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Thyroid Hormone Resistance in Identical Twin Sisters with Atrial Fibrillation: Case Report and Review of the Literature

Mark B. Zimering[1,2,3*]

[1]*Center for Health, Education, Medicine and Dentistry, 1771 Madison Ave, Lakewood, NJ*

[2]*Endocrinology, Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ*

[3]*Veterans Affairs New Jersey Healthcare System, 385 Tremont Ave, East Orange, New Jersey*

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***Corresponding author:** Mark B. Zimering, Medical Service (111), Veterans Affairs New Jersey Healthcare System, 385 Tremont Ave, East Orange, New Jersey; E-mail: Mark.Zimering@va.gov*

Abstract

Aim: To report identical twin sisters harboring the A317T mutation in the thyroid hormone beta receptor gene (TR β) who developed atrial fibrillation and refractory congestive heart failure in the sixth decade of life. To critically assess whether the A317T mutation may be responsible for increased cardiotoxicity compared to other thyroid hormone beta receptor gene mutations.

Methods: A 59-year-old woman referred for evaluation of abnormal thyroid function tests had been experiencing frequent spells of tachycardia associated with dyspnea, and dizziness necessitating multiple hospitalizations. Elevation in free thyroxine (T4), total triiodothyronine (T3) and inappropriately normal thyroid stimulating hormone (TSH) was consistent with a clinical diagnosis of thyroid hormone resistance. Magnetic resonance imaging of the brain was negative for a TSH-secreting pituitary adenoma. A blood sample was sent for thyroid hormone receptor gene mutational analysis, but it would require eight weeks to complete processing.

Results: A modified L-T3 suppression test was used to assess thyroid-pituitary axis feedback. After three weeks' of cytomel (L-T3) (25 micrograms daily) TSH decreased by 50%, and free T4 level decreased by 22% compared to baseline levels. Genetic testing revealed a heterozygous A317T mutation in the thyroid hormone beta receptor gene. Serial two-dimensional echocardiography demonstrated evolution to left atrial enlargement over a three- year period. Prior published literature suggests a less than 10% prevalence of atrial fibrillation in adults with thyroid hormone resistance harboring various TR-β gene mutations. Yet all five of five (100%) adults having the A317T mutation were reported to experience atrial fibrillation by age 50.

Conclusions: A new kindred with resistance to thyroid hormone harboring the A317T disease-causative mutation is described in which identical twin sisters had a mid-life onset of atrial fibrillation and refractory congestive heart failure.

Keywords: Resistance to Thyroid Hormone; Mutation; Atrial Fibrillation; Congestive Heart Failure; Identical Twins

Introduction

Resistance to thyroid hormone (RTH) is a rare, autosomal dominantly-inherited syndrome caused by heterozygous mutation(s) in the thyroid hormone receptor-beta (TR-β) gene [1]. Resistance to thyroid hormone has an estimated prevalence of 1 in 40,000 live births [1]. Since the initial report by Refetoff et. al. [2] in 1967, more than 3000 cases have been reported world-wide. Mutation(s) commonly affect the T3- binding-domain of the thyroid hormone receptor-beta gene [1] altering transcription in genes containing a thyroid hormone response element (TRE). At the level of the pituitary and hypothalamus, loss of normal feedback suppression of thyroid stimulating hormone (TSH) (by T3) causes elevation in T4, T3 and inappropriately non-suppressed TSH -a biochemical hallmark in RTH [1].

The clinical manifestations in RTH may be highly variable ranging from hypothyroidism, short stature and impaired intellectual development [3] to hyperthyroidism, goiter and tachycardia [3].

Cardiac disease is an infrequent, but potentially life-threatening clinical manifestation in RTH [4] which is thought to be mediated by an intact TR-α receptor isoform expressed in vascular and cardiac cells. TR- α not only mediates genomic effects, but also rapid non-genomic effects in vascular cells via coupling of cytosolic TR- α receptor to the PI-3 kinase/Akt signaling pathway [5]. A possible role for the rapid non-genomic TR- α signaling pathway in the heart and vasculature in mediating unusual cardiovascular signs and symptoms occurring in adult RTH has not been previously reported.

We now describe an adult woman with RTH suffering with chronic atrial fibrillation who experienced recurrent episodes of lightheadedness and dyspnea requiring frequent hospitalizations for the treatment of refractory congestive heart failure. The episodic dizziness could be triggered by minimal physical exertion and was associated with rapid ventricular response(s) (e.g. HR ~170 bpm).

