Endocrinology: Interpreting Endocrine Tests
GP Refresher course 2012
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Why are we talking about this?
• Endocrine telephone advice clinic
• Set up in May 2010
• Service for GP’s
  – Referral by telephone, fax or email (or C&B)
  – Discussion of new patients not known to hospital
  – Care closer to home
  – Telephone consultation rather than email correspondence
  – Improved clinical care and two-way education
• First audited at 18 months after setup

Demographics
• Slow set-up phase and publicity!
• 167 referrals in first 18 months
• Used by 95 GPs at 48 different practices
• 23 of these practices were within Tower Hamlets
• 36 GPs (38%) used the service more than once, some multiple times

Referral themes
Outcomes:
124 (74.3%) were dealt with by telephone only
37 (22.2%) required a new patient endocrine appointment (sometimes for patient reassurance or because too late to cancel)
A handful were referred to other clinics: infertility (2), urology (1), lipids (1) and rheumatology (1).

Satisfaction survey
• 75% found it easy to make a referral.
• 89% received a timely call-back.
• 86% would use the service again.
• 79% believed that the service enabled them to manage a patient in primary care that otherwise would have been referred in.
• Very positive qualitative feedback
What are we going to do

• Focus on the thyroid specifically
• Time at the end to discuss other areas (or maybe on another day)
• Key take home messages about interpretation of tests
  – General
  – Specific

Key general take-home messages

• Only request an investigation if you are clear about how it might help you
• Only request an investigation if you understand how to interpret the results
• ONLY INTERPRET THE RESULTS IN THE CONTEXT OF THE CLINICAL INFORMATION – HISTORY AND EXAMINATION FINDINGS
• If in doubt, seek help

Thyroid gland

Cellular production

Thyroid hormones

Actions

• Metabolic rate
• Thermoregulation
• Appetite
• Specific tissue effects (bone, brain)
• Sensitivity of sympathetic system
• Feedback
• Nuclear vs Extranuclear effects
What can go wrong?

• Too much
• Too little
• Just right
  (but structurally not)
  (maybe, like the porridge, a bit lumpy?)

Thyroid number crunching

• Thyroid problems account for over 50% of our telephone consults
• Good UK data comes from the Whickham survey (nr Gateshead)
• N=2779; 20 year follow up for 97% of the sample published in 1995; just under 30% had died, most of the survivors were still living in the North-East
• At time of follow up median age of survey survivors was 58 (range 38-93)


Thyroid function - Whickham

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean incidence of spontaneous hypothyroidism</td>
<td>3.5 / 1000 survivors/ year (2.8-4.5)</td>
<td></td>
</tr>
<tr>
<td>Mean incidence of all-cause hypothyroidism</td>
<td>4.1 / 1000 survivors/ year (3.3-5.2)</td>
<td>0.5 (0.3-1.2)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>0.8 / 1000 survivors/ year (0.5-1.4)</td>
<td>negligible</td>
</tr>
<tr>
<td>Frequency of goitre at first survey</td>
<td>23%</td>
<td>5%</td>
</tr>
<tr>
<td>Frequency of goitre in survivors at follow up</td>
<td>10%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Age-specific hazard rates increase for hypothyroidism in women but not for hyperthyroidism

Hyperthyroidism

Prevalence

• Prevalence of overt thyrotoxicosis is about 0.5% (more frequent in women than men)
• 1%-2% of patients have a below-normal TSH level (‘compensated’ or ‘subclinical’ hyperthyroidism)
• Low TSH is seen in 3% of the population older than 80 years

Risk Factors

• Autoimmune
• TMNG or single nodule
• Drugs causing uncontrolled release of thyroid hormone
• Risk factors for thyroid inflammation

Hypothyroidism

Prevalence

• more common in women
• total prevalence of 1% to 2%
• increases with age (~10% adults >65 years)
• In the U.S. population, prevalence of biochemical hypothyroidism is 4.6%, but clinically evident hypothyroidism is present in 0.3%
• Congenital hypothyroidism is among the most common congenital disorders, with an incidence of 1/4000 newborns

