Clinical and biochemical suspicion of pheochromocytoma due to fluctuating thyroid tests in a patient with medullary thyroid cancer

CH Hariman, L Pelluri, S Sankar, MO Weickert
University Hospitals Coventry & Warwickshire, Coventry, UK

Abstract

Introduction: Phaeochromocytoma is a rare and potentially life threatening condition. It can present with non specific symptoms of palpitations, headache and hypertension. Such symptoms in a patient with background of previous medullary thyroid carcinoma cannot be ignored and would warrant further investigation for possible MEN II.
Case report: A 45 year old gentleman presented with labile hypertension, headaches and palpitations. He had a history of a recurrent medullary thyroid carcinoma, previously managed with total thyroidectomy and external beam radiotherapy. He has been on a relatively high replacement dose of 225 micrograms of L-Thyroxine but initially showed a higher normal TSH of 4.33 mU/L, indicating that the dose was adequate. Phaeochromocytoma was suspected and investigated given his persistent symptoms. Three separate collections of urinary catecholamines showed mildly elevated levels of free noradrenaline between 635-944 nmol/collection (ULN <601 nmol/collection). Genetic testing confirmed RET oncogene as negative. Nuclearscintigraphic imaging did not support presence of a pheochromocytoma or paraganglioma. The patient's thyroid function tests were repeated and showed over-replacement with suppressed TSH and above normal fT4, despite unchanged replacement doses. L-Thyroxine replacement was reduced to 175 micrograms to attain a biochemical euthyroid state. Both his symptoms and urinary catecholamines returned to normal .
Conclusion: Impaired absorption of L-Thyroxine can result in fluctuating thyroid function tests, thereby both clinically and biochemically imitating a possible pheochromocytoma.

History

45 year old man with known history of metastatic medullary thyroid carcinoma with previous total thyroidectomy, bilateral neck dissection and radiotherapy treatment presented to clinic in 2010 with symptoms of feeling generally unwell, recurrent sweats and palpitations.

He was taking 225 micrograms of Levothyroxine, on many occasions directly before ort alongside food ingestion.

He underwent multiple urinary collections between 2010 - 2012 for urinary noradrenaline for suspected Phaeochromocytoma ,due to his presistent symptoms (Table 1). On repeated occasions, his urinary noradrenaline levels were elevated rising a suspicion of possible Phaeochromocytoma.

He underwent an MIBG Scintigraphy scan and an Ocrtreotide scan (Image 1) which had shown moderate to marked focal increased uptake in the right supraclavicular region/ superior mediastinum, in keeping with metastatic medullary thyroid carcinoma recurrence, but no increased uptake elsewhere.

His Levothyroxine was reduced to a calculated replacement dose of 175 micrograms OD and he was advised to take L-Thyroxine at least 30 min before food intake and isolated from other tablets. Subsequently, his symptoms of sweats and palpitations abated, and his urinary catecholamine normalised (Table 2)

	Urine Adrenaline nmol/ collection (NR < 101)	Urine noradrenaline nmol/ collection (NR <601)	Urine Volume L	TSH mU/L	fT4 pmol/L
07/05/2010	84	944	4.002	4.33	
15/09/2011	39	635	2.293		
14/03/2012	18	588	3.630	<0.02	34.1

Table 1

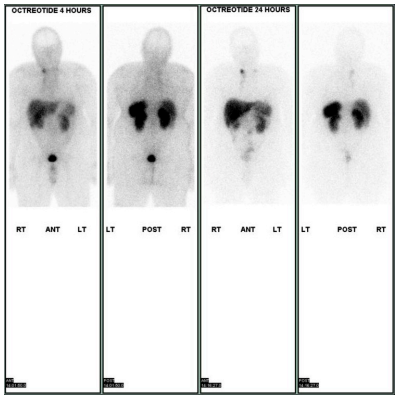

Image 1

	Urine Adrenaline nmol/ collection (NR <101)	Urine noradrenaline nmol/ collection (NR <601)	Urine Volume L	TSH mU/L	fT4 pmol/L
25/09/2012	35	295	2.458	0.69	17.2

Table 2

Literature review

Thyroxine and catecholamine homeostasis

Thyroid and catecholamine homeostasis may be closely interlinked (1)(2). Thyrotoxic patients, regardless the cause, can display similar clinical presentation to patients with intermittent catecholamine excess such as Phaeochromocytoma.

Thyroid hormones correlate and interact with levels of urinary/plasma catecholamines (3)(4)(5)(6). However, in our presented case, his initial thyroid function tests were normal. This was likely related to impaired and fluctuating absorption of Levothyroxine, which was initially ingested alongside food. Most notably, many foods which are typically consumed at breakfast, such as coffee, fruit juices and cereal fibres have been shown to affect the absorption of Levothyroxine. (7)(8)(9)(10).

Intermittent thyroxine absorption

The effects of food ingestion, especially the intake of dietary fibre, soy products, coffee and various common drugs such as calcium supplementations, proton-pump inhibitors on the reliability of Levothyroxine absorption is well documented (11)(12). Levothyroxine also enhances the effect of catecholamines without increasing the adrenergic drive (13)(14). A combination effect of high doses of Levothyroxine triggered by intermittent reduced absorption had very likely precipitated this patient's symptoms despite his varying degree of urinary catecholamine.