Case Report

A 59- year-old woman presented to the endocrinology clinic for evaluation of abnormal thyroid function tests. She had been hospitalized (one week earlier) for dyspnea secondary to atrial fibrillation with rapid ventricular response. She was treated with intravenous diltiazem and discharged home on oral diltiazem

and metoprolol. The patient had reported experiencing frequent episodes of dizziness and dyspnea on minimal exertion, e.g. after walking a few yards on level ground. Serial thyroid function determinations revealed consistently elevated free thyroxine (t4) and total triiodothyronine (t3) levels in the setting of 'inappropriately' normal thyroid stimulating hormone (TSH) levels (table 1).

The past medical history was notable for major depressive disorder treated with trazadone and aripiprazole, asthma treated with ventolin inhaler and advair, and hypercholesterolemia treated with atorvastatin. The patient denied taking any nutritional supplements, including biotin, which can interfere with certain thyroid hormone assays. The patient had smoked half a pack of cigarettes per day for the past thirty years. Family history was remarkable for mother who had died at age 88 years and suffered with hyperthyroidism and atrial fibrillation, an identical twin sister previously diagnosed with RTH (case 2; figure 1), three adult children (ages 41, 33 and 28 years old) alive and in good health, and five grandchildren (ranging in age from 7-14 years old) who were all reportedly asymptomatic (figure 1), i.e. no hyperthyroidism, goiter or cardiac ailment.

