Endocrinology, Diabetes & Metabolism CASE REPORTS

A Stephenson and others | FNAH undiagnosed for two generations

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Report of a family with three generations of undiagnosed familial nonautoimmune hyperthyroidism

Alexandra Stephenson[1], Zoya Punjwani[2], Markus Eszlinger[3], Beata Sawicka[4], Artur Bossowski[4] and **Ralf Paschke[5]**

[1]Department of Biochemistry and Molecular Biology & Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Alberta, [2]Department of Medical Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, [3]Department of Oncology, Biochemistry and Molecular Biology, and Pathology and Laboratory Medicine, Cumming School of Medicine & Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Alberta, [4]Department of Pediatrics, Endocrinology, Diabetology with Cariology Division, Medical University, Bialystok, Poland, and [5]Departments of Medicine, Oncology, Pathology and Laboratory Medicine, and Biochemistry and Molecular Biology & Arnie Charbonneau Cancer Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta

Correspondence should be addressed to R Paschke
Email
ralf.paschke@ucalgary.ca

Summary

Familial nonautoimmune hyperthyroidism (FNAH) is rare and occurs due to a constitutively activating thyroid-stimulating hormone receptor (TSHR) germline mutation. Forty-one families with FNAH have been reported so far. In the study, 17 of 41 families were not diagnosed with FNAH until three generations or more were described with hyperthyroidism. We report a case of FNAH diagnosed in the third generation. The index patient was diagnosed with hyperthyroidism at age 3. Large fluctuations in thyroid hormone levels occurred during anti-thyroid drug treatment, and he developed a goiter. The patient's mother had similar history, requiring two surgical interventions and radioiodine treatment. The younger brother of the index patient did not experience large thyroid hormone level fluctuations, nor increased thyroid growth. A heterozygous TSHR c.1357A>G mutation, resulting in a M453V amino acid exchange, was detected in all three patients leading to FNAH diagnosis, with complete genotype–phenotype segregation. Based on Sorting intolerant from tolerant (SIFT) and PolyPhen2 scores of 0.01 and 0.99, respectively, an effect on protein function can be assumed. As illustrated by this family with FNAH, total thyr oidectomy is necessary for patients with nonautoimmune hyperthyroidism. Development of goiter is common, anti-thyroid drug treatment is often difficult, and remission of hyperthyroidism does not occur after discontinuation of anti-thyroid drug treatment. Thus, early diagnosis and appropriate treatment of FNAH is necessary to avoid predictable, unnecessary complications and further surgical interventions.

Learning points:

- In the study, 19/42 cases of familial nonautoimmune hyperthyroidism (FNAH), including the reported case, were not diagnosed as FNAH until the third generation; this lead to suboptimal treatment and frequent relapses of nonautoimmune hyperthyroidism (NAH).
- Detection of thyroid-stimulating hormone receptor (TSHR) mutations in patients with suspected FNAH to confirm diagnosis is essential to ensure proper treatment for the patient and further affected family members.
- NAH will persist without proper treatment by total thyroidectomy.
- Symptoms and age of onset may vary between family members
- All family members with a TSHR germline mutation should be monitored with thyroid-stimulating hormone and for symptoms throughout their lives.

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Background

The most common cause of hyperthyroidism is Graves' Disease. A less common form of hyperthyroidism is nonautoimmune hyperthyroidism (NAH) (1). There are three subcategories, that is, hot nodules caused by somatic thyroid-stimulating hormone receptor (TSHR) mutation (2), sporadic TSHR germline mutation (SNAH) (3) and inherited TSHR germline mutations (familial, FNAH). A description of dominantly transmitted nonautoimmune hyperthyroidism was first published in 1982, and the molecular etiology was described in 1994 (4, 5). Since this time, 41 cases of families with FNAH have been published (6).

Although these descriptions have been available for nearly 30 years, the majority of the 41 previously published case reports of families with FNAH have multiple generations that have gone undiagnosed. There is only one family where NAH was diagnosed in the first generation (although the case report was published later when the second generation was diagnosed with FNAH (7)). There are 22 families where two generations were described with hyperthyroidism at the time of FNAH diagnosis in the respective index case. There are a further 14 families with findings reported for 3 generations and 4 families with findings reported for 4 generations with documented hyperthyroidism at the time of FNAH diagnosis in the respective index case (6). The number of generations undiagnosed may be underestimated since the availability of family records and knowledge of family member's health concerns is a limiting factor. In this case report, we describe an additional family with FNAH that was diagnosed in the third generation. Therefore, there are a total of 42 families with FNAH, 41 of which with two or more affected generations at the time of diagnosis. Based on this case report, we analyze the consequences of a missed diagnosis of FNAH and emphasize the importance of early detection and treatment.