Risk Factors

• Family or personal history of autoimmune disease
• Women in the postpartum period
• Personal history of neck or head irradiation
• Primary pulmonary hypertension
• Genetic syndromes: Turner’s and Down syndromes
• Patients treated with amiodarone, interferon-alpha, or lithium
• Persons over 65 years of age

Thyroid cancer

In 2008, 2,154 people were diagnosed with thyroid cancer in the UK. Thyroid cancer is within the top twenty most common cancers for UK females (number 18), with 1,596 new cases diagnosed in 2008. This compares to 558 cases in males - giving a male:female ratio of 1:3.

Estimated lifetime risk of thyroid cancer in 2008 is 1 in 650 for men and 1 in 243 for women in the UK.
Our thyroid GP queries

What shall we cover?

Too much
Easy?
- Thyrotoxicosis

Challenges
- ‘subclinical’
- Pregnancy
- Drugs
- Thyroiditis

Too little
Easy?
- Hypothyroid

Challenges
- ‘subclinical’
- Pregnancy

Just Right

• Approach to the patient with a goitre
• Approach to the patient with a thyroid nodule

Symptoms and signs of thyroid dysfunction

Thyroid hormone regulation

HYPERTHYROIDISM
Thyrotoxicosis

- A 34 year old lady comes to see you. She complains of a change in bowel habit. You elicit a history of 2 stone weight loss but no PR bleeding or melaena.
- On direct questioning you ask directly about anxiety, sleep, fidgeting, sweating, palpitation and periods.
- What other questions would you like to ask the patient?
- What is going through your mind?
- What features do you try and elicit on examination?
- What do these tell you?
- What investigations would you like to perform?

First investigations

- TSH < 0.02 (range 0.3 – 4.2)
- Free T4 32.6 pmol/l (range 9.0-25.5)

Anything else you would like to know on investigation?

What next?

- Total T3 6.7 nmol/l (range 2.5-5.7 pmol/l)
- TPO antibodies raised at 700
- TSH receptor antibodies raised

- Discuss the biochemistry?
- Do you need any imaging?
- What do you do next?
- What is the differential diagnosis?
- What are the treatment options? What aspects will need to be considered in treatment choices?

Thyrotoxicosis – when is it a challenge?

- When it is ‘subclinical’ or compensated
- When the patient is pregnant
- When the blood tests don’t make sense
- When it is iatrogenic and unwanted
- When it is iatrogenic and desirable
- When the treatments are contraindicated

Challenge 1

- 65 year old man
- Well
- Presents with a TIA, noted to be in atrial fibrillation, possibly longstanding
- No other symptoms or signs
- Routine investigations:
  - TSH < 0.02  T4 20.9 pmol/l
- Any other information you would wish for?
- Additional investigations you might like?
- Differential diagnosis?
Evidence for Action?

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Benefits of treatment</th>
<th>Serum TSH = 0.1–0.45 mU/L</th>
<th>Serum TSH &lt; 0.1 mU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to overt hyperthyroidism</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Adverse cardiac endpoints apart from atrial fibrillation</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>None</td>
<td>None</td>
<td>None / evidence with increasing age</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>* Insufficient</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Systemic hyperthyroid and neuropsychiatric symptoms</td>
<td>None</td>
<td>Insufficient</td>
<td>None</td>
</tr>
<tr>
<td>Reduced bone mineral density</td>
<td>None</td>
<td>None</td>
<td>Fair</td>
</tr>
<tr>
<td>Fractures</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

* Data did not distinguish between serum TSH concentrations of 0.1–0.45 mU/L and TSH concentrations less than 0.1 mU/L.

TSH = thyroid-stimulating hormone.

Quality of evidence on the risks and benefits of treatment of subclinical hyperthyroidism.

Action?

