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The etiology and treatment of refractory Hypothyroidism - management issues: A cross sectional observational study

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Abstract: ***Introduction:*** Primary hypothyroidism is considered to be refractory to treatment when there is clinical or biochemical evidence of hypothyroidism (level of TSH above the target range, usually 5.5 mIU/L) even after 6 weeks of treatment with Levothyroxine at a dosage of 1.9 mcg/kg/day. This study intended to find out the common factors responsible for the refractory nature of the hypothyroidism. The study also highlights how simple correction measures would improve the outcomes. ***Materials and Methods:*** This is a prospective, Cross sectional and observational study conducted in the Department of Endocrinology, Sapthagiri Institute of Medical Sciences and Research center. The study population included 25 patients with treatment refractory hypothyroidism. The patients were identified after screening about 900 patients with primary hypothyroidism, between age group of 15-50 years and BMI of 19-25 kg/m2. Levothyroxine absorption test was performed when deemed necessary. ***Results:*** In 10 patients (40%) the reason for refractory nature of the hypothyroidism was found to be due to keeping the levothyroxine containers in the kitchen close to flame or above the refrigerator and due to disposing of the silica pack from the container. In 8 (32%) patients the reason was inappropriate timing of Levothyroxine with food and beverages or due to the usage of concomitant medications. 6 (24%) patients used generic Levothyroxine, which could be less effective. Remaining 1 patient (4%) were subjected to Levothyroxine absorption test, which suggested that malabsorption is the etiological factor. ***Conclusions:*** The most common reason for the refractory nature of the hypothyroidism was found to be due to improper storing conditions of the medication. The other reasons included switching over to the generic brands of levothyroxine, and not maintaining the adequate time gap between consumption of Levothyroxine and interfering medications like antacids. Malabsorption was found to be uncommon reason for refractory hypothyroidism.

Keywords: Treatment refractory hypothyroidism, Levothyroxine (LT_4), Thyroid Stimulating Hormone (TSH), Malabsorption.

INTRODUCTION

Primary Hypothyroidism is one of the common endocrine disorder seen in outpatient departments and its treatment essentially depends on adequate replacement of Levothyroxine to make Thyroid stimulating hormone (TSH) normal. [1] In most patients TSH is normalized with appropriate Levothyroxine (LT4) dosage, but clinicians occasionally encounter a subset of hypothyroidism patients where standard thyroid hormone replacement fails to make normalize TSH. [2]

Primary hypothyroidism is considered to be refractory to treatment when there is clinical or biochemical evidence of hypothyroidism (level of TSH above the target range, usually 5.5 mIU/L) even after 6 weeks of treatment with Levothyroxine at a dosage of 1.9 mcg/kg/day. [3] There is a need to search for the reason for the refractory nature of hypothyroidism before up titrating the dose of levothyroxine as it has a narrow therapeutic index. An appropriate intervention is required before repeated adjustments of the dosage is done, as administration of supraphysiological doses of Levothyroxine may be associated with cardiovascular and other adverse effects. [4]

The most common cause for this treatment refractory hypothyroidism is non-compliance with medication. [5] Other etiologies include improperly storage of the drug, timing of medication with food, usage of concomitant drugs (like PPI, iron, calcium) and malabsorption. [6] Early detection of these common issues during history taking can mitigate unnecessary investigations and usage of supra physiological dose of LT4. The literature on the treatment refractory hypothyroidism focusing on these subtle factors is scarce. The current study hereby gives a glimpse of the common factors which are responsible for the treatment refractory hypothyroidism and it also highlights how simple directions would improve the outcomes. [7]

Materials and Methods

This is a prospective, Cross sectional and observational study conducted in the Department of Endocrinology, Sapthagiri Institute of Medical Sciences and Research center. The study population included 25 patients with treatment refractory hypothyroidism. The patients were identified after screening about 900 patients with primary hypothyroidism, between age group of 15-50 years and BMI of 19-25 kg/m2, who were attending our Outpatient department from November 2018 to November 2019. Patients were identified after obtaining the detailed medical history, in which we have enquired the compliance with medication, any symptoms suggestive of malabsorption, storage of Levothyroxine container, timing of medication with food or beverages, switching the brand and usage of other concomitant medication.

Patients were recruited if they were found to be having TSH more than 5.5 mIU /L even with the regular usage of the LT_4 dose of 1.9 µg/kg/day. Patients who were non-compliant with the medication, overweight or obese (BMI > 25 kg/m^2), children younger than 15 years of age, pregnant women, patients using oral contraceptive pills (where requirement will be higher) and central hypothyroidism were excluded from the study. The patients were reevaluated at the end of 6 weeks after rectification of flaws in the usage of Levothyroxine like changing the storage, giving a proper gap with food or concomitant medications. Levothyroxine absorption test was performed if the level of TSH was persistently above the target range despite corrections of above mentioned flaws.