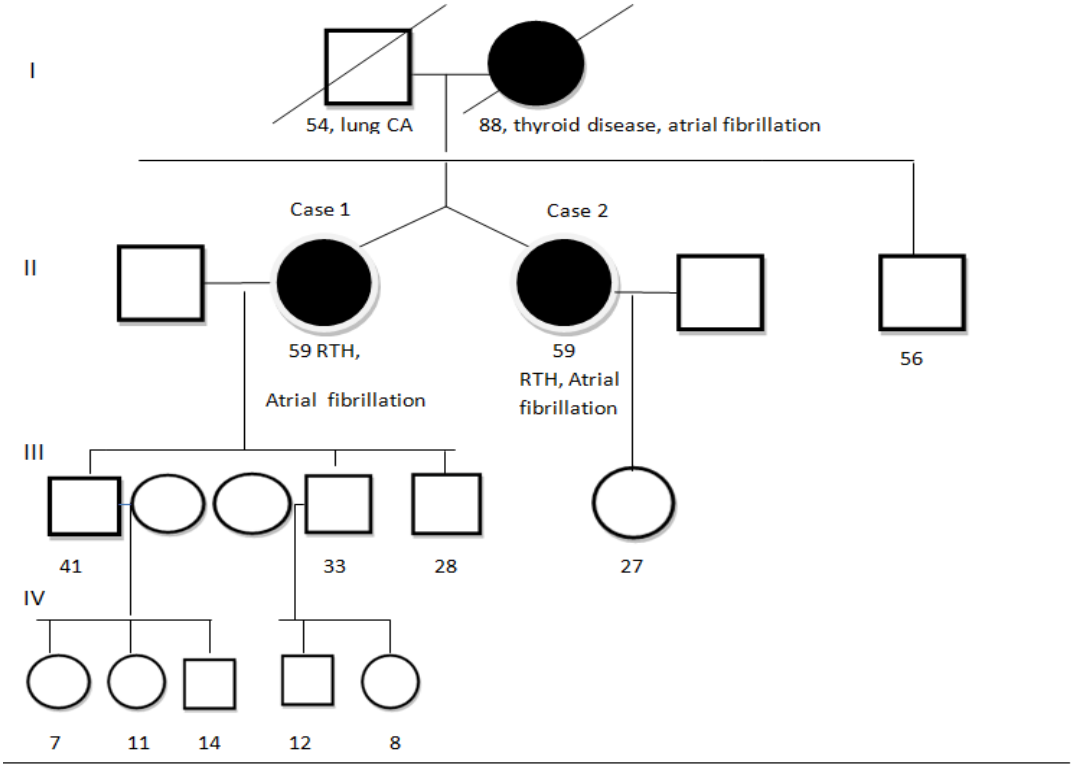

Fig 1: New resistance to thyroid hormone kindred harboring A317T mutation in TRβ

Physical examination revealed an anxious older woman with resting tremor and pressured speech. Height 63 inches, weight 159 lbs. Seated blood pressure was 122/87 mm hg, resting heart rate was 77 bpm (irregularly irregular), respirations were 14 breaths per minute (non-labored), and the patient was a febrile. After the patient stood up, walked a few steps and sat down on the examining table, her heart rate increased suddenly to 170 bpm. The skin was warm and dry. There was no proptosis or exophthalmos, and the visual fields were normal to confrontation testing. There was no jugular venous distension at 15 degrees. The thyroid was symmetrically enlarged, approximately 25 grams, and there were two palpable (1-2 cm) nodules, one in each lobe. Lung exam revealed scattered wheezes, decreased breath sounds at the right base and no rales. Cardiac examination was remarkable for rapid, irregular rate and rhythm, no s4, s3 gallop or rub was appreciated. There was no edema of the lower extremities. Neurologic exam was non-focal and deep tendon reflexes were brisk.

Laboratory and Imaging Studies

Magnetic resonance imaging of the brain was performed and it was negative for a pituitary mass lesion. Thyroxine binding globulin (TBG) was within the normal assay range (Table 1). Anti-thyroid autoantibody levels: thyroid stimulating immunoglobulin (TSI), anti-thyroglobulin and anti-thyroid peroxidase (TPO) were within the normal assay ranges: TSI 97% (0-139%); Thyroglobulin Ab < 1 (0-0.9)IU/ml, Anti-TPO Ab 13 (0-34) IU/ml. An iodine-123 radioactive thyroid uptake and scan revealed an enlarged gland with two cold nodules. The four-hour radioactive iodine uptake was 23.2%, normal range (3-10%); the 24 hour uptake 67.3%, normal range (10-40%). Serum albumin and total cholesterol were both within the normal ranges, and alkaline

phosphatase was elevated at 174 (39-117) U/L. A blood sample was drawn and sent out for resistance to thyroid hormone mutational analysis testing.

Modified L-T3 suppression test

Owing to the patients' refractory congestive heart failure requiring frequent hospitalizations, and the unexpectedly long delay in obtaining the results of thyroid hormone resistance mutational analysis, a 'modified L-T3 suppression test' (without serial I131 thyroid uptake determination) was performed to substantiate a working clinical diagnosis of resistance to thyroid hormone. Low-dose cytomel (L-T3) 25 micrograms was given once daily in the morning to evaluate suppressibility of TSH. After three weeks' L-T3 treatment, repeat thyroid function tests demonstrated a 22% decline in the free T4 level, unchanged total T3 level and a 50% decline in TSH level compared to basal levels (T+171 vs T+115 days; Table 1;Figure 2). During the treatment interval, the patient reported a reduction in her symptoms of dyspnea and dizziness and was not hospitalized. After discontinuation of L-T3, however, free T4 and TSH levels reverted to their pre-treatment levels (T+ 201 days; Table 1; Figure 2), and dizziness and dyspnea also recurred requiring the patient to be hospitalized again and treated for congestive heart failure.

Table 1: Indices of thyroid hormone function testing during 10 months' observation.

	T+319	T+201	T+171	T+150	T +115	T=0 (days)
T3 (71-180 ng/dL)	204	391	242		244	262
Free T4 (0.82-1.77 ng/dL)	3.41	3.23	2.79		3.57	3.74
TSH (.45-4.5 uIU/mL)	4.67	3.92	2.06		4.08	5.1*
Free T3 (2-4.4 pg/mL)				8.2		
TBG (13-39 ug/mL)				23		

*upper limit normal 5.2 uIU/mL

T3-total triiodothyronine, free T4, thyroxine, TSH- thyroid stimulating hormone, TBG- thyroxine binding globulin.

T+ 150 days- corresponds to the date of initial presentation to outpatient endocrinology clinic.

