

Searching for the cause of unexplained high levels of calcium in infants: The Canadian and European experience

Submission date 06/12/2015	Recruitment status No longer recruiting	☐ Prospectively registered ☐ Protocol
Registration date 13/01/2016	Overall study status Completed	☐ Statistical analysis plan ☒ Results
Last Edited 14/01/2022	Condition category Genetic Diseases	☐ Individual participant data

Plain English summary of protocol

Background and study aims

Calcium is one of the most important minerals in the body. As well as building strong bones and teeth, it plays an important role in helping blood to clot, nerves to send messages and muscles to contract. Idiopathic infantile hypercalcemia (IIH) is a rare disorder in young children (typically aged 3-7 months) in which very high levels of calcium are present in the blood (hypercalcemia) and urine (hypercalciuria). Too much calcium can lead to a number of problems, such as weakened bones (as the calcium in the blood is often taken from the bones, stomach problems (such as nausea and vomiting), and even heart and brain problems. One of the most common features of IIH is problems with the kidneys, such as kidney stones (build-up of calcium deposits in the kidneys) or kidney failure, as the kidneys have to work harder than usual to get rid of excess calcium. The usual treatment for IIH is to temporarily reduce calcium or vitamin D (a vitamin required for the body to absorb calcium) intake. In most cases, the cause of IIH is unknown however previous study showed that 30% of infants suffering from IIH in Europe have a change (mutation) in a protein (CYP24A1) that breaks down vitamin D (CYP24A1). When this mutation in CYP24A1 occurs, normal vitamin D breakdown is interrupted causing vitamin D levels to build up and too much calcium to be absorbed in the intestine. Another study has shown that some people, who experience hypercalcemia as adults, also have this mutation. The aim of this study is to investigate how common the CYP24A1 mutation is in infants suffering from IIH and their families, across Europe and North America.

Who can participate?

Children who have suffered from hypercalcemia and hypercalciuria, without a known cause, with their biological parents and siblings.

What does the study involve?

The families come to the Children's Hospital where they give consent to take part in the study. The child and other available family members (parents and siblings) all have a blood test in order to test blood calcium levels, DNA (genetic material) and vitamin D levels. A urine sample is also collected which is tested for calcium. The family history for each participant is then reviewed to see how many relatives have had calcium problems or kidney stones. Children taking part also

have a bone density test (to test bone strength), which involves a type of x-ray procedure while the child is lying down.

What are the possible benefits and risks of participating?

Participants could benefit from gaining knowledge about whether they are carriers of the CYP24A1 mutation. They can then ensure that they do not consume too much calcium and reduce the likelihood of developing kidney stones. There are no significant risks of taking part however participants may experience discomfort, bruising and pain during blood tests.

Where is the study run from?

Six children's hospitals in Canada.

When is the study starting and how long is it expected to run for?

September 2013 to December 2016

Who is funding the study?

Canadian Institutes of Health Research (Canada)

Who is the main contact?

Dr Celia Rodd

Contact information

Type(s)

Scientific

Contact name

Dr Celia Rodd

Contact details

Children's Hospital of Winnipeg
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Winnipeg
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Additional identifiers

Protocol serial number

CIHR ERA-13293

Study information

Scientific Title

Idiopathic Infantile Hypercalcemia: European-Canadian Consortium

Acronym

IIH

Study objectives

Mutations in CYP24A1 lead to aberrant control of vitamin D hormone levels in blood and tissues and impaired mineral ion homeostasis, leading to soft-tissue calcification as a result of long-term hypercalcemia.

Ethics approval required

Old ethics approval format

Ethics approval(s)

1. University of Manitoba Research Ethics Board, 15/04/2015, ref: DBMS-033-14 IIH-ECC
2. University of Calgary, 12/02/2013, ref: REB13-0216
3. Montreal Children's Hospital Research Ethics Board, 06/06/2011, ref: 11-163
4. The Research Ethics Board of the University of Laval, 18/02/2015, ref: 2015-2240

Study design

Multi-centre cross sectional observational study

Primary study design

Observational

Study type(s)

Screening

Health condition(s) or problem(s) studied

Idiopathic infantile hypercalcemia

Interventions

Children with hypercalcemia and hypercalciuria or isolated hypercalciuria without an identified aetiology will be approached to try to determine if they have mutations in CYP24A. Most children will have a single sample of blood taken for vitamin D metabolomics and DNA mutational analyses. If the family consents, we may consider examining a few other novel genes involved in hypercalcemia such as sodium phosphate transporters NaPilla and -lic. The blood will be stored for a maximum of 7 years and then discarded as per protocol. For some young infants, we may consider obtaining several samples while hypercalcemic to see if there is a difference in the vitamin D metabolite profile. The samples will be stored the same amount of time (7 years).

Intervention Type

Other

Primary outcome(s)

Number of children with presumed IIH that have CYP24A1 mutations is determined using DNA mutational analyses at the end of the study period.

Key secondary outcome(s)

Utility of vitamin D metabolite ratios to diagnose and manage children with known CYP24A1 mutations is determined using LC-MS/MS (tandem mass spectrometry) at the end of the study period.

Completion date

31/12/2017

Eligibility

Key inclusion criteria

Children inclusion criteria:

1. Documented hypercalcemia on at least 2 occasions without any known etiology
2. Idiopathic hypercalciuria without any known etiology

Family members inclusion criteria:

None

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Child

Sex

All

Total final enrolment

41

Key exclusion criteria

Children exclusion criteria:

Children with known causes of hypercalcemia or hypercalciuria

Family members inclusion criteria:

None

Date of first enrolment

01/01/2013

Date of final enrolment

31/12/2016

Locations

Countries of recruitment

Canada

Study participating centre

Montreal Children's Hospital (McGill)

1001 Decarie Boulevard

Montreal

Quebec

Canada
H4A 3J1

Study participating centre
Children's Hospital of Winnipeg
840 Sherbrook Street
Winnipeg
Canada
R3A 1R8

Study participating centre
Alberta's Children's Hospital
2888 Shaganappi Trail
Calgary
Canada
T3B 6A8

Study participating centre
Laval-Centre Mere Enfant Soleil
2705 Boulevard Laurier
Québec
Canada
G1V 4G2

Study participating centre
IWK Health Centre
5980 University Avenue
Halifax
Canada
B3K 6R8

Study participating centre
Ottawa Children's Hospital
401 Smyth Road
Ottawa
Canada
K1H 8L1

Sponsor information

Organisation

Canadian Institutes of Health Research

ROR

<https://ror.org/01gavpb45>

Funder(s)

Funder type

Government

Funder Name

Canadian Institutes of Health Research

Alternative Name(s)

Instituts de Recherche en Santé du Canada, The Canadian Institutes of Health Research (CIHR), Canadian Institutes of Health Research (CIHR), Canadian Institutes of Health Research | Ottawa ON, CIHR - Welcome to the Canadian Institutes of Health Research, CIHR, IRSC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

Canada

Results and Publications

Individual participant data (IPD) sharing plan

Not provided at time of registration

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/08/2021	14/01/2022	Yes	No