ISSN 2475-5451

Case Report

International Journal of Diabetes & Metabolic Disorders

Hypothyroidism: A Rare Presentation of Central Hypothyroidism With Thyroxine Malabsorption

Amit Badshah*, Irfan Khan and Parag Singhal

*University Hospitals Bristol, Weston NHS Foundation Trust, Department of Medicine, Weston-Super-Mare, UK.

***Corresponding author:**
Amit Badshah, University Hospitals Bristol, Weston NHS Foundation Trust, Department of Medicine, Weston-Super-Mare, UK, E Mail : dramitbadshah@gmail.com

Submitted: 14 Jan 2020; **Accepted**: 18 Jan 2021; **Published**: 25 Jan 2021

Keywords: Hypothyroidism, Autoimmune, Iodine, Pituitary, Tumours, Endocrinology.

Introduction

Hypothyroidism remains a global problem with prevalence of 1-2% in iodine replete areas of the world. Primary or Autoimmune Hypothyroidism remains the most common type of hypothyroidism worldwide while Goitrous hypothyroidism most commonly occurs in endemic iodine deficient areas. Among all causes of hypothyroidism, central hypothyroidism is associated with acquired disorders of pituitary or hypothalamus like tumours, infiltrative disorders and accompanied by deficiency of other pituitary hormones.

Isolated central hypothyroidism however remains a very rare disease and is about 1000-fold rarer than primary hypothyroidism [1]. Central hypothyroidism apparently accounts for about one of 1,000 hypothyroid patients and it's prevalence was estimated to range from 1:20,000 to 1:80,000 in the general population [2].

Case Report

We report a 45y old female patient who presented to Endocrinology clinic in 2017 with symptoms of hypothyroidism. She was diagnosed with Primary Hypothyroidism in 2014 based on abnormally elevated TSH, positive Anti-TPO antibodies and symptoms of Hypothyroidism. She continued to feel excessively tired, had brittle nails, constipation and also complained of hair loss. Whilst being on 100mcg Levothyroxine her TSH was 0.73 (Normal range 0.27-4.2 mIU/L) and T4 was not done as is the case with most primary hypothyroid patients. Her anti TPO antibodies were positive (Values: 164). Given her positive antibodies and she was treated as primary hypothyroidism before being referred to Endocrinology.

Despite having normal TSH whilst being on 100mcg of thyroxine, she continued to remain symptomatic. Given the autoimmune nature of hypothyroidism and its well-known association with other autoimmune endocrine disorders, she had a short Synacthen test to rule out Adrenal Insufficiency. Short Synacthen test was normal with cortisol being 392, 799 and 1011 at 0 , 30 and 60 min respectively . After a few months her T4 and TSH level was checked simultaneously and she was found to have low TSH and T4 (TSH=< 0.02 mIU/L , T4= 10.5pmol/L) despite being on adequate replacement as per body weight. In view of low T4 and supressed TSH her blood sample was sent to another hospital to rule out lab error and assay interference. The repeat TFT had the same results with low TSH and T4 (Table 1 and Table 2).

She did not have any other medical problem and was not on any medications which would interfere with thyroxine absorption. Her general physical examination was unremarkable and had only few signs of hypothyroidism like hair loss and brittle nails. Her pituitary hormone profile done twice that year was normal apart from supressed TSH . Her pituitary profile was repeated next year and she had not developed any other pituitary hormone deficit. Her Coeliac antibodies were negative.

Table 1: TSH Levels Over Five Years.

Date	TSH levels (miu/l)
24-12-2014	1.1
20-01-2017	0.06
30-06-2017	O.73
18-12-2-17	< 0.02
20-04-2018	< 0.02
29-01-2019	<0.02
27-02-2019	<0.02
27-03-2019	<0.02
16-05-2019	**<0.02**
16-05-2019	**<0.02**
16-05-2019	**<0.02**
16-05-2019	**<0.02**
30-07-2019	<0.02
(Bold values depict the thyroxine absorption text)	

Table 2: T4 Levels Over Two Years.

Date	T4 levels (pmol/L) Range : 12-22pmol/L
20-01-2017	17.1
18-12-2017	10.5
20-04-2018	8.1
29-01-2019	4.8
27-02-2019	4.0
27-03-2019	7.0
16-05-2019	**7.8**
16-05-2019	**8.1**
16-05-2019	**8.3**
16-05-2019	**8.6**
30-07-2019	8.7
(Bold values depict the thyroxine absorption test)	

Given the above thyroid hormone profile a central cause of hypothyroidism was suspected and MRI of pituitary was done. The MRI did not show any abnormality in pituitary or hypothalamus. The only other abnormality detected during the course of investigation was Vitamin D deficiency which may have partly contributed to the patient's symptoms. This was however corrected adequately but did not resolve patient's symptoms. Even with increase in Levothyroxine doses to 200 mcg the patient's symptoms persisted.

