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Case Report

Advanced Bone Age Present in a Neonatal Case of Sporadic Non-Autoimmune Hyperthyroidism before Onset of Symptoms: A Case Report and Review of Literature

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Abstract

Familial and sporadic nonautoimmune hyperthyroidism are caused by TSHR mutations. 20 sporadic cases in children and 22 families with 25 well described children with have been described with nonautoimmune hyperthyroidism. 26 of these children presented with advanced bone age, indicative of untreated hyperthyroidism. We report a case of sporadic nonautoimmune hyperthyroidism for which the diagnosis of hyperthyroidism was established by chance prior to the onset of symptoms due to thyroxine treatment of the mother during pregnancy. Although the child was diagnosed based on suppressed TSH and increased free T3 and T4 at 4 months of age, an advanced bone age of 1.5 years was already present. There were no dysmorphic features present, her heart rate was in the upper normal range. She showed an enlarged thyroid as assessed by ultrasound. The thiamazole dose had to be increased repeatedly. At 13 months of age the patient had a further increase in thyroid gland volume and a further increase in bone age of 2.5 years. Using high resolution melting PCR followed by Sanger sequencing of peripheral blood DNA, a heterozygous Thyroid Stimulating Hormone Receptor (TSHR) c.1895C >T mutation, resulting in a T632I amino acid change was detected, it has previously been functionally characterized as constitutively activating. This case demonstrates that premature bone aging can be present even without the onset of hyperthyroidism symptoms. Detection of germline TSHR mutation is important to direct therapy as nonautoimmune hyperthyroidism does not generally respond well to antithyroid drug treatment and total thyroidectomy is necessary for these patients.

Keywords: Thyroid stimulating hormone receptor; Thyrotropin receptor

Introduction

Nonautoimmune Hyperthyroidism (NAH) can occur due to an inherited germline mutation (familial, FNAH) or a sporadic mutation (SNAH). To date, there are 20 cases of SNAH and 22 families with 25 well described children (<18 years of age) with FNAH [1]. In 15 reports (8 cases of SNAH and 7 cases of FNAH) with a documented range of time between onset of symptoms and treatment of 0 to 10 months, advanced bone age was present at 1.3-8.8 times the chronological age (Table 1). Untreated hyperthyroidism, indicated by advanced bone age, can lead to complications in children and neonates such as craniosynostosis, tachycardia, mental retardation [41]. We present a case of SNAH with premature bone aging present before the onset of hyperthyroidism symptoms.

Case Report/Case Presentation

The patient was a female born in the 37th week of gestation in Katowice, Poland. Birth weight was 2600g and birth length was 50cm. APGAR score was 8 points at the first minute, and 9 points after five minutes. The patient's mother was diagnosed with transient gestational hypothyroidism at 19 weeks gestation and treated with levothyroxine during pregnancy. She had no symptoms of thyroid dysfunction, but was treated due to a TSH of >2.5 *uIU/ml* based on the standard procedure for pregnant women at the time.

Due to this, the neonate's thyroid function was investigated at 2 and 4 months of age, and hyperthyroidism was diagnosed at 4 months based on suppressed TSH and increased free T3 and T4 (fT3 and fT4) (Table 2). The general pediatrician initially believed suppressed TSH to be laboratory bias as the patient did not show any signs of hyperthyroidism which delayed specialist referral.

After diagnosis, the patient was hospitalized to normalize thyroid hormone levels. Physical examination revealed no dysmorphic features and the resting heart rate was within the normal range, although it was borderline high (heart rate 140/min; normal range: 100-180 [42]). Anti-thyroid antibodies were negative both for anti-TPO and anti-TSH receptor. Thyroid ultrasound showed her thyroid to be enlarged, with heterogenous echogenicity, some areas of hypoechogenicity, increased vascular flow, and no presence of nodules (Figure 1). The thyroid volume was 3.38mL at 17 weeks (Table 2) as compared to the average size of 1.1mL for European newborns [43]. The volume of each lobe was calculated by the formula: V (ml)=0.479*d*w*l (cm). [44]. An X-ray of the patient's hand and wrist revealed an advanced bone age of 1.5 years at a chronological

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Table 1: Summary of all 15 previous NAH cases and this case where advanced bone age was quantified and onset of symptoms was documented.