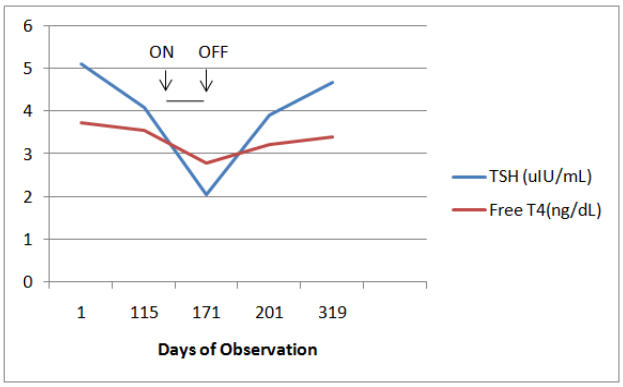

Figure 2: Effect of L-T3 suppression (25 micrograms daily) on TSH and free T4 level. Serum thyroid stimulating hormone (TSH), and free thyroxine (T4) were determined at the five indicated time points on the x-axis during a 319 day observation period. Cytomel (L-T3), 25 micrograms was prescribed to be taken once daily in the morning during a three week period starting on day T+150 (ON) and ending on day T+171 days (OFF). All TSH and free T4 levels were performed using the same laboratory assay except for the day 1 TSH level which had a slightly higher upper limit of normal value, i.e. 5.2 uIU/mL compared to the remaining TSH values (upper limit, 4.5 uIU/mL).

Mutational analysis

RTH mutational analysis was performed at Quest Diagnostics, Nichols Institute, (San Juan Capistrano, CA). It revealed heterozygous positivity for the c.949G> A (p.Ala317Thr) variant in the thyroid hormone receptor beta (THRB) gene. This variant has previously been reported to cause autosomal dominant RTH. For example, Parilla *et. al.* [3] reported inappropriately elevated TSH, normal resting heart rate < 80 bpm during sleep, and reduced intellectual functioning, but no liver biosynthetic abnormalities or short stature in an 11-year old boy harboring the p.Ala317Thr mutation.

Case 2

The patient's identical twin sister (Case 2) was heterozygous positive for the same c.949G> A (p.Ala317Thr) variant in the thyroid hormone receptor beta (THRB) gene. Seven years before the diagnosis of RTH and atrial fibrillation in Case 1, Case 2 had presented with chest pain and shortness of breath and was found to have new-onset atrial fibrillation with rapid ventricular rate. Her free T3 was found to be elevated at 7.8 pg/mL (2.3-4.2) with a free T4 of 4.65 ng/dL (0.82-1.77) and a TSH of 6.14 uIU/mL (0.45-4.5). Thyroxine binding globulin, TSH receptor antibodies and anti-thyroglobulin antibodies were all within the normal ranges. Serum cholesterol, and alkaline phosphatase were within the normal ranges and the patient was treated with furosemide, coumadin, spironolactone, metoprolol and ramipril. Because of recurrent episodes of congestive heart failure due to atrial fibrillation she had undergone an unsuccessful attempt at radiofrequent catheter ablation for treatment of atrial fibrillation. She was treated with anti-thyroid drugs for a brief period prior to the diagnosis of RTH, but it had been discontinued after her TSH increased to 16.8 µIU/mL with an elevated total T4 of 26 µg/dL, normal range (4.5-12.0 µg/dL).

Cardiac evaluation

During previous hospital admissions for congestive heart failure the patient (Case 1) had undergone repeated two-

dimensional echocardiography which showed a progressive increase in left atrial size from 3.3 cm to 4 cm over a three-year observational period (Figure 3). Mild mitral and tricuspid valve regurgitation, and decreased left ventricular ejection fraction of 50-55% were also noted on recent two-dimensional echocardiography. Cardiac catheterization for evaluation of atypical chest pain had revealed non-hemodynamically significant stenosis consistent with a diagnosis of non- obstructive coronary artery disease

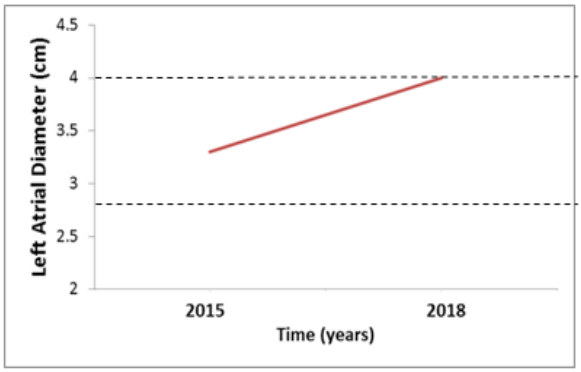

Figure 3: Longitudinal change in left atrial size in 59 year old woman (case 1) harboring heterozygous A317T mutation in TRβ gene. Left atrial size was determined by serial echocardiography performed approximately three years apart, i.e. ~T- 975 days (2015) and T+ 120 days (2018). The lower and upper limit of the normal range for age-matched adult women (2.8-4.0 cm) is indicated by the dashed lines.

