Thyroid and parathyroid disease: A medical perspective.

Professor Karim Meeran
Endocrine Unit
12th May 2008
Making the diagnosis of primary hyperparathyroidism

• Should NOT involve nuclear medics!

• We need you once the diagnosis is made
Case 1

- 17 year old lady referred (privately) directly for surgery.
- c/o “unwell”
- PTH: 130pM (1.1 – 6.8)
- Sestamibi reported as two hyperplastic glands.
Case 1

- Booked for surgery.
- Seen by endocrine SPR before surgery.
- What would you do...

Calcium 1.70 mM (2.2 – 2.6)

Vitamin D undetectable

PTH: 130pM (1.1 – 6.8)
Sestamibi reported as two hyperplastic glands.
Case 1

- Calcium 1.70mM (2.2 – 2.6)
- Vit D undetectable
- Secondary hyperparathyroidism
Case 1

- Calcium 1.70mM (2.2 – 2.6)
- Vit D undetectable
- Secondary hyperparathyroidism
- Replace vitamin D
Case 2

- 48 year old lady well.
- Calcium 2.9 mM (2.2 – 2.6)
- Phosphate 0.7 mM (0.8 – 1.4)
- Vit D normal
- PTH 16 pM (1.1 – 6.8)
Case 2

- 48 year old lady well.
- Calcium 2.9mM (2.2 – 2.6)
- Phosphate 0.7mM (0.8 – 1.4)
- Vit D normal
- PTH 16 pM (1.1 – 6.8)
- Sestamibi: at least 1 abnormal visible gland.
- Ultrasound: possibly 2 visible glands
- Multinodular goitre…
Case 2

- Surgery confirmed large parathyroid...
- Postop calcium fell initially (hours) but rose back to 2.9mM within a few days
- Patient remained well.

24 hour urine collection: v low calcium.
Familial hypocalciuric hypercalcaemia (FBH)
Imaging in nuclear medicine

- Should be used to LOCALISE
- NOT to make diagnosis

- It is very tempting to assume that just because you think you can see something that it is there...
Case 3: 50 year old

- Fractures, renal colic, Depression.
- Calcium 2.90 mM (2.2 – 2.6)
- Phosphate 0.6 mM (0.8 – 1.4)
- Vitamin D normal
- \[ \text{PTH} = 3.1 \text{ pM} (1.1 – 6.8) \]
- Request for sestamibi and ultrasound.
- Would you agree to do one?
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  \]
- Request for sestamibi and ultrasound.
- Would you agree to do one?
- This is primary hyperparathyroidism.
Key messages

• Do not interpret PTH without calcium.
• Exclude FHH before surgery
• Check vitamin D and ensure vitamin D repletion.
• High calcium with “normal” PTH is primary hyperparathyroidism.
Case 4: Asymptomatic 60y

• Incidental Ca 2.81 nmol/L
  – (PTH 14.7 pmol/l. PO4 0.8 nmol/l)
  – Vitamin D 25 (25 – 100)
  – 24 hour urinary calcium excretion 1.89, 2.59
  – (NR <7.5 mmol/day)
  – Urinary Calcium creatinine ratio 0.010, 0.011 (FHH <0.010)

• Could be FHH or PHPT.
### FHH or PHPT?

<table>
<thead>
<tr>
<th>Results</th>
<th>08/06</th>
<th>1/07</th>
<th>08/07</th>
<th>11/07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca mmol/l</td>
<td>2.97</td>
<td>2.86</td>
<td>2.97</td>
<td>2.87</td>
</tr>
<tr>
<td>PTH pmol/l</td>
<td>9.4</td>
<td>6.5</td>
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<tr>
<td>PO4 mmol/l</td>
<td>0.85</td>
<td>0.66</td>
<td>0.85</td>
<td>0.75</td>
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<tr>
<td>Vit D pmol/l</td>
<td>35</td>
<td>24 *</td>
<td></td>
<td>33</td>
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- What other tests can we do?

  ?Imaging??
### FHH or PHPT?

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- **Neck US:** multinodular goitre
- **Renal US:** maybe 2mm echogenic focus: ? Small stone.
- **No nephrocalcinosis.**
- **Sestamibi:** no definite abnormality in view of goitre.
- **Dexa LS T -1.1, FN +0.8**
FHH or PHPT?

