ANOMALOUS THYROID RESULTS – YET ANOTHER CAUSE

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Thyroid function tests (TFTs') are one of the most common tests requested. Interpretation of most TFTs' are straight forward. TFTs' can be confusing in an important subgroup of patients. We present such a case in a previously healthy individual.

Case description:

A 22 years old college going individual was referred to the Thyroid Clinic with symptoms of dizziness, palpitations and episodes of shakiness of his hands which he could not elaborate more. He had persistent anomalous thyroid test (table 1) results with free T3 level being in the normal range, slightly raise FT4 levels and normal TSH of 1.08 mU/l. There was no history of weight loss, increased bowel movements of hair loss. He was an adoptee and had been told that his biological mother probably had a thyroid abnormality diagnosed in Hong Kong. He had recently split from his girlfriend and was coming to terms in coping with the separation.

Table 1 Thyroid Function tests:

	09.12.15	04.01.16	24.03.16	03.05.16	20.08.16
TSH (0.30-4.40 mU/L)	0.76	1.08	1.04	0.65	0.47
FT4 (9.0-22.0 pmol/L)	23.2	22.5	46.2	21.2	20.1
FT3 (5.0-7.5 pmol/L)	5.9	5.2		4.6	

Clinical examination revealed a healthy young man with no signs of thyroid dysfunction, goitre or orbitopathy. His pulse rate was 60/min and with dropped beats. His systems examination was normal. ECGs showed isolated ventricular ectopics with broad complexes. His echocardiogram was normal. He was reviewed in the cardiology clinic and was later discharged.

Possible differentials at this point included assay interference, thyroid hormone resistance and a TSH secreting pituitary adenoma.

I*nvestigations:*

Investigations were undertaken to rule out TSHoma and the alpha subunits [0.26 IU/L (<3.00)] were normal. Screening for thyroid harmone resistance was done and the SHBG was normal [35 nmol/L (14-71)]. Investigations to rule out assay interference on a different platform (DELFIA) was also undertaken. The free T4 was 22.7 pmol/L (9.0-22.0), free T3 was 7.7 pmol/l (5.0-7.5). Also the serial dilutions showed a linear pattern and PEG showed good recovery. The above tests ruled out assay interference.

Serum sample was sent to Cambridge for further analysis and the total T4 was 259 nmol/L (69.0-141) and Thyroid binding globulin was 14.3ug/ml (14.0-31.0). The discrepancy between the levels of total T4

and free T4 indicated the possibility of a binding protein abnormality. Also the Familial dysalbuminaemic hypethyroxinaemia (FDH) screen was positive.

Discussion:

Familial dysalbuminaemic hypethyroxinaemia (FDH) is an important cause of thyroid function tests being discordant. It was initially Identified in 1979 by Henneman et and the term was introduced in 1982. Precise defect identified only in 1994 independently by Petersen et al [3]. It is the most common inherited cause of increase in serum TT4 in the Caucasian population. It has the highest prevalence in communities of Portuguese or Hispanic origin. It is an autosomal dominant disorder with a prevalence rate is 0.08-0.17% and is the most common form of inherited euthyroid hyperthyroxinaemia. It has no sex predilection and any age group be affected. Patient's family history is an important aspect.

It is caused by a heterozygous mutation in albumin gene on chromosome 4q13 which causes an increased affinity for thyroxine (relative to its affinity to T3) to albumin than for thyroxine binding globulin [4,5]. The mutation increases affinity for T4 by upto 60%. A few different variants have been described which leads to varying affinity of T4 to albumin. Arginine to histidine substitution in codon 218 lead to 10 to 15 fold greater affinity of T4 to albumin, arginine to proline substitution can lead to 14 to 27 fold greater affinity, arginine to histidine substitution in codon 222 can lead to 9 times greater affinity and arginine to isoleucine substitution has also been described. In another variant where a L66P mutation resulted in 40 fold increased affinity to T3 and only 1.5 fold affinity to T4. The condition was called familial dysalbuminemic hypertriiodothyroninemia [7]

Individuals are clinically euthyroid with elevated total T4 and elevated or normal free T4 values within normal TSH levels. FT3 may be slightly elevated. Coexistence of acquired high TBG or significant thyroid malfunction may confound the diagnosis of dysalbuminemic hyperthyroxinemia.