Treatment of subclinical hyperthyroidism:

- The consensus guideline highlighted the differences in expert opinions and published guidance on the management of subclinical thyroid diseases. There is uncertainty whether people with persistent subclinical hyperthyroidism should be treated.
- A recent survey of UK endocrinologists (40% response rate: 279 responded) indicated treatment for subclinical hyperthyroidism is more likely in the presence of paroxysmal atrial fibrillation or osteoporosis (Vaidya et al, 2007).
- Specialists referred for persistent subclinical hyperthyroidism recommended to investigate any evidence of underlying nodular or Graves’ disease (based on clinical, immunological, or imaging findings) and to consider the need for treatment (e.g., with iodine-131 or antithyroid drugs) (BTA et al, 2006).
- No randomized controlled trial has evaluated the effect of radioiodine or antithyroid drug treatment on long-term morbidity or mortality in subclinical hyperthyroidism.

Long-term follow up:

- Regular monitoring of thyroid function is recommended to exclude progression to overt hyperthyroidism and to determine whether biochemical abnormality is persistent, particularly in untreated individuals with undetectable thyroid stimulating hormone (TSH).
- More frequent follow-up is recommended for elderly individuals because of the increased risk of atrial fibrillation and increased cardiovascular mortality.

Challenge 2:

- A 24 year old lady with attends your antenatal clinic following a positive pregnancy test. She complains of excessive vomiting. Her TSH is undetectable with a free T4 of 22.0 pmol/l

Pregnancy issues

1) Pregnancy-specific thyroid reference ranges
2) Hyperemesis and Hyperthyroidism – the role of HCG
3) Antithyroid drugs in pregnancy
4) Graves disease during pregnancy

Ranges for T4:

• 1st trimester 11.6 – 19.2 pmol/l
• 2nd trimester 9.3 – 16.3 pmol/l
• 3rd trimester 8.0 – 15.2 pmol/l

For TSH:

Note: up to 20% of pregnant women can have an undetectable TSH and be euthyroid.

Hyperemesis and Hyperthyroidism – the role of HCG

• Alpha subunit common to several hormones

Antithyroid drugs in pregnancy.

• Lowest dose possible.
• PTU preferred to CBZ (although actually only relevant for organogenesis)
• Generally safe

Graves disease during pregnancy

• Should remit
• Watch for postpartum relapse
Challenge 3:
• A 21 year old Somalian lady presented with a small goitre. She is asymptomatic. She has had some blood tests performed.
• TSH 4.4
• Free T4 32.1 pmol/l total T3 2.7 pmol/l
• What might be going on here?

Apparent hyperthyroidism, TSH not suppressed
• Assay interference
• Thyrotropinoma
• Thyroid hormone resistance syndromes
• Recent iatrogenic excess

How to distinguish?
1) Interpret only in the context of the clinical picture
2) Sport for your endocrine colleagues!

Challenge 4:
• A 64 year old gentleman under the care of the cardiology clinic attends the surgery. He has been having treatment for intermittent atrial fibrillation but has been asymptomatic for 2 years. He has now developed severe and persistent palpitations. On examination his pulse is 110 and is irregularly irregular, he looks sweaty, thin and unwell and he has a small goitre.
• TSH <0.02 free T4 30.5 total T3 4.5
• What is going on?

Amiodarone-induced hyperthyroidism
• Amiodarone is a potent antiarrhythmic drug
• It contains approximately 37% iodine by weight.
• Standard maintenance therapy (200 mg od) can provide more than 100 times the daily iodine requirement.
• Variable elimination half-life: 50-100 days
• Total body iodine increased for up to 9/12 after stopping
• Thyroid abnormalities in up to 14-18% of users
• Lower doses (150-330 mg) associated with incidence of 3.7% thyroid dysfunction
• Hypothyroidism is easy to manage, hyperthyroidism not so
• Type 1 (abnormal gland); Type 2 (previously normal gland, destructive thyroiditis)

Other drugs affecting the thyroid
• Lithium
• Iodine (including radiographic contrast)
• Interferon alfa
• Interleukin 2
• Tyrosine kinase inhibitors

Challenge 5:
• A 45 year old lady is fit and well but takes levothyroxine long term as she has previously had a total thyroidectomy at the age of 40. At routine checkup her TSH is <0.02 and her free T4 is 20.3 pmol/l
   — What else do you need to know before advising her about her dosage?