- Two of her daughters had calcium checked.
- One was hypercalcaemic and well.
- Probable FHH but investigations continue.
A follow-up conference of the NIH and the National Institute of Diabetes and Digestive and Kidney Diseases in 2002 recommended parathyroidectomy for the following patients:

1. those <50 years of age,
2. who cannot participate in appropriate follow-up
3. with a serum calcium level >1.0 mg/dL (0.25 mmol/L) above the normal range
4. with urinary calcium >400 mg/24 h
5. with a 30% decrease in renal function,
6. or with complications of PHPT, including nephrocalcinosis, osteoporosis (T-score <2.5 SD at the lumbar spine, hip, or wrist), or a severe psychoneurologic disorder
Vitamin D repletion in patients with Primary Hyperparathyroidism and coexistent Vitamin D Insufficiency
Andrew Grey et al, JCEM 90(4):2122-2126, 2005

• Report the effects of vitamin D repletion on biochemical outcomes over 1 year in 21 patients with mild $1^\circ$HPT(Ca<3mmol/L) and co-existent Vit D insufficiency (<50nmol/l)

• Cholecalciferol 50,000 units per week for one month, then monthly for 12 months

• Results conclusions:
  – Modest reduction in PTH
  – Reduced markers of bone turnover and
  – No exacerbation of hypercalcemia
  – Mean urinary calcium excretion unchanged (2 patients had mild increase)
FIG. 1. Levels of serum 25(OH)D in patients with PHPT and vitamin D insufficiency treated with cholecalciferol for 1 yr

FIG. 2. Serum calcium (A) and PTH (B) values in patients with PHPT and vitamin D insufficiency treated with cholecalciferol for 1 yr.
Thyroid disease

- Graves disease
- Toxic nodular goitre
- De Quervain’s viral thyroiditis
28 year old rugby player

• Assessed performance by comparing pre and post exercise pulse rate (using special watch)
  • Resting rate 50
  • Peak rate 140
28 year old rugby player

- Resting rate 60
- Peak 170
- Thought he was doing well
- ? Weight loss
28 year old rugby player

• Palpitations and breathlessness
• Watch went “haywire”
• Noted irregular pulse: rate 110
• Can no longer train
• ECG: uncontrolled AF
Cardiologists Plan

• Beta blockade

• Rapidly cardioverted

• Discharged home well.
Further results

- FT4: 55 pM (10-24)
- TSH undetectable
- Ab +ve: Graves’ disease
- Referred to endocrinology
Our initial plan

• Beta blockade: propranolol 80 tds

• Carbimazole 40 mg daily

• Review in 6 weeks
Problem

• Patient cannot train while on beta blockers
  – Resting pulse 45
  – Peak 85

• Cannot afford 3 months off work

• Carbimazole slow in onset of action
Needed urgently to go back to train

• Team manager: ? 6 weeks

• Team doctor: any way of discontinuing beta blockers sooner?
Action of lithium

- Studies in 1970’s showed block in release of radiolabelled iodine, similar to effects of iodide.

- Temple (1972) JCI: Studied iodide kinetics with lithium in 7 thyrotoxics.

- Decreased $^{131}$I release from gland.
Alternative strategy

- Early definitive radioiodine with lithium to control thyroid function.

- Cannot give carbimazole or propyl-thiouracil with radioiodine
Protocol

• Stop anti-thyroid drugs 3 days before RAI and start lithium carbonate (Priadel) 800mg nocte.

• 735 MBq RAI

• Continue lithium for 7 days after RAI (total 10 day course).
# Results

<table>
<thead>
<tr>
<th>Time</th>
<th>Diagnosis</th>
<th>Day - 3</th>
<th>Day 0</th>
<th>Week +1</th>
<th>Week +3</th>
<th>Week +6</th>
<th>Week +9</th>
<th>Week +12</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>25.5</td>
</tr>
<tr>
<td>fT4 (pmol/L)</td>
<td>55.0</td>
<td>39.7</td>
<td>38.5</td>
<td>25.6</td>
<td>43.8</td>
<td>36.5</td>
<td>11.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Intervention</td>
<td>Stop CBZ. Start Lithium</td>
<td>RAI</td>
<td>Stop lithium Stop beta blockers</td>
<td>Start T4 100μcg</td>
<td>Increase T4 125μcg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean lithium level 0.5 mmol/L (range 0.4-0.5 mmol/L).
lithium

FT4

NR

RAI
Outcome

• Stable and on thyroxine within 2 months of RAI

• (Back to training within 7 days of RAI)
Comparison of Radioiodine with Radioiodine plus Lithium in the Treatment of Graves’ Hyperthyroidism*

FAUSTO BOGAZZI, LUIGI BARTALENA, SANDRA BROGIONI, GIOVANNA SCARCELLO, ALESSANDRO BURELLI, ALBERTO CAMPOMORI, LUCA MANETTI, GIUSEPPE ROSSI, ALDO PINCHERA, AND ENIO MARTINO

Dipartimento di Endocrinologia e Metabolismo, Ortopedia e Traumatologia, Medicina del Lavoro (F.B., L.B., S.B., G.S., A.B., A.C., L.M., A.P., E.M.), University of Pisa, 56122 Pisa, Italy; and Reparto di Epidemiologia e Biostatistica, Istituto di Fisiologia Clinica (G.R.), National Research Council (C.N.R.), 56100 Pisa, Italy.