The BNF suggests that Levothyroxine should be taken "preferably before food intake". More specific advice, e.g. to suggest taking Levothyroxine at least 30 min before food and isolated from other tablets would be preferable in this context.

Other possible causes of false positive urinary test

Although this gentleman was unlikely to have a Phaeochromocytoma following his MIBG and Octreotide scan, there may be other causes of his falsely elevated urinary catecholamines. Certain commonly used drugs such as B-complex vitamins, erythromycin antibiotics, salycilates, tetracyclines, chlorpromazine, amitriptylline, methyldopa, beta-blockers, and calcium channel blockers may cause an incorrect elevated level of fractionated urinary metadrenaline and free catecholamines by fluoroscene interference (15)(16).

The use of Lamotrigine, and the newer antipsychotic Aripiprazole or a combination of the two medication has also been associated with false-positive elevation of urinary catecholamines(17).

Discussion

1.As this patient's care was transferred from abroad (New Zealand), what could have been done to reduce errors?

2.Weight and BMI should be used to calculate Levothyroxine dose

3.BMI should be a preferred method of calculating thyroid requirements in patients who are under or overweight(18)

Conclusion

Patients who are in a state of excess thyroid hormone display similar clinical features to patients with Phaeochromocytoma. An incorrect clinical management of a patient with metastatic medullary thyroid carcinoma with over replacement with thyroxine has lead to further unnecessary investigations.

Contact Details

Dr. Christian H Hariman MBChB MRCP

WISDEM Centre
University Hospital Coventry & Warwickshire
Clifford Bridge Road
Coventry
CV2 2DX
christian.hariman@uhcw.nhs.uk

References

1.George A Bray. Studies on the interaction of thyroid hormones and catecholamines. 1964. Journal of Clinical Investigation 43: 2; 285 – 294

2.Victor Parsons, Ian Ramsay. Thyroid and adrenal relationships. 1968. Postgraduate Medical Journal 44: 377 - 384

3.Stoffer, S. S., N. S. Jiang, C. A. Gorman, and G. M. Pickler. 1973. Plasma catecholamines in hypothyroidism and hyperthyroidism, Journal of Clinical Endocrinology and Metabolism 36: 587.

4.Christensen, N. J. 1973. Increased levels of plasma noradrenaline in hypothyroidism. Journal of Clinical Endocrinology and Metabolism 35: 359, 1973.

5.Pierre Coulumbe, J.H. Dussault, J. Letarte, S.J. Simard. 1976. Catecholamines Metabolism in thyroid diseases I. Epinephrine secretion rate in hyperthyroidism and hypothyroidism. Journal of Clinical Endocrinology and Metabolism 42(1): 125-131.

6.Pierre Coulumbe, J.H. Dussault, P. Walker. 1977. Catecholamines Metabolism in Thyroid disease II. Norepinephrine secretion rate in hyperthyroidism and hypothyroidism.

7.Benvenga S, Bartolone L, Pappalardo MA, Russo A, Lapa D, Giogianni G, Saraceno G, Timarchi F. 2008. Impaired intestinal absorption of Levothyroxine caused by coffee. Thyroid. 18(3): 291-301.

8.Benvenga S, Bartolone L, Squadrito S, et al. 1995. Delayed intestinal absorption of levothyroxine. Thyroid 5(4):249-253

9.Bailey DG. 2010. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. British Journal of Clinical Pharmacology; 70(5): 645-655.

10.Liel Y, Harman-Boehm I, Shany S. 1996. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. The Journal of clinical Endocrinology & Metabolism; 81(2): 857-859.

11.Nalini Singh, Shawna L. Weisler, and Jerome M. Hershman.2001. The acute effect of calcium carbonate on the intestinal absorption of Levothyroxine. Thyroid. 11(10): 967-971

12.Eligar PV, Eligar VS. 2011. Levothyroxine: factors affecting its intestinal absorption and metabolism. The West London Medical Journal; 3(4): 9-14

13.Gelfand, RA; Hutchinson-Williams, KA; Bonde, AA; Castellino, P; Sherwin, RS. 1987. Catabolic effects of thyroid hormone excess: the contribution of adrenergic activity to hypermetabolism and protein breakdown. *Metabolism: clinical and experimental* ***36 (6): 562–9***

14.Levey GS, Klein I. 1990. Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. American Journal of Medicine 88(6): 642-646

15.Wendell T Caraway, Carl W Kammeyer. 1972. Chemical Interference by drugs and other substances with clinical laboratory test procedures. Clinica Chimica Acta 41: 395 – 434

16.Huda Al-kutubi. Joanne Greenwood, Atul Kalhan, Maneesh Udiawar, Aled Rees. 2011. An Analysis of false positive urinary catecholamine and metabolite results in a tertiary endocrine centre. Endocrine Abstracts (2011) 25 P59

17.Vijay Shivaswamy, Whitney S Goldner, Joseph Erwin. 2007. Possible new causes for false-positive diagnosis of phaechromocytoma: Lamotrigine, Aripiprazle or the combination. Primary Care Companinon Journal of Clinical Psychiatry; 9(2): 154.

18.Ojomo KA, Schneider DF, Reiher AE, Lai N, Schaefer S, Chen H, Sippel RS. 2013. Journal of American College of Surgeons; 213(3): 454-460

University Hospitals Coventry and Warwickshire NHS Trust