• A 48 year old lady under your care is fit and well but takes a number of medications suggested by the endocrine clinic for hypopituitarism, induced by previous pituitary irradiation for NFPA. She currently takes levothyroxine 125 mcg. Her TSH is <0.02 and her free T4 is 20.3 pmol/l
   — How do you advise her regarding her medication?
Sometimes low TSH is desirable

- TSH suppression is part of the therapy following surgery (with or without radioiodine ablation) for differentiated thyroid cancer
- TSH will be low in secondary hypothyroidism. For these patients TSH cannot be used as a yardstick for therapy titration. Aim to keep the patient asymptomatic and with a T4 in the upper half of the reference range.

Challenge 6 (and beyond):

- The thyrotoxic patient who is symptomatic and starting antithyroid drugs but who is intolerant of beta blockade due to asthma
- The thyrotoxic patient who develops a side effect on antithyroid medication
- The thyrotoxic patient who will not comply with antithyroid medication because of a desire to lose weight / displacement eating disorder (?effect of thyrotoxicosis on mental state)

HYPOTHYROIDISM

People who may be at increased risk of hypothyroidism

- Those with other autoimmune disease, e.g. type 1 diabetes, Addison’s disease, coeliac disease
- Those with a genetic condition such as Down or Turner syndromes
- Those who have had treatment with radioactive iodine therapy or surgery for hyperthyroidism
- Those who have had radiotherapy to the neck for head and neck cancer
- Those with a history of postpartum thyroiditis

adapted from Vaidya, 2008
Hypothyroidism

• A 59 year old lady comes to see you. She feels tired all the time and seems to be gradually gaining weight.
• On direct questioning you ask directly about her hair and skin, her energy levels, sense of mental ‘sharpness’ and her bowel habit.
• What other questions would you like to ask the patient?
• What is going through your mind?
• What features do you try and elicit on examination?
• What do these tell you?
• What investigations would you like to perform?

First investigations

• TSH 15 (range 0.3 – 4.2)
• Free T4 8.8 pmol/l (range 9.0-25.5)

Anything else you would like to know on investigation?

What next?

• Total T3 3.5 pmol/l (range 2.5-5.7 pmol/l)
• TPO antibodies raised at 700
• Other autoantibodies (liver/kidney/microsomal; GPA etc negative)
• Discuss the biochemistry?
• Do you need any imaging?
• What do you do next?
• What is the differential diagnosis?
• What should the treatment be? What aspects will need to be considered in treatment?

Hypothyroidism – when is it a challenge?

• When it is subclinical or compensated
• When there is a concurrent cortisol deficiency
• When the blood tests don’t make sense (usually pituitary; also amiodarone)
• When the blood tests don’t make sense (non compliance or non absorption or late compliance before a blood test)
• When the patient ‘still doesn’t feel right’ or has been ‘reading on the internet’

Challenge 1:

• A 59 year old lady comes to see you. She feels tired all the time and seems to be gradually gaining weight.
• On direct questioning you ask directly about her hair and skin, her energy levels, sense of mental ‘sharpness’ and her bowel habit.
• Her TSH is 6.1 and her total T4 is 14.0 pmol/l
• How do you counsel her? What do you do?

