The importance of urinary calcium measurement and genetic studies in differentiating Familial Hypocalciuric Hypercalcaemia (FHH) from Primary Hyperparathyroidism (PHPT)

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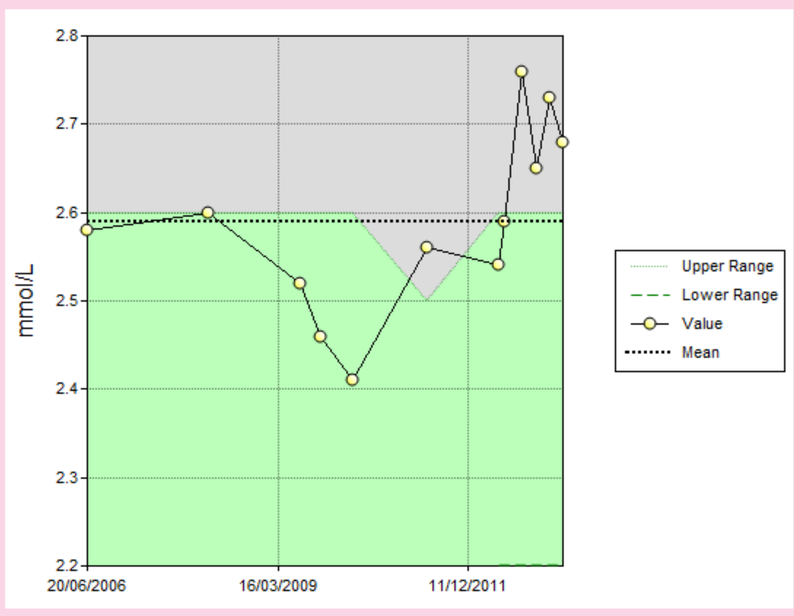
CASE HISTORY (Mother)

- A 56 year old lady with mild hypercalcaemia since 2004
- Diagnosed as Primary Hyperparathyroidism and had Parathyroidectomy in 2008 (Histology showed hyperplasia)
- No symptoms and no bony or renal complications
- Her vitamin D level was normal (on supplements)
- Ongoing mild hypercalcaemia post-surgery

INVESTIGATIONS

Tests	Results	Normal values
Corrected Calcium	2.76 mmol/L	2.2 – 2.6
PTH level	9.7 pmol/L	1.6 – 6.9
Urinary calcium output	3.96 mmol	2.5 – 7.5
Ca/Cr clearance	0.0142	(>0.02 for PHPT)

Corrected Calcium levels



Received	Result
20 Jun 2006 16:56	2.58
14 Mar 2008 15:11	2.60
10 Jul 2009 14:32	2.52
23 Oct 2009 14:47	2.46
13 Apr 2010 15:24	2.41
06 May 2011 12:29	*2.56
16 May 2012 11:14	2.54
13 Jun 2012 16:00	2.59
13 Sep 2012 14:29	*2.76
06 Dec 2012 15:39	*2.65
06 Feb 2013 15:12	*2.73
19 Apr 2013 14:19	*2.68

CASE HISTORY (Son)

- A 21 year old man with mild hypercalcaemia since 2010
- PTH at the upper end of normal
- Diagnosed as Primary Hyperparathyroidism and planned to have Parathyroidectomy in March 2011
- No symptoms and no bony or renal complications
- His vitamin D level was normal (Not on supplements)

INVESTIGATIONS

Tests	Results	Normal values
Corrected Calcium	2.76 mmol/L	2.2 – 2.6
PTH level	63.8 ng/L	16 - 66
Urinary calcium output	<0.01 mmol	2.5 – 7.5
Ca/Cr clearance	0.0098	(>0.02 for PHPT)

Corrected Calcium levels

28/02/08	04/08/10	21/09/10	31/01/11	17/03/11	
143	141	144	143	143	Na
4.7	4.7	4.5	4.1	4.7	K
5.6	4.5	5.0	4.7	4.9	Urea
88	74	77	74	72	Creat
	>90	>90	>90	>90	eGFR
					CRP
4.2					GLUC
2.70	2.64	2.76	2.60	2.72	CA
2.64	2.48	2.64	2.48	2.60	CCA
43	48	46	46	46	ALB
74	77	72	73	76	Total Protein
8	9		15	10	BILI
28	22		26	23	AST
					ALT
					ALP
	18.2				Free T4
	0.88				TSH

FINAL DIAGNOSIS

- We advised to withhold parathyroid surgery for the son in view of his age, positive family history and very low urinary calcium excretion.
- Genetic analysis confirmed that both the mother and the son were heterozygous for c.61G>A (p.Gly21Arg) Calcium Sensing Receptor (CASR) variant.
- This gene has been reported in the literature to be associated with Familial Hypocalciuric Hypercalcaemia (FHH).
- The planned surgery for the son was later cancelled
- Both the mother and the son remained asymptomatic during their subsequent clinic follow up visits with continued mild biochemical derangements.