FDH can be confused with hyperthyroidism or thyroid hormone resistance. Binding of drugs by albumin and the release of thyroid hormone to the tissues are not altered in ways that have clinical significance. The importance in diagnosing FDH and differentiating it from other conditions is that it is harmless and if not identified then it could lead to erroneous thyroidectomy or drug therapy [3]. The analogue methods used for measuring free T4 levels in FDH can result in artefactually high FT4 levels but is normal when measured by direct methods such as ultrafiltration or equilibrium dialysis methods [6].

Factors in serum can give false estimations and these include 1) heparin which can cause an artefactual elevation in measured concentrations of FT4/FT3 by displacement of T4 and T3 from their carrier proteins, 2) anti-iodothyronine antibodies which can bind the tracer and give false estimations, 3)HAAs or heterophile antibodies that block the assay antibody and variant thyroid hormone binding proteins (e.g. albumin in FDH) with altered affinity for T4 [1].

Radio immune assays (competition assay) used in diagnosing FDH :

Radio immune assays are useful in diagnosing FDH. In 1-step assay labelled T4 (the tracer) competes with serum T4 for a fixed number of anti-T4 antibody binding sites. Free harmone concentration is determined by the fractional occupancy of antibody binding sites. Equilibrium between T4 and its binding proteins is conserved during measurement, so that the amount of tracer displaced reflects the 'free' rather than 'total' hormone concentration. It is protein-dependent and is prone to under- or overestimate FT4.

In the 2 step assay wash step prior to tracer addition. It may reduce but not completely eliminate such interference. If the problem persists, hormone measurement following equilibrium dialysis (ED) remains the gold-standard for eliminating FT4 assay interference.

	Total T4	Free T4	Increase in TT4
Transthyretin variants	raised	normal	150-200nmol/l
TBG variants	raised	normal	250 nmol/l
Albumin variant	raised	Raised of normal	180-240 nmol/l

Time-of-flight mass spectrometry is a novel procedure for diagnosing familial dysalbuminaemic hyperthyroxinaemi. It is rapid (<10 min) and performed on <2 μL of serum and it requires minimal sample preparation.

References:

1) Elsevier.com. (2019). ClinicalKey | Elsevier. [online] Available at: https://www.elsevier.com/solutions/clinicalkey [Accessed 2 Jun. 2019].

2) Osaki et al. Familial dysalbuminemic Hyperthyroxinemia in a Japanese Man Caused by a point albumin Gene Mutation (R218p). Japanese Clinical Medicine 2016:7 9–13 doi:10.4137/JCM.s38990

3) Endocrine Press | Endocrine Society. Press.endocrine.org. 2019. [accessed 2 Jun 2019] Available from: http://press.endocrine.org/doi/full/10.1210/jcem.85.8.6746

4) ClinicalKey. Clinicalkey.com. 2019. [accessed 2 Jun 2019] Available from: https://www.clinicalkey.com/#!/content/medline/2-s2.0-6173750

5) 1. OMIM Entry - # 615999 - HYPERTHYROXINEMIA, FAMILIAL DYSALBUMINEMIC; FDAH [Internet]. Omim.org. 2021 [cited 15 March 2021]. Available from: http://www.omim.org/entry/61599

6) 2. Registration - Thyroid Disease Manager [Internet]. Thyroid Disease Manager. 2021 [cited 15 March 2021]. Available from: http://www.thyroidmanager.org/chapter/assay-of-thyroid-hormones-and-related-substances/

7) 3. Euthyroid Hyperthyroxinemia Clinical Presentation: History, Physical, Causes [Internet]. Emedicine.medscape.com. 2021 [cited 15 March 2021]. Available from: http://emedicine.medscape.com/article/118562-clinical#b5