Evidence for Action?
But this assumes NO symptoms

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Strength of association</th>
<th>Benefits of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to overt hypothyroidism</td>
<td>Good</td>
<td>Variable*</td>
</tr>
<tr>
<td>Adverse cardiac end points</td>
<td>Insufficient*</td>
<td>No evidence</td>
</tr>
<tr>
<td>Elevation in serum total cholesterol and LDL-C levels</td>
<td>Insufficient*</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>Insufficient*</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Systemic hypothyroid symptoms</td>
<td>No clear evidence</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td>No clear evidence</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Quality of Evidence on the Strength of Association and Risks/Benefits of Levothyroxine Treatment of Subclinical Hypothyroidism for Patients With a Serum TSH Level of 4.5 to 10.0 mIU/L (consensus to treat >10)
Special case: Treatment during pregnancy

Challenge 2:
- A 34 year old lady who is under your care with type 1 diabetes and pernicious anaemia attends the surgery feeling tired all the time
- Her blood tests show a TSH of 13.1 and a free T4 of 7.7
- You prescribe thyroxine 50mcg daily to increase after a period to 100mcg daily
- You hear that she has been admitted to hospital with worsening hypos and with low blood pressure. She has felt significantly worse after starting the thyroxine replacement therapy.
- What do you think is going on?

Cortisol deficiency
- Autoimmune hypothyroidism may coexist with other autoimmune conditions which occasionally include adrenal insufficiency (Addison’s disease)
- Commencement of thyroxine replacement in the presence of cortisol deficiency may precipitate an Addisonian crisis
- 9am cortisol of >500nmol/l implies that adrenal function is adequate without recourse to further dynamic testing of the axis

Challenge 3:
- A 60 year old man attends the surgery complaining of fatigue
- He has dry skin and dry hair and is complaining of mental ‘slowness’ and also constipation, although his weight has not been increasing
- His TSH is 0.4 with a free T4 of 6.6 pmol/l
- What would you do next and what do you think might be happening?
- What do you need to do?

Challenge 4:
- Blood test results that don’t make sense
- Patterns to think about:
  - Low TSH low T4
  - Drug induced patterns
  - Non compliance
  - Non absorption
- Do the right evaluation before considering whether and how to replace

Challenge 5:
- A 24 year old lady who has been receiving thyroxine replacement therapy for autoimmune hypothyroidism comes to see you at the surgery. She complains that she feels fatigued and that she is unable to lose weight. You reassure her that her thyroid function tests are entirely normal. She has been reading a great deal on the internet and wonders if additional T3 or a more “natural” form of thyroid replacement might be more suitable for her.
‘I still don’t feel right doctor’

- Does the manufacturer matter?
- What about T4/T3 combinations?
- What about ‘armour thyroid’

THE PATIENT WITH A NECK SWELLING

Possibilities

- Smooth goitre
- Multinodular goitre
- Dominant Nodule in a nodular goitre
- Single thyroid nodule – benign or malignant
- Thyroid other abnormality (eg thyroglossal cyst)
- Non-thyroid swelling

Assessment

- Details of history (location, duration, change, pain etc)
- Risk factors for thyroid cancer including radiation exposure, family history, genetic predisposition (and state if none)
- Impact on
  - swallowing
  - breathing
  - cosmesis
- Assessment of thyroid status
- Examination for nature and impact of the swelling (include effect on voice, presence of stridor = urgent referral)
- Thyroid function tests BEFORE DECIDING WHAT TO DO NEXT
- ‘Knee-jerk’ USS thyroid without thought or TFTs can lead to a path of no return to unnecessary thyroidectomy

If in doubt

- Your own clinical assessment
- TFT’s !!!
- One-stop neck lump assessment
- Or if you are asking for USS be very specific in your request
  - What you know about the patient and malignancy risk
  - What you want reviewed on the scan (single or multiple nodules? ANY SUSPICIOUS FEATURES?)

Take home messages

- We have focussed on thyroid assessment and TFT evaluation
- We have covered easy findings and challenging pitfalls
- Only request an investigation if you are clear about how it might help you
- Only request an investigation if you understand how to interpret the results
- ONLY INTERPRET THE RESULTS IN THE CONTEXT OF THE CLINICAL INFORMATION – HISTORY AND EXAMINATION FINDINGS
- If in doubt, seek help
Thank you for your attention

Happy to discuss questions either on the thyroid issues we have raised or on any of the other common topics in the GP phone clinic.....