East Kent Hospitals University NHS Foundation Trust

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA: GUIDELINES FOR INVESTIGATION

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Version Control

Version	Date	Author	Status	Comment

Consultation Schedule

Name & Job Title of Individual / Meeting name	Date consulted
Diabetes Clinical Meeting	5-8-2020
Dr S Joseph	1-12-2020

Ratification Schedule

Name of Meeting / Committee	Date approved / authorised
Clinical Biochemistry Senior Staff meeting	15-7-2021

Contents

1. Introduction, background and purpose

This policy gives guidance on investigations to identify patients with familial hypocalciuric hypercalcaemia.

Parathyroid hormone (PTH) is secreted by the parathyroid gland in response to a fall in plasma calcium concentrations. It acts to increase plasma calcium concentrations by stimulating bone resorption, increasing calcium reabsorption in the kidney and increasing hydroxylation of 25-hydroxycholecalciferol. Primary hyperparathyroidism (PHPT) is one of the most common causes of hypercalcaemia. It is characterised by hypercalcaemia and hypercalciuria. Definitive treatment is by removal of one or more of the parathyroid glands.

Familial hypocalciuric hypercalcaemia (FHH) is a group of disorders caused by mutations in the calcium-sensing receptor (CaSR) or the intracellular signalling pathways associated with the receptor. There are some phenotypic differences (Ref 5).

FHH1 – loss-of-function mutations in CaSR gene on Chromosome 3. Mild elevations in calcium with normal or slight increases in PTH (Ref 2)

FHH2 – loss-of-function mutations in the GNA11 gene on Chromosome 19 which codes for Gα11 protein, involved in intracellular signalling

FHH3 – loss-of-function mutations in the AP2S1 gene on Chromosome 19 which codes for the σ2 subunit of adaptor-related protein complex 2 (AP2σ2), required for clathrin-mediated endocytosis of plasma membrane proteins. Hypercalcaemia can be significant and symptomatic.

Hypocalciuric hypercalcaemia can also be caused by autoantibodies to the CaSR.

Individuals with FHH have hypercalcaemia that is not corrected by parathyroidectomy. NICE primary hyperparathyroidism guidelines (NG132) (Ref 6) recommend urine tests to identify patients with probable FHH in order to avoid unnecessary neck surgery. Assessment of 24 hour calcium excretion may be useful to guide treatment of PHPT. In EKHUFT the calcium creatinine clearance ratio (CACRC) is recommended for excluding FHH as it has the best discrimination (Refs 1,5, 7). Genetic analysis may occasionally be required when CACRC results are inconclusive.

2. Definitions

FHH	familial (benign) hypocalciuric hypercalcemia
PTH	parathyroid hormone
CACRC	calcium creatinine clearance ratio
CaSR	calcium sensing receptor
PHPT	primary hyperparathyroidism

3. Scope

This policy outlines familial hypocalciuric hypercalcaemia testing for patients within secondary care.

4. Guidance

4.1 Calcium creatinine clearance ratio

This test should be restricted to the secondary care assessment of patients with suspected PHPT. As with any other laboratory investigation full and explicit clinical details should be provided. All requests will be reviewed after analysis and appropriate interpretation added to the report.

$$\text{CACRC} = \frac{[\text{calcium}]_{\text{urine}}}{[\text{creatinine}]_{\text{urine}}} \times \frac{[\text{calcium}]_{\text{serum}}}{[\text{creatinine}]_{\text{serum}}}$$

4.1.1 Patient preparation

Unreliable CACRC results are seen in Vitamin D deficiency/insufficiency (Ref 1, 4), very low calcium intake and mild CKD. Drugs that affect calcium metabolism or renal handling of calcium will also cause unreliable results; this includes bisphosphonates, diuretics and lithium (Ref 1). If possible diuretics should be excluded for 2 months (Ref 3).
The patient should be fasting.