Approximately five months after her initial presentation to the endocrinology clinic (T+299 days), the patient experienced a new episode of bradycardia (HR 48) and hypotension. She was admitted to the hospital, diagnosed with tachy bradycardia syndrome (sick sinus syndrome) and treated with placement of a permanent pacemaker and diuretics. Two weeks later, however, she was readmitted to the hospital and treated with the anti-arrhythmic drug sotalol, anti-arrhythmic drug because of hypotension secondary to rapid ventricular response (HR 147), recurrent dizziness. At a follow-up outpatient endocrinology evaluation a few days later (T+ 319 days) free T4 level was approximately 193% of the upper limit of normal and the TSH was near the upper limit of normal (Table 1). The patient's seated, resting heart rate was 60 bpm, blood pressure 98/68 mm Hg, and there was no significant orthostatic change in the heart rate 62 bpm, or blood pressure 92/70 mm Hg after standing for several minutes.

Discussion

Our patient (Case 1) presented with goiter, tachycardia and an emotional disturbance (major depressive disorder) consistent with prior reports that these are among the most common signs and symptoms experienced by patients having RTH [1]. Serious cardiac manifestations have been reported much less frequently in adult RTH. For example, in two case series encompassing a wide range of different RTH mutations, the prevalence of atrial fibrillation in adults (mean age of ~ 40 years) was reported to be ~ 6% [6] and 7% [4], respectively; and dyspnea was reportedly experienced by only 4% of adult RTH patients [4]. The low prevalence of cardiotoxic symptoms in these published series may have reflected (in part) inclusion of a larger number of younger RTH patients in such studies. For example in a study of cardiac manifestations in children and adults with RTH, Kahaly et. al. [4] reported that increasing age was a significant risk factor for the occurrence of cardiotoxic signs and symptoms in fifty-four RTH patients. Higher baseline TSH was also a risk factor significantly associated with cardiotoxicity in RTH [4]. Finally, left atrial (LA) size was significantly increased (within the normal ranges) in both adults and children having RTH compared to their age-matched counterparts lacking RTH [4].

In rare cases of homozygous mutation in the TRβ gene [7], free T4 levels were reported to have been markedly elevated (e.g. 6-fold higher than the upper range of normal) which likely contributed to onset of left atrial enlargement at ages 9, and 13 years followed by death from refractory congestive heart failure in two boys harboring homozygous TRβ gene mutations.

Our patient and her identical twin sister (harbored the A317T mutation) and both developed atrial fibrillation and refractory congestive heart failure in the sixth decade of life. A review of published literature in additional adult RTH patients harboring the same A317T mutation revealed that all three of three adults (age 50 or older) were reported to have suffered with atrial fibrillation [8, 9]. For example, Brooks et. al. [8] described a 62-year- old man who presented with atrial fibrillation followed by cerebellar infarction. The patient's identical twin brother harbored the same Ala317Thr mutation in the TR-beta gene and also experienced a cerebellar infarction secondary to unrecognized atrial fibrillation [8]. Guo et. al. [9] reported on a 24-year-old Chinese man who presented with palpitations, and tremor and was found to harbor the Ala317Thr mutation in TR-beta gene. His 50-year-old mother harbored the same TR-beta gene mutation and had atrial fibrillation [9]. In contrast, Adams et. al. [10] reported that children age 12 and 22 years harboring the Ala317Thr mutation in TR-beta gene were asymptomatic at clinical presentation except for goiter. These findings are consistent with advancing age as a known strong risk factor in atrial fibrillation [11], and a role for persistent atrial tachycardia in driving atrial remodeling underlying the development of persistent atrial fibrillation [12].

Left atrial enlargement was a significant predictor of atrial fibrillation recurrence following radio-frequent ablation [13]. In our patient (Case 1), overt left atrial enlargement had already developed within one year of the diagnosis of atrial fibrillation; and her twin sister (Case 2) (whose data on left atrial size was not available to us) failed radiofrequency catheter ablation to correct underlying chronic atrial fibrillation. Taken together, these data suggest a likely association between the A317T mutation in TRβ gene (in five of five older adults) and atrial fibrillation development by the sixth decade of life. Although the underlying mechanism for the association is unknown, one possibility is higher circulating T4, and T3 levels associated with the A317T mutation.