Case presentation

The index patient (III/1; Fig. 1) is a male, born by cesarean section in terms of unrelated parents. During gestation, his mother (age 28) was treated with anti-thyroid drugs for hyperthyroidism. Thyroid hormones and anti-thyroid antibodies were assessed based on the patient's bradycardia and family history of thyroid disorders. At 7 days of age, hypothyroidism was diagnosed (Table 1) and l-thyroxin therapy was initiated. Following rapid normalization of thyroid-stimulating hormone (TSH), normal levels of anti-

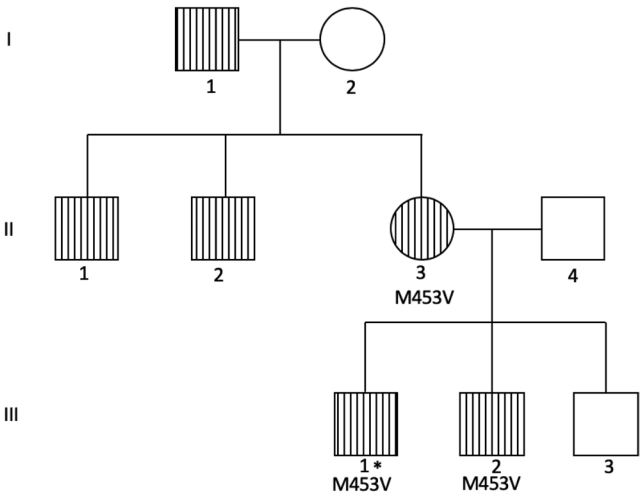

Figure 1
Pedigree for reported family where circles and squares with lines represent a history of hyperthyroidism. Non-filled-in individuals did not have symptoms of hyperthyroidism. Index patient is identified with *. Individuals with 'M453V' have been confirmed to carry the TSHR p.M453V mutation. II/4 has also been tested and is negative for TSHR mutations. Samples from I/1, II/1 and II/2 were not available for molecular testing but the respective family members had documented hyperthyroidism symptoms. III/3 has not shown any symptoms and has not had molecular testing.

thyroid antibodies (ECLIA E170, Roche Diagnostics) and normal thyroid ultrasound, l-thyroxin dose was gradually decreased until it was discontinued at 6 months of age. At this time, the patient's motor and mental development was normal. At 2 years, his weight and height were normal. At 3 years of age, tachycardia and weight loss were observed by the mother. Hyperthyroidism was diagnosed based on thyroid hormone results (Table 1). A bone age of 7 years was detected based on the Greulich–Pyle method. Thyroid peroxidase (TPO) and antithyroglobulin antibody (ATG) were normal (ECLIA E170, Roche Diagnostics). Ultrasound showed normoechogenic, homogenous thyroid of normal volume (Table 1). The patient was treated with methimazole and propranolol. When hypothyroidism developed after 6 months of therapy (age 3 years 6 months; Table 1), the dose of methimazole was reduced and thyroid hormone levels normalized (age 3 years 7 months; Table 1). At 4 years of age, physical examination and ultrasound found an enlarged thyroid with a nodule (Table 1) (8). Weight and height were normal at age 5, 6 and 10 years 6 months when thyroid hormone levels were also found to be normal (Table 1). At 11 years 5 months, the patient's fT4 was elevated. Without medication adjustment, 2 months later the patient was once again hypothyroid and required a reduction in dose of methimazole (age 11 years 7 months; Table 1). The most recent thyroid ultrasound

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Table 1 Anthropomorphic, thyroid hormone, medication dose and ultrasound result data for the index patient.

