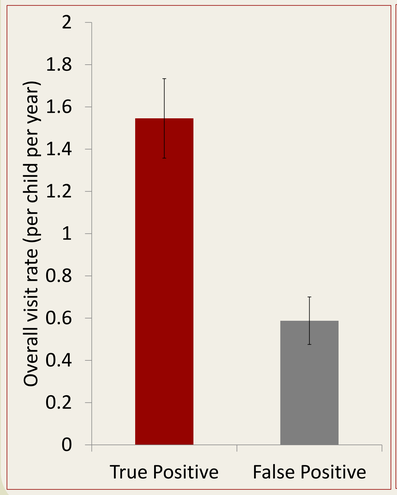
Hospitalizations

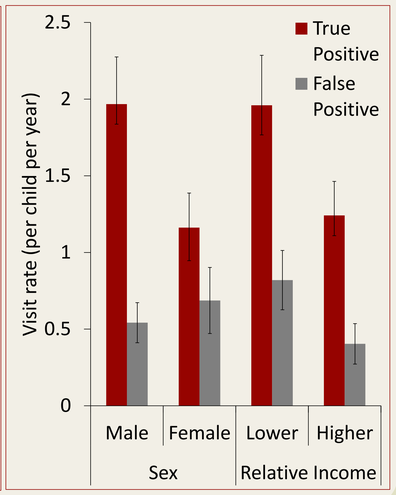
- True positive cohort: 70 inpatient hospitalizations, average hospitalization rate of 0.42 admissions per child per year (range 0-2.9 per child per year)
- False positive cohort: 27 inpatient hospitalizations, average hospitalization rate of 0.15 admissions per child per year (range 0-3.0 per child per year)

Emergency Department Visits

- True positive cohort: total of 259 emergency department (ED) visits over follow-up period, with an average rate of 1.6 ED visits per child per year (range 0-7.4 visits per child per year)
  - Most common listed diagnoses: disorder of fatty acid metabolism, respiratory infection, otitis media, fever, vomiting
- False positive cohort: total of 105 ED visits, average rate of 0.6 ED visits per child per year (range 0-3.4 visits per child per year)
  - Most common listed diagnoses: respiratory infection, otitis media

ED visit rates overall and by sex and relative income





Discussion

- Over an average follow-up time of approximately 4 years, Ontario children diagnosed with MCADD through newborn screening visited a physician at a frequency that was similar to children with false positive screening results
  - Yet rates of hospital inpatient admissions and ED visits were >2.6 times higher for children with MCADD than for those in the false positive cohort despite 25.6% of births being categorized as pre-term in the latter group
- The rates of hospitalizations and ED visits we observed in the false positive cohort are similar to visit rates in Ontario children with negative newborn screening results (0.20 hospitalizations and 0.64 ED visits per child per year)
- Physician visit rates and particularly ED visit rates were somewhat higher in males than in females with MCADD, and in children with MCADD who resided in lower versus higher income areas; but rates based on small numbers

Limitations and next steps

- Interpreting differences in health services use is challenging given small patient populations: further sociodemographic and geographic stratification will be possible as the cohort size grows and follow-up period increases
- Clinical details are limited in health care administrative datasets: this study is part of a larger program of work that will integrate clinical and patient/family-reported information with administrative data to provide richer information
- Screen positive babies born in North-Western Ontario may seek diagnosis and treatment in the province of Manitoba: this project will be expanded to include other Canadian provinces to allow more complete case ascertainment
- We will compare visit rates for the true and false positive cohorts to matched cohorts from the screen negative population and estimate total costs of care

Conclusion

- MCADD is a treatable metabolic disorder with an important impact on the health care system and on families
- There is strong potential to adapt and expand these methods to investigate other rare diseases, taking advantage of unique opportunities in Ontario
- Investigating patterns of health services use and their association with sociodemographic characteristics is important for:
  - understanding the burden of disease and impacts of screening & treatment
  - identifying potential inequities in access to care and generating hypotheses about ways to improve care

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