The mean free T4 level reported by Kahaly et. al. [4] in forty-one adult RTH patients harboring seventeen different TRβ gene mutations was 155% of the upper limit of normal compared to the A317T mutation which resulted in mean free T4 level ~ 200% of upper limit of normal range [14]. Thus increased free T4 and T3 (and high normal TSH) may drive increased cardiotoxicity associated with the A317T mutation. Partial resistance to thyroid hormone action in the heart may occur as a result of a mutant TRβ gene, however, the presence of intact TR-α receptors in heart tissue can mediate genomic [15] and non-genomic effects of excess circulating thyroid hormones.

A non-genomic hemodynamic effect of thyroid hormone is acute decrease in peripheral vascular resistance mediated by cytosolic TR-α receptor activation of the PI3K/Akt signaling pathway leading to increase endothelial nitric oxide synthase (eNOS) expression in endothelial cells [10]. Our patient's dramatic increase in heart rate following minimal exertion may have been triggered (in part) by baroreceptor-mediated reflex mechanism resulting from peripheral arterial vasodilatation (and blood pooling) due to increased basal tone in the TR-α/ PI3K/ Akt/eNOS pathway in endothelial cells. Diuretic medication cause renin-angiotensin system activation which may trigger increases in heart rate via effects on the sympathetic nervous system. The combination of metoprolol, useful in the treatment of systolic heart failure [16], and diltiazem for ventricular rate control, is known to unmask underlying sinus node dysfunction[17], as occurred in our patient.

Ninety percent of RTH mutations occur in the TRβ gene, clustering in three regions involved in T3- ligand binding [1]. In a study by Hayashi et al [8], there was a significant correlation between the extent of T3- binding loss (in a subset of TRβ gene mutations) and the free T4 level. Thus mutations affecting the TRβ ligand binding domain which caused moderate-severe impairment of T3 binding, including the A317T mutation, were associated with higher free T4 level [8]. Recent X-ray crystallography data of two different mutant TR β receptors complexes to TRIAC (3,5,3'-triiodothyroacetic acid) suggest the A317T mutation causes enlargement of the TRβ ligand binding pocket associated with an ~ 100-fold increase in the rate of the T3 binding off- reaction compared to that observed in the wild-type TRβ receptor [18]. The R316H mutation also caused 100-fold loss in T3 binding, and impaired TRβ homodimerization [18], but was associated with lower free T4 levels (~ 140% of upper normal range) than the A317T mutation [8]. TRβ normally forms 'transcriptionally- active' heterodimers with the retinoic acid RXR receptor-responsible for the "dominant- negative' effect of heterozygous TRβ mutations [1]. Agonists of the retinoic acid receptor (RXR) have been reported to exert a negative allosteric effect on T3 binding to TRβ [19] further complicating the interpretation of how a particular mutation results in its characteristic mean thyroid hormone level.

A hallmark of the clinical signs and symptoms in resistance to thyroid hormone is the lack of a strong overall correlation between genotype and phenotype [1]. Yet in two sets of identical twins harboring the A317T mutation in the TRβ gene there was a close concordance in midlife onset of atrial fibrillation. Identical twins are a special case in which genetic identity at loci encoding co-factors involved in thyroid hormone's biological effect may reduce overall phenotypic variability in clinical expression. It has not yet been determined whether any of the children of Cases 1 or 2 may harbor the A317T mutation or the future clinical expressivity of the gene in those affected children. There is currently no treatment to prevent cardiotoxicity associated with the A317T or any other TRβ disease-causative mutation. Still the presented evidence of apparent high clinical expressivity of cardiotoxicity suggests that surveillance of affected adult children (for atrial fibrillation) using serial monitoring of left atrial size (echocardiography) may be warranted to minimize the risk of stroke due to undiagnosed atrial fibrillation.

Although 3 weeks of L-T3 suppressed the TSH level and lowered the free T4 level by 22%, it cannot be proposed as a long-term treatment to mitigate against cardiotoxicity in RTH since L-T3 itself could potentially exacerbate the occurrence of dangerous tachyarrhythmias as well contributing to additional untoward side effects mediated via wild-type TRα receptors present in the central nervous system, gut, and bone.

Conclusions

This is the first report of the A317T mutation in the TRβ gene occurring in identical twin sisters who both experienced chronic atrial fibrillation and refractory congestive heart failure in midlife. More study is needed to determine the underlying mechanisms mediating the acute and chronic effects of elevated T4, and T3 on the heart and vasculature including a possible role for rapid non-genomic, TR-α mediated signaling in the patient's recurrent episodic dizziness, dyspnea and tachycardia.

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