Age	Weight (kg)	Weight percentile	Height (cm)	Height percentile	TSH* (μIU/mL)	fT3* (pg/mL)	fT4* (ng/dL)	Methimazole dose (mg/kg/day)	Propranolol dose (mg/kg/day)	Abnormal ultrasound results
7 days					**5.88**					
2 years	14.5	90	92	90						
3 years	20	90–97	107	90–97	***0***	**8.09**	**2.61**	1	1	3 mL; LL: 27×12×10 mm; RL: 25×11×10 mm
3 years 6 months					**16.64**		*0.705*	0.5		
3 years 7 months					2.03		1.4			
4 years	22	90–97	112	90	***0.005***	*1.77*	**5.15**			Enlarged: LL: 7.2 mL; RL: 7.0 mL, slightly hypoechogenic with a 0.6×0.6 cm nodule in the right lobe
5 years	23	90	116	90						
6 years	26	75–90	126	90						
10 years 6 months	39	50–75	153	90	0.37	4.71	1.37			
11 years 5 months	49	75–90	157.6	75–90	0.93	4.08	**5.15**			
11 years 7 months	51.2	75–90	158	75–90	**6.77**	3.79	0.86	0.15		
11 years 10 months	56.2	75–90	160	90	***0.28***		1.11			
12 years										Hypoechogenic and enlarged: RL: 2×2.3×3.55 cm, volume: 8.5 mL; LL: 2×2×4.12 cm volume: 8.48 mL
13 years 6 months	64	90	163	50–75				0.1		

*Serum levels of fT4, fT3 and TSH were determined with electrochemiluminescence 'ECLIA' with a Cobas e 411 analyzer (Roche Diagnostics). Normal values for fT3 between 2.6 and 5.4 pg/mL, for fT4 ranged between 0.71 and 1.55 ng/dL and for TSH between 0.32 and 5.0 (μIU/mL). Mean normal thyroid volume and upper limit for boys age 3 years: 2.5 mL, 4.25 mL; 4 years: 2.9 mL, 5.5 mL; 12 years: 6.6 mL, 11.4 mL.
Bold thyroid hormone values are above normal, and bold italicized values are below normal.
fT3, free triiodothyronine; fT4, free thyroxine; LL, left lobe; TSH, thyroid- stimulating hormone; RL, right lobe.

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measurements at the age of 12 years showed an enlarged, hypoechogenic thyroid (Table 1) (9). Presently, the child is 13 years of age, his height is 90th percentile and his body mass is 50–75th percentile (10). The patient continues methimazole treatment while thyroidectomy is planned. While no side effects of anti-thyroid drug treatment have been observed, significant variations in thyroid hormone levels were an issue throughout the treatment.

The index patient's younger brother was the second male child born by cesarean section in good condition (10 points on Apgar scale) to the mother described below. At 6 years of age, the patient was presented with tachycardia and low body mass. Suppressed TSH of <0.01 µIU/mL (ref: 0.32–5.0), free triiodothyronine of 8.24 pg/mL (ref: 2.6–5.4), free thyroxine of 2.76 ng/mL (ref: 0.71–1.55) based on ECLIA assay by Cobas and negative ATG, TPO and TSHR antibodies by ECLIA E170, Roche Diagnostics. Ultrasound showed a normoechogenic, homogenous thyroid with normal volume and excessive flow. Methimazole therapy of 0.5 mg/kg/day (taken orally in two doses/day) and propranolol 0.5 mg/kg/day (taken orally in two doses/day) was started. Normalization of thyroid hormones 7 months after the start of anti-thyroid drug treatment led the treating physicians to decrease the dose of methimazole and stop beta blocker therapy. He is presently 8-years old with normal height and body mass. The most recent ultrasound at 7 years of age showed a normoechogenic thyroid with slightly increased blood flow. This patient did not experience the thyroid hormone level fluctuations observed in the index patient and was never hypothyroid. A third child was also born in 2018 and did not show signs or symptoms of hyperthyroidism at the age of 1 year.

The index patient's mother was diagnosed with hyperthyroidism at 6 years of age based on physical examination, hormone tests, ultrasound and scintigraphy. Thyroid stimulating hormone receptor antibody (TSHRAb were not determined; anti-TPO and anti-Tg were negative, although the assays used were not known. Her father and two siblings had also been diagnosed with hyperthyroidism. For 6 years, she was treated with high doses of methimazole and propanolone. Attempts at reduction of anti-thyroid drugs were not successful with thyroid hormone levels fluctuating through treatment. At 12 years of age, she had a subtotal thyroidectomy for an enlarged thyroid gland. At this time, the patient had normal TSH and thyroid hormone levels with 5 mg 3×/day of methamizole and 20 mg 2×/day of beta blocker. Preoperative ultrasound and scintigraphy showed a significantly enlarged hypoechogenic multinodular goiter including nodules with and without increased technetium uptake. Two years after surgery, she was hospitalized for symptoms of hyperthyroidism, and her treatment was modified. At the age of 24, due to significant compression of the patient's trachea, she was treated with radioiodine therapy. However, there was low I^{131} uptake by the largest thyroid tumor. The patient declined further surgery following the radioiodine treatment. At the age of 30, she had a total thyroidectomy due to an enlarged multinodular goiter compressing her trachea. Preoperative ultrasound findings showed enlarged, asymmetric, hypoechogenic multinodular goiter with excessive vascular flow compressing the trachea. Postoperatively, treatment with 100 ug/day of l-thyroxin was started. Her father and affected siblings (Fig. 1) also underwent total thyroidectomy for hyperthyroidism; however, no further clinical data are available. No clinical or biochemical adverse events were observed during the treatment of any of the patients.