ABSTRACT

Effectiveness of radioiodine for Graves' hyperthyroidism depends also on its intrathyroidal persistence. The latter is enhanced by lithium by blocking iodine release from the thyroid. One hundred ten patients with Graves’ hyperthyroidism were randomly assigned to treatment with radioiodine or radioiodine plus lithium, stratified according to goiter size (≤40 or >40 mL) and evaluated for changes in thyroid function and goiter size, at monthly intervals, for 12 months.

Cure of hyperthyroidism occurred in 33 of 46 patients (72%) treated with radioiodine and in 45 of 54 patients (83%) treated with radioiodine plus lithium. The probability of curing hyperthyroidism was higher and its control prompter (P = 0.02) in the radioiodine-plus-lithium group. Patients with ≤40 mL goiters had similar persistence of hyperthyroidism (13%), but lithium-treated patients had hyperthyroidism controlled earlier (P = 0.04). Among patients with >40 mL goiters, hyperthyroidism was cured in 6 of 15 patients (40%) treated with radioiodine alone and in 12 of 16 patients (75%) treated with radioiodine plus lithium (P = 0.07), and cure occurred earlier in the latter (P = 0.05). Goiters shrank in both groups (P < 0.0001), more effectively and promptly (P < 0.0005) in the radioiodine-plus-lithium group. Serum free T₄ and T₃ levels increased shortly after therapy only in the radioiodine group (P < 0.01).

Lithium carbonate enhances the effectiveness of radioiodine therapy, in terms of prompter control of hyperthyroidism, in patients with small or large goiters. In the latter group, lithium also increases the rate of permanent control of hyperthyroidism. (J Clin Endocrinol Metab 84: 499–503, 1999)
Action of lithium

• Bogazzi et. al. (1999)
• Patients randomised
• 55 RAI alone (521 + 148 MBq)
• 55 Lithium + RAI (556 + 141 MBq)
• (not blinded)
• Lithium 900 mg/day for 6 days starting on day of RAI
Action of lithium

- Cure occurred in 45 of 54 patients who had lithium (83%)

- Cure occurred in 33 of 46 patients (72%) of controls
A Randomized Controlled Trial to Evaluate the Adjuvant Effect of Lithium on Radioiodine Treatment of Hyperthyroidism

C.S. Bal,1 Ajay Kumar,1 and R.M. Pandey2

Objective: To evaluate the role of lithium (Li) as an adjuvant in radioiodine therapy of hyperthyroidism. Methods: A randomized controlled trial was carried out on 350 hyperthyroid patients with a mean follow-up period of 32.3 ± 9.8 months (range, 12–60 months). The patients were randomized into two groups with 175 patients in each group: (1) radioiodine group (controls)—no lithium was given to these patients at any stage of their treatment and (2) radioiodine and lithium group (Li group)—lithium carbonate, 300 mg three times a day, for 3 weeks starting on the day of radioiodine administration. All patients were made euthyroid with antithyroid drugs prior to radioiodine therapy. Results: Mean age was 41.8 ± 11.5 years (range, 18–71) in the control group and 41.8 ± 12.2 years (range, 19–73) in the Li group. Mean first dose and cumulative dose of $^{131}$I were 229 ± 85 MBq and 326 ± 204 MBq in controls and 233 ± 110 MBq and 344 ± 281 MBq in the Li group. Average number of radioiodine therapy administered was the same (1.4) in both groups. The cure rate (euthyroid plus hypothyroid) after the first dose of radioiodine in the control and the lithium groups was 68.4% and 68.9%, respectively ($p = ns$). The overall cure rate at the end of the study was also the same in both groups (96.7% and 96.3%, respectively). Even in patients with a rapidly discharging gland or in patients with a large goiter, no significant statistical difference was observed in radioiodine therapy outcome between the two groups. Ten percent of the patients complained of mild to moderate side effects of lithium. Conclusion: The role of lithium as an adjuvant in radioiodine therapy of hyperthyroidism is insignificant.
Bal et al. (2002)

- Randomised
- N=175 per group
- Lithium 300 mg tds from day of RAI
- 230 MBq
- Cure rate 68.4% vs. 68.9%
Radioiodine

• Swallow a capsule containing about 500 MBq (13.5 mCi) of the isotope I (131)
• Contraindicated in pregnancy
• Need to avoid children and pregnant mums for a few days
Pregnancy and RAI

• Radioiodine contraindicated in pregnancy and breastfeeding.