There was no history of thyroid surgery, critical illness, anti-thyroid medications (like lithium, amiodarone) , hemochromatosis, unexplained diarrhoea, head trauma or any other systemic disease which could account for abnormal thyroid function tests. She subsequently underwent a

supervised thyroxine absorption test to differentiate between non-compliance and malabsorption. Even with 700mcg single oral dose levothyroxine her T4 levels never went above 8.6 pmol/L.
Thyroxine absorption test : Curve depicting flat response on oral 700mcg Levothyroxine

Review of Literature

Review of literature reveals that there have been sporadic cases of adult onset isolated central hypothyroidism all over the world. One of the earliest reported cases of isolated central hypothyroidism were in 1950 [3-7] and it was postulated that isolated central hypothyroidism could be an initial stage of lymphocytic adenohypophysitis (LAH). The aetiology of LAH was unclear and an autoimmune process was suspected as anti-pituitary antibodies were detected in five out of the six patients in their first report [3]. They suggested that the condition is most likely a hypothalamic disease, as evidenced by a surge in TSH secretion after TRH stimulation.

As per the latest ETA guidelines on central hypothyroidism [8] the pathological mechanisms accounting for CeH are impaired thyrotrope stimulation or alterations in the thyroid hormone feedback set point (e.g., TRH resistance or TBL1X mutations) [9-11], reduced pituitary reserve of thyrotropin (e.g., TSHβ mutations or an insufficient thyrotrope population) and poor intrinsic biological activity of secreted TSH molecules [12-14].

As part of further investigation our patient was planned for TRH stimulation test to differentiate between pituitary and hypothalamic etiology. This was however not done as it would not have changed the overall management and she would still need higher dose thyroxine. The implications of diagnosis of isolated central hypothyroidism could point towards autoimmune nature of disease in pituitary gland or hypothalamus and may lead to delay in diagnosis of panhypopituitarism in future. This case reminds us about the possibility of development of central hypothyroidism even in the setting of primary hypothyroidism and also whether T4 should be routinely tested along with TSH. The significance of Anti-TPO antibodies in our patient remains uncertain as it's also found in up to 20% general population.

References

1. Luca P. Central Hypothyroidism: Pathogenic, Diagnostic, and Therapeutic Challenges. The Journal of Clinical Endocrinology & Metabolism,2012; 97(9): 3068-3078.
2. Price A , Weetman AP. Screening for central hypothyroidism is unjustified. BMJ,2001; 322:798
3. Yamakita N, Komaki T, Takao T, Murai T, Hashimoto K, et al. Usefulness of thyrotropin (TSH)-releasing hormone test and nocturnal surge of TSH for diagnosis of isolated deficit of TSH secretion. J Clin Endocrinol Metab,2011; 86:1054-1060
4. K. Hashimoto, N. Yamakita, T. Ikeda, T. Matsuhisa, A. Kuwayama, T. Sano, et al. Longitudinal study of patients with idiopathic isolated TSH deficiency: possible progression of pituitary dysfunction in lymphocytic adenohypophysitis. Endocr J, 53 (2006), pp. 593-601
5. Burke CW, Moore RA, Rees LH, Bottazzo GF, Mashiter K, et al. Isolated ACTH deficiency and TSH deficiency in the adult. Journal of the Royal Society of Medicine. 1979;72(5):328-335.
6. Gharib H, Abboud CF. Primary idiopathic hypothalamic hypothyroidism: report of four cases. The American journal of medicine. 1987;83(1):171-174.
7. Prieto-Tenreiro A, Diaz-Guardiola P. Isolated idiopathic central hypothyroidism in an adult, possibly caused by thyrotropin releasing hormone (TRH) deficiency. Hormones. 2010;9(2):176-180.
8. Persani L, Brabant G, Dattani M, Bonomi M, Feldt-Rasmussen U, et al. 2018 European Thyroid Association (ETA) guidelines on the diagnosis and management of central hypothyroidism. European thyroid journal, 2018;7(5):225-237.
9. Bonomi M, Busnelli M, Beck-Peccoz P,Costanzo D, Antonica F, et al. A family with complete resistance to thyrotropin-releasing hormone. N Engl J Med, 2009;360:731-734.
10. Sun Y, Bak B, Schoenmakers N, van Trotsenburg AS, Oostdijk W, et al. Loss-of-function mutations in IGSF1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement. Nat Genet, 2012;44:1375-1381.
11. Heinen CA, Losekoot M, Sun Y, Watson PJ, Fairall L, et al. Mutations in TBL1X are associated with central hypothyroidism. J Clin Endocrinol Metab, 2016;101:4564-4573.
12. Faglia G, Bitensky L, Pinchera A, Ferrari C, Paracchi A, et al. Thyrotropin secretion in patients with central hypothyroidism: evidence for reduced biological activity of immunoreactive thyrotropin.J Clin Endocrinol Metab, 1979;48:989-998.

13. Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G, Weintraub BD. Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism. Effect of treatment with thyrotropin-releasing hormone. N Engl J Med,1985;312:1085-1090.
14. Horimoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, et al. Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: comparison between in vivo 3,5,3′- triiodothyronine response to TSH and in vitro bioactivity of TSH. J Clin Endocrinol Metab, 1995;80:1124-1128.
15. Persani L, Ferretti E, Borgato S, Faglia G, Beck-Peccoz P. Circulating thyrotropin bioactivity in sporadic central hypothyroidism. J Clin Endocrinol Metab,2000;85:3631-3635.
16. Persani L, Tonacchera M, Beck-Peccoz P, Vitti P, Mammoli C, et al. Measurement of cAMP accumulation in Chinese hamster ovary cells transfected with the recombinant human TSH receptor (CHO-R): a new bioassay for human thyrotropin. J Endocrinol Invest,1993;16:511-519.