4.1.2 Sample requirements

Paired blood and urine samples are required:

Spot urine sample
Second void urine collected into a plain (white top) container.
Request *CACRC* on Sunrise.
Blood sample
A blood sample collected in to a SST (yellow top) within 24 hours of the urine.
Request calcium and creatinine on Sunrise.

4.1.3 Interpretation of results

CACRC >0.020	FHH unlikely
CACRC 0.011 – 0.020	unable to distinguish FHH and PHPT, genetic testing may be useful
CACRC ≤0.010	supports a diagnosis of FHH (Ref 1, 3)

Eighty percent of patients with FHH will have CACRC ≤0.010. However falsely low results are seen in Vitamin D deficiency/insufficiency, very low calcium intake, mild CKD and patients on drugs that affect calcium metabolism or renal handling of calcium, including bisphosphonates, lithium, thiazide

diuretics and amioride. Correction of any of these will lead to hypercalciuria if the patient has PHPT.

4.2. Genetic testing

Differentiation between FHH and PHPT is more difficult in the absence of a family history of hypercalcaemia and if the CACRC is between 0.011 and 0.020. Genetic testing may be useful for investigating patients with an intermediate CACRC result or for confirming a diagnosis of FHH3. It may also be used if family studies are required clinically. The Oxford FHH genetic panel includes the CASR, GNA11 and AP2S1 genes.
EDTA (purple top) whole blood is required and a completed genetics request form.
Use the genetics form from https://southeastgenomics.nhs.uk/professionals/

National Genomic test directory testing criteria:
R152 Hypocalciuric hypercalcaemia
Hypercalcaemia with hypocalciuria (calcium clearance: creatinine clearance ratio < 0.02), usually with normal PTH. Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

5. Consultation and approval

Consultation has been through e-mail and face-to-face communication between clinical biochemistry staff, Endocrinology MDM, Dr Stonny Joseph. Records are kept on the S drive (S:\Path\SnrStaff\Comms with users\Clinical guidelines).

6. Review and revision arrangements

Document control and review will be managed through Pathology Q Pulse. The document will be reviewed at two years from implementation date, by the author.

7. Training

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professional zone of Trustnet. Information may also be contained within the Pathology and/or Paediatric MicroGuide

8. Document control including archiving arrangements

Document control and review will be managed through Pathology Q Pulse. Archive of this document will be on QPulse.

9. Monitoring

Within the Trust, compliance with this policy must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

10. References and associated documents

1. Christensen SE et al. Clin Endocrinol 2008; 69: 713-20. Discriminative power of three indices of renal calcium excretion for the distinction between familial hypocalciuric hypercalcaemia and primary hyperparathyroidism: a follow-up study on methods.

2. Gunn IR, Gaffney D. Ann Clin Biochem 2004; 41: 441-58. Clinical and laboratory features of calcium-sensing receptor disorders: a systematic review

3. Hannan FM et al. Human Molecular Genetics 2015; 24: 5079-92. Adaptor protein-2 sigma subunit mutations causing familial hypocalciuric hypercalcaemia type 3 (FHH3) demonstrate genotype-phenotype correlations, codon bias and dominant-negative effects

4. Jayasena CN et al. Ann Clin Biochem 2011; 48: 126-9. Utility of the urine calcium-to-creatinine ratio to diagnose primary hyperparathyroidism in asymptomatic hypercalcaemic patients with vitamin D deficiency

5. Lee JY and Shoback DM. Best Pract Res Clin Endocrinol Metab 2018; 32:609-19. Familial hypocalciuric hypercalcaemia and related disorders

6. NICE NG132. www.nice.org.uk/guidance/ng132. Hyperparathyroidism (primary): diagnosis, assessment and initial management

7. NICE May 2019. Hyperparathyroidism (primary): diagnosis, assessment and initial management. [B] Evidence review for diagnostic tests, NICE guideline NG132

11. Appendices