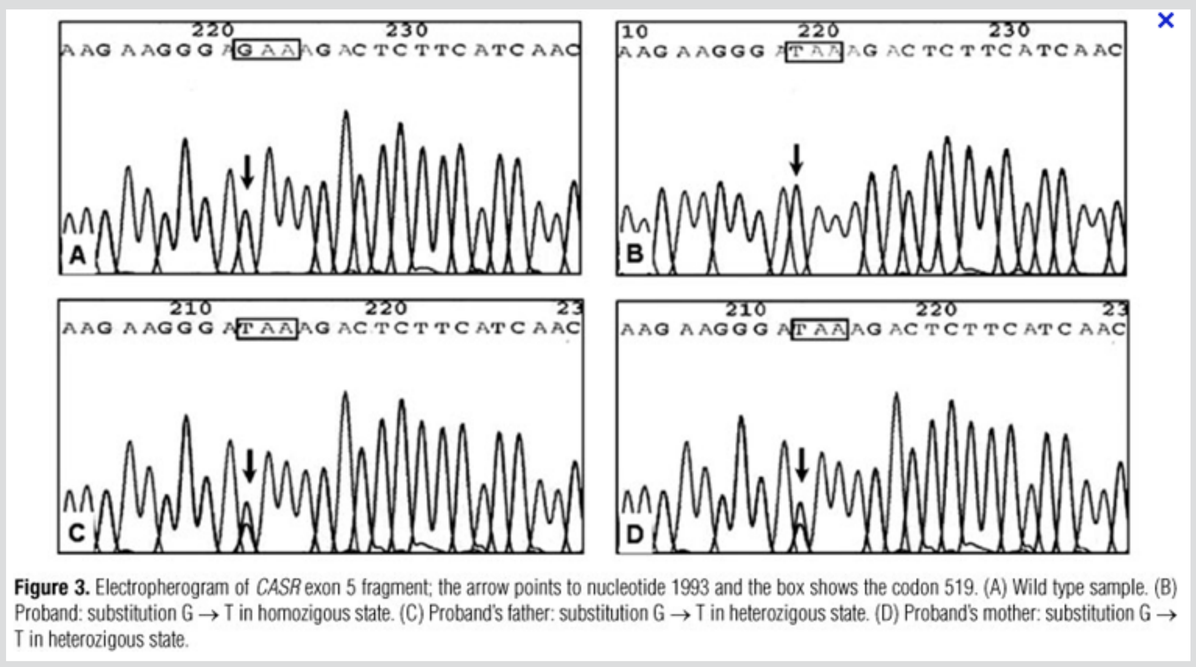


Figure 3. Electropherogram of *CASR* exon 5 fragment; the arrow points to nucleotide 1993 and the box shows the codon 519. (A) Wild type sample. (B) Proband: substitution G → T in homozigous state. (C) Proband's father: substitution G → T in heterozigous state. (D) Proband's mother: substitution G → T in heterozigous state.

CONCLUSION AND LEARNING POINTS

- Familial Hypocalciuric Hypercalcaemia (FHH) is a benign condition, occurs as a result of inactivating mutation in the calcium sensing receptor (CASR) gene and is autosomal dominant
- Inactivating mutation of the CASR affects the kidneys, enhancing calcium re-absorption and resulting in hypocalciuria
- Usually affects younger patients than patient with PHPT and usually with a positive family history
- Mild hypercalcaemia, normal or mildly raised PTH and very low Ca/Cr clearance ratio (typically <0.01) are typical features
- No renal or bone complications reported in literature
- Surgery is not indicated in an otherwise normal parathyroid glands, so it must be avoided.

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A rare endocrine cause of severe resistant hypoglycaemia

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CASE HISTORY

- 68 year old lady
- Paroxysmal symptoms (sweating, palpitations, syncope and pre-syncope) for several weeks.
- History of significant weight loss.
- Chronic heavy smoker, but no alcohol intake
- Not on insulin or any other regular medications.