The study implemented Levothyroxine absorption test where LT_4 (10 µg/kg or maximum 600 µg) is administered to observe its absorption profile by measuring free T_4 level at 3rd hour. The incremental value of more than 0.40 ng/dL at 3rd hour may be useful to identify individuals where workup of malabsorption is unwarranted.

Results

On repeat evaluation of these 25 patients with treatment refractory hypothyroidism TSH was normalized in 24 (96%) patients after the correction of above mentioned factors in the usage of Levothyroxine, which were responsible for high TSH. In 10 patients (40%) the reason for refractory nature of the hypothyroidism was found to be due to keeping the levothyroxine containers in the kitchen close to flame or above the refrigerator and due to disposing of the silica pack from the container. In 8 (32%) patients the reason was inappropriate timing of Levothyroxine with food and beverages or due to the usage of concomitant medications. 6 patients (24%) used generic LT_4, which could be less effective. only 1 patient (4%) was subjected to Levothyroxine absorption test, in which the observed delta Free t4 was 0.3 ng/dl suggesting that malabsorption is the etiology for the treatment refractory hypothyroidism.

Discussion

The usual step in the management of treatment refractory hypothyroidism is up titration of the dose of LT_4 to make TSH normal. This exposure to a supra physiological dose of Levothyroxine can potentially have adverse effects on bone and cardiovascular systems. [8] The prevalence of treatment refractory hypothyroidism in clinical practice is about 28% across the studies[8]. Low prevalence of 5 % observed in our study could be due to exclusion of patients who were noncompliant with the medication and possibly also because of selection of patient and small sample size. The most common etiology in our study was improper storage of Levothyroxine, which contributed to 40% of over all cases. Enquiring about the storage of medication is an extremely important factor during history elicitation. Guidelines recommend Levothyroxine must be stored at 20-25^0 C and protected from light and moisture. [9] Only few studies address this issue of improper storage as an etiology of refractory hypothyroidism. Study by Bevenga et al quoted 4.5% is the contribution. 32% of refractory hypothyroidism is due to usage of medication without adequate gap with food and beverages or due to usage of concomitant medication (eg. proton pump inhibitors, iron& calcium supplements) which have been shown to alter the bioavailability of an ingested dose. [10] Evidence suggest to consume levothyroxine in fasting state and avoid food or beverages preferably for 60 minutes and also recommends an interval of 4 hours for the ingestion of iron and calcium supplements. [11]

TSH was elevated in 24% patients following switch to generic Levothyroxine from the existing one. This switching often happens at the pharmacy without the knowledge of treating physician. [12] So checking the container is of paramount importance when a relatively stable hypothyroidism patient becomes refractory to treatment on follow up visits. Jeremi M Carswell et al in their prospective randomized crossover study postulated that generic and branded Levothyroxine are not bioequivalent & suggested not to substitute Levothyroxine formulations. [13, 14] This study found only 4% patients of refractory hypothyroidism can be attributed to malabsorption as an etiological factor. Several case reports in the literature also observed that most of the refractory hypothyroidism are due to pseudo malabsorption rather to true malabsorption. [15] The Levothyroxine absorption test performed for one patient had shown delta Free T4 was 0.3 ng/l, which was suggestive of intestinal malabsorption and this patient was subsequently referred to a Gastroenterologist for further evaluation and management of underlying gastrointestinal pathology.

Treating physicians should exercise meticulous attention in history taking which includes storage, timing of medication with food and beverages, usage of interfering medications & changing of the brand of Levothyroxine in patients with treatment refractory hypothyroidism. Diagnostic tests for associated gastrointestinal disorders which affect absorption of Levothyroxine are required after careful exclusion of above mentioned common factors during history. Correction of these factors can avoid unnecessary LT_4 dose adjustments and investigations for caregivers, patients, thereby reducing costs of health care system.

Though there were several case reports on treatment refractory hypothyroidism, to the best of our knowledge this study is first of its kind on real world evidence. Limitation of this study is that we relied completely on the patient history.

CONCLUSION

The common reasons for the refractory hypothyroidism are simple factors like switching over to generic brands, storage issues (like exposure to heat, light, throwing out silica), not maintaining adequate gap between Levohyroxine and Iron/calcium supplements. Malabsorption is an uncommon etiology for refractory hypothyroidism at least in Southern India. So careful history taking with detailed information on these factors, can mitigate unnecessary work up in most patients.

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