Investigation

Based on high resolution melting (HRM) PCR and Sanger sequencing (11), followed by evaluation based on SIFT and PolyPhen2 scores to predict whether amino acid substitutions were deleterious (12, 13), we detected a *TSHR* c.1357A>G; M453V germline mutation in several family members with NAH with complete genotype–phenotype segregation (Fig. 1). This is the first time this mutation has been described in association with hyperthyroidism. Based on SIFT and PolyPhen2 scores of 0.01 and 0.99, respectively, we can assume that this mutation has an effect on the protein function. However, functional characterization for this mutation is necessary to prove constitutive activity. As the mutation was detected in the mother and her children, this mutation is categorized as a familial constitutively activating germline mutation causing FNAH. A further adult male (I/1; Fig. 1) in the first generation and two in the second generation (II/1, II/2; Fig. 1) are also suspected to have the mutation based on their available descriptions. Unfortunately, no medical documentation or DNA samples are available for these family members.

Treatment

Total thyroidectomy is recommended for all FNAH patients to prevent future thyroid hormone level fluctuations. Anti-thyroid drug treatment, based on thyroid hormone levels, will continue until surgery is performed.

Outcome and follow-up

Both children are presently awaiting total thyroidectomy, the waiting period for which has been prolonged at the

request of the parents. Follow-ups to evaluate thyroid hormone levels are being continued annually.

Discussion

The index patient had excessive thyroid growth due to the TSHR germline mutation and increased TSH for two periods of at least 1 month after the first detection of the elevated TSH (Table 1) caused by intermittent inappropriately high doses of methimazole. The initial period of increased TSH was detected after a period of 6 months without thyroid hormone measurements and the second period after 2 months without thyroid hormone determination. It is unknown how long the child had increased TSH during these periods of time. The mother also presents with a history of excessive thyroid growth. Unfortunately, due to the limited availability of her medical records, it is not possible to identify whether she endured periods of increased TSH. Interestingly, the second child did not have the same fluctuations of thyroid function during treatment and had a much more straightforward anti-thyroid drug dosage history. The two individuals of the family in this report where, in addition to the constitutive TSHR activity, high TSH had a likely aggravating role in disease progression argue for early total thyroidectomy in this family.

This case supports early diagnosis and treatment of FNAH. This can be accomplished by identifying TSHR mutations in patients or families with difficulty in treating hyperthyroidism. Had the male in the first generation been properly diagnosed, all three patients described above, as well as the two males in the second generation, could have received total thyroidectomy at an earlier time point. This would have been especially beneficial to the mother (II/3; Fig. 1) who underwent two surgical interventions and radioiodine treatment, as well as ineffective metamizole therapy. Unfortunately, late diagnosis of FNAH is not uncommon with 17 of 41 published families with FNAH presenting with three or more generations with hyperthyroidism at the time of diagnosis (6). Knowledge of familial TSHR germline mutations allows for earlier hyperthyroidism and goiter relapse risk assessment to determine the appropriate therapy for patients with FNAH. Patients with FNAH require total thyroidectomy. Without it, anti-thyroid drug therapy would have to be maintained indefinitely since remission of hyperthyroidism can not be expected. Moreover, anti-thyroid drug therapy of FNAH is complicated by variations of the severity of hyperthyroidism, often difficult to adapt anti-thyroid drug treatment, especially during childhood, and is subject to compliance problems and adverse events. Remission of hyperthyroidism does not occur in FNAH and total thyroidectomy is necessary (14).

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent was obtained from the two children's mother for publication of her and her children's clinical details.

Author contribution statement
Alexandra Stephenson performed lab analysis and drafted report, Zoya Punjwani assisted with sample preparation, Markus Eszlinger oversaw lab work and confirmed results, Artur Bossowski and Beata Sawicka are treating physicians, Ralf Paschke is a consulting physician who runs the lab where molecular tests were completed and revised report.

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