EXAMINATION

- Cachectic and had a non-tender palpable liver.
- No signs of decompensated chronic liver disease.
- Bedside capillary blood glucose reading was 0.9 mmol/L (NR 3.8-6.1).

INVESTIGATIONS

Tests	Results	Normal values
ALP	383 iu/L	30 - 130
ALT	50 iu/L	0 - 50
GGT	635	0 - 76
Bilirubin	15 umol/L	<21
AFP	>1000 Mcg/L	<5.8
Glucose	1.2 mmol/L	4 - 7
Insulin	Undetectable	
C-peptide	Undetectable	
IGF-I	Undetectable	

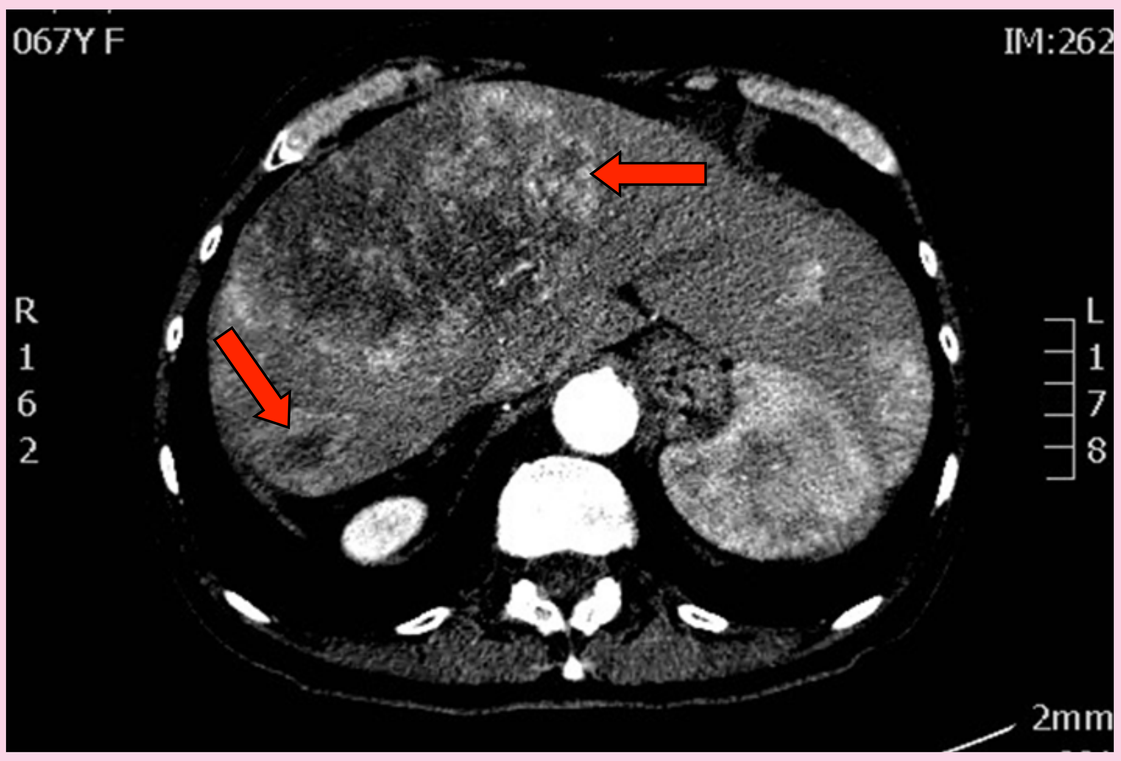


Image 1: CT abdomen showing multiple liver lesions

DIAGNOSIS

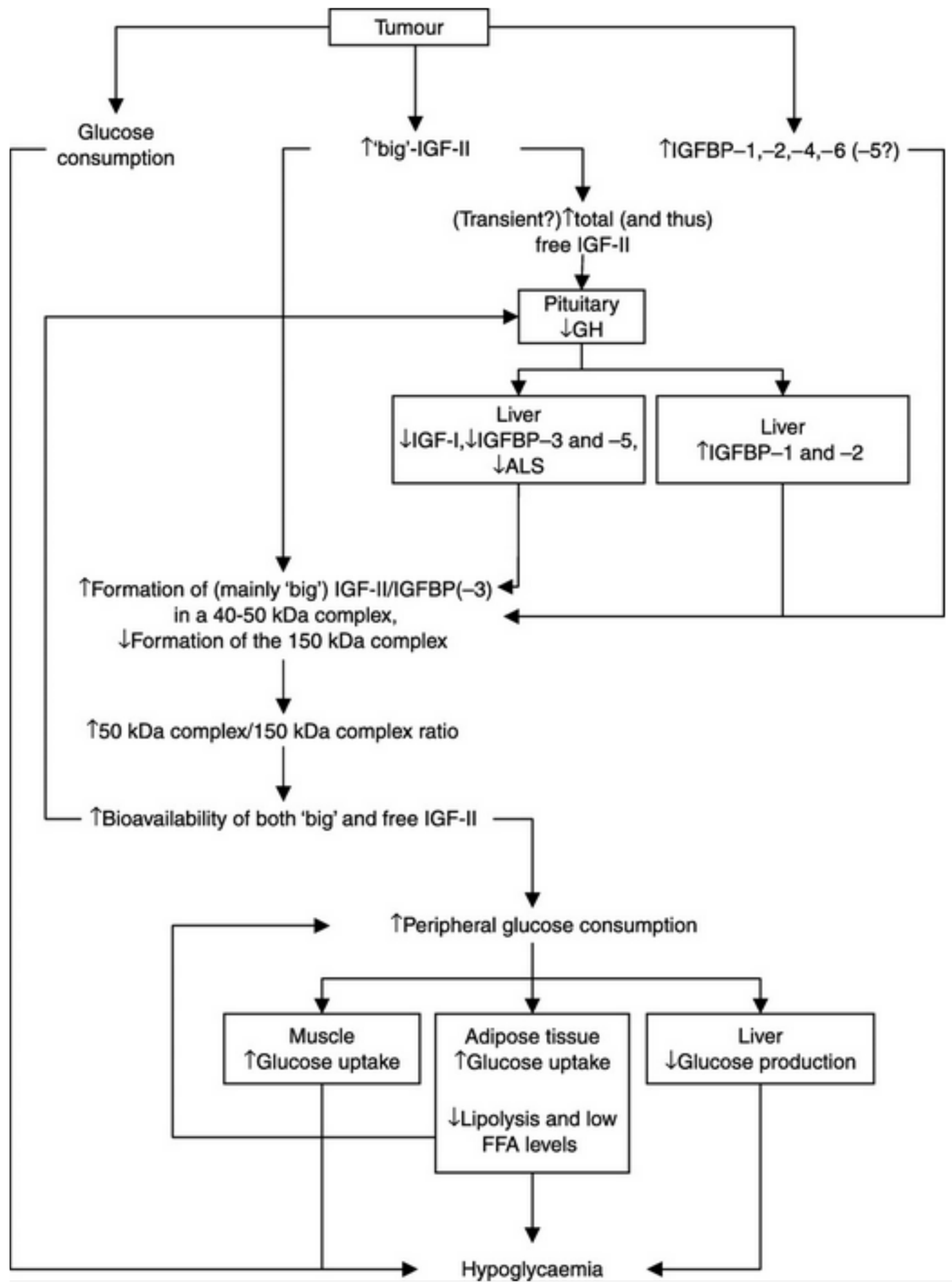
- Histology: high grade hepatocellular carcinoma
- Serum IGF-II concentration: 102 nmol/L (NR <10)
- IGF-II / IGF-I ratio >10

Non-Islet Cell Tumour Hypoglycaemia (NICTH) (Paraneoplastic hypoglycaemia)

POOR PROGNOSIS

- Patient continued to have hypos despite 10% IV-dextrose infusions and eating her normal 3 meals a day.
- Brief respite with IV-hydrocortisone
- Multiple hypoglycaemic seizures causing brain damage
- Deteriorated and deemed unfit for de-bulking surgery

IGF-II-INDUCED HYPOGLYCAEMIA PATHWAY



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TUMOUR-INDUCED HYPOGLYCAEMIA

Parameters	Islet Cell Tumours	Non-Islet Cell Tumours
Glucose	↓	↓
Insulin	↑	↓
C-Peptide	↑	↓
IGF-II/IGF-I ratio	Normal	Elevated (>10:1)

CONCLUSION AND LEARNING POINTS

- Non-Islet Cell Tumour Hypoglycaemia (NICTH) is a rare paraneoplastic phenomenon due to high IGF-II secretion by the tumour cells.
- Can be the presenting symptom of some advanced tumours, particularly tumours of epithelial and mesothelial origins
- Treating hypoglycaemia in such cases can be challenging as they tend to be severe and resistant to glucose replacement.
- Several other treatment options have been tried in literature (case reports only) such as glucocorticoids and somatostatin analogues, but nothing proven to be effective.

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