• Use in women of childbearing age?
Case 6

- 30 year old Graves during pregnancy
- Managed on 50mg PTU during pregnancy
- FT4=12pM, TSH <0.05 throughout
- Delivered early May 2007
- 15th June 2007: FT4=27pM (11-24)
- 21st June 2007: “felt palpitations”
- 29th June 2007: FT4=102 pM
Plan

• Stop breast feeding.
• Increase PTU to 400 mg
• Should have come under control in 2 months… did eventually by October!
• May 2008: Wants another baby
• Still on 50 mg PTU with TSH <0.05
Who would use RAI now?
Exophthalmos and RAI

• Occurs in smokers.
• Many doctors put off using RAI.
• Risk very small
• Can be prevented by using steroids
• Avoid hypothyroidism post RAI
Bartelena (NEJM)

• Showed that exopthalmos was more likely to occur in smokers who had RAI than other treatments and that this could be prevented with steroids.

• BMJ editorial (Walsh, Dayan and Potts).
Radioiodine and thyroid eye disease

Use with caution

Ophthalmopathy is a characteristic feature of Graves' disease, although it is usually mild or subclinical. Enlargement of the extraocular muscle can be shown by computed tomography or magnetic resonance scanning in most patients with autoimmune hyperthyroidism, but only in 10-25% of cases does this result in clinically important problems such as proptosis, conjunctival oedema, or ophthalmoplegia—andal the dreaded complication of optic nerve compression is mercifully rare.1 When it does occur, however, severe thyroid eye disease is difficult to treat and may result in disfigurement, diplopia, or visual loss. Radioactive iodine (I-131) is widely used to treat the thyrotoxicosis of Graves' disease, but, despite its demonstrable efficacy and safety,2 there have long been concerns about its possible adverse effect on thyroid eye disease. Recently definitive evidence for this link has been presented.3 As a result, all doctors should now be aware that radioiodine should be used with caution in patients with ophthalmopathy.

In their large, well designed study Bartalena et al treated 445 patients with Graves' hyperthyroidism and mild or no ophthalmopathy with methimazole until euthyroid, then randomly allocated them to continued

The trial excluded patients with pre-existing moderate or severe eye disease, in whom such an exacerbation could have been disastrous. The study conclusively shows an adverse effect of radioiodine on thyroid eye disease compared to methimazole. It confirms the results of a previous randomised trial,4 which was criticised on methodological grounds.5

The mechanism by which radioiodine exacerbates ophthalmopathy is poorly understood, as is the pathogenesis of thyroid eye disease in general. Two plausible theories have been advanced.1 The first is that radiation induced thyroid damage releases one or more antigens which are shared by thyroid and retro-orbital tissues, resulting in immune mediated ophthalmopathy. Putative antigens include a 64 kDa protein which has been isolated from eye muscle and thyroid16 and the receptor for thyroid stimulating hormone, which is expressed in retro-orbital tissues as well as in thyrocytes.7 Recently an animal model for thyroid eye disease has been developed in mice treated with syngeneic lymphocytes sensitised to the human thyroid stimulating hormone receptor.7 This strengthens the role of the receptor in thyroid eye disease and should lead to further productive research. The mechanism by which radioiodine may exacer-
Editorial

- BMJ editorial (Walsh, Dayan and Potts): “use with caution”

- “Avoid RAI in anyone with exophthalmos”.
• 443 randomised to RAI, or methimazole or RAI with pred.
• 150 got RAI
• 23 of 150 worse eye disease (16%)

4 of 148 methimazole worse (3%)
19 of 82 smokers (23% risk)

• 4 of 148 methimazole worse (3%)
• Much controversy (Nouri et al).
• Balanced update (Bartalena: 2002)
• RAI should not be avoided in patients with exophthalmos
• Avoid hypothyroidism
• Stop smoking
• Use steroids in smokers.
Viral thyroiditis
Natural history of viral thyroiditis

- Virus attacks thyroid gland causing pain and tenderness
- Thyroid stops making thyroxine and makes viruses instead
- Thus no iodine uptake (ZERO)
Thyroid scan in viral thyroiditis
Viral thyroiditis

• Radioiodine uptake zero
• Stored thyroxine released
• Thus toxic with zero uptake

• Four weeks later, stored thyroxine exhausted, so hypothyroid.
Viral thyroiditis

• After a further month, resolution occurs (like in all viral diseases).

• Patient then becomes euthyroid again.
Viral thyroiditis

- 1 month hyperthyroid
- 1 month hypothyroid
- Resolution.