Case	Familial or Sporadic NAH	Age at symptom onset	Symptoms	Age at start of antithyroid treatment	Duration of symptoms prior to treatment	Bone age (months)	Chronological age (months) at time of bone age measurement	Bone Age/ Chrono-logical Age	Closure of Epiphyseal Plate or Craniosyno-stosis	Bone age method
Watkins et al. 2008 Endocrie Practice	Sporadic	from birth	increased activity, disturbed sleep, jittery, exaggerated startle response, poor weight gain	26 days	15 days	4.5	1.5	3	posterior fontanelle fused and anterior gfontanelle 1x1cm	Greulich and Pyle
Holzapfel et al. 1997 JCEM	Sporadic	before birth	restlessness, sweating, appetite and elevated HR	6 months	>6 mo	63	6	10.5	closed fontanel	not given
Nishihara et al. 2006 Endocrine Journal	Sporadic	10 days	tachycardia	10 days	5 months*	66	5	13.2	closure of anterior fontanel	not given
Chester et al. 2008 JPEM	Sporadic	2 months	low weight gain	4 months	2 months	36	4.5	8	craniosynostosis	Method of Sontag, Snell and Anderson using Greulich and Pyle standards
Suponrsilchai et al. 2009 Clinical Endocrinology	Familial	4 months	poor weight gain	8 months	4 months	82	24	3.4	not present	not given
Chawla et al. 2015 Thyroid	Sporadic	4 months	craniosynostosis	6 months	2 months	52.8	6	8.8	squamosal suture craniosynostosis	Tanner and Whitehouse Method
Olivier-Petit et al. Clinical Case Reports	Familial	6 weeks	diarrhea and tachycardia	20 months	18.5 months	60	20	3	craniosynostosis	not given
Kingo et al. 2015 International Journal of Pediatric Endocrinology	Sporadic	1 month	tachycardia, low weight, failure to thrive	3 months	2 months	24	3	8	no information	not given
Karges 2005 Journal of Endocrinology	Familial	6 months	hyperactive, insomnia	4 years	3.5 years	66	48	1.375	no information	not given
Vaidya 2004 Clinical Endocrinology	Familial	18 months	significant motor and speech delay	19.5 months	1.5 months	69.6	39.6	1.7	not present	not given
Fuhrer 1999 Thyroid	Sporadic	6 months	atopic dermatitis	11 months	5 months	72	54	1.3	no information	not given
Schwab 1996 Exp Clin Endocrinol Diabetes	Familial	from birth	low birth weight, small head circumference, progressive weight loss	3.5 weeks	3.5 weeks	0.8	12.8	16	low head circumference	not given
Schwab 1996 Exp Clin Endocrinol Diabetes	Familial	before birth	reduced birth weight, small head circumference, poor weight gain, sleeplessness, jitteriness and mild exophthalmos	6 months	6 months	60	6	10	low head circumference	not given
Guemas 2003 Horm Res	Familial	from birth	accelerated growth, tachycardia, language learning retardation and thermophobia.	4 years	4 years	96	48	2	no information	not given
Agretti 2012 Eur J Pediatr	Sporadic	14 months	diarrhea and increased growth velocity	24 months	10 months	42	30	1.4	not present	Greulich and Pyle
Present Case	Sporadic	N/A	none	16 weeks	0 days	18	4	4.5	not present	Greulich and Pyle

*Treated unsuccessfully with inorganic iodine therapy from 10 days to 5 months.

Table 2: Patient measurements, notes on Bone Age (BA) and thyroid ultrasound measurements (USG) of Right Lobe (RL) and Left Lobe (LL).

Weeks of Age	Weight [kg]	Height [cm]	Head circumference [cm]	Notes
16	5.4	67	41	Admission to clinic
17				BA: 1,5 yrs, USG: low heterogenous echogenicity with higher blood flow; RL - 10x12x29 mm; LL - 8x16x28 mm; thyroid volume 3.38 mL (Figure 1)
19	6.62			discharge from the clinic
20 24 25 28 33 36 46	6.9 7 8 8.6 9.1 10.2 10.7	67.5 68 70 71 74 75 80	41.5 42 42 43 45 45.5 46	First visit in the out-patient clinic
52 56 64 73 83	11.5 12 12 13	80 83 84 85 87	46.5 47 47 47 47.5	BA - 2 yrs 6 months; USG: RL - 14,6x13, 3x34,2 mm; LL - 13x14x31,2 mm; thyroid volume 5.90 mL
90 94 98 103 107	13.2 13 13.5 14.1 14.5	89 89 90.5 91.5 92	47.5 47.5 48 48.5 49	BA - 3 yrs; USG: RL - 12,9x16,1x36,4 mm; LL - 13,1x13, 5x34, 5 mm; thyroid volume 6.54 mL
111	15.3	94.5	49	BA - 4 yrs 2 months; USG: RL - 14,9x17, 4x38,7 mm; LL - 14, 7x13, 4x41, 2 mm; thyroid volume 8.69 mL

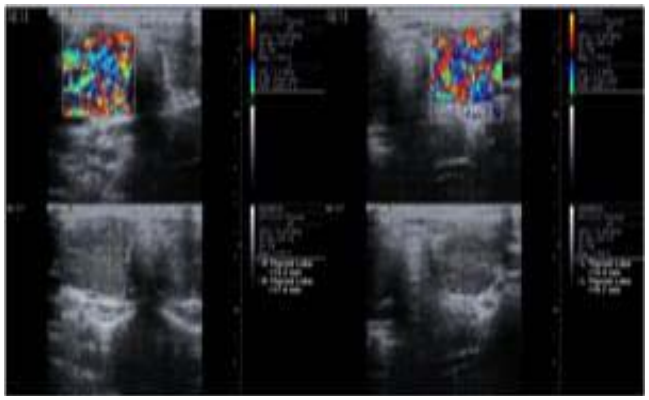

Figure 1: Ultrasound results for the patient on December 12, 2017 at 16 months of age with thyroid lobe measurements noted in the upper images. Lower images represent corresponding arterial vascularization for each thyroid lobe.

age of 4 months, using Greulich and Pyle's bone age assessment.

The patient was treated with 5 mg/day of thiamazole and was discharged 3 weeks later with test results showing TSH <0.005 *μIU/mL* (N: 0.270-4.20 *μIU/mL*; Elecsys TSH assay by Cobas); fT4 –2.69 (N: 0.65-2.3Elecsys fT4 III assay by Cobas); fT3–6.74 (N: 2.15-5.83Elecsys fT3 III assay by Cobas).

After several dose increases with transient periods of normalization of thyroid function, the patient failed to go into remission with antithyroidal medications alone (Figure 2). Bone age was measured again at a chronological age of 1 year; at this time, the patient had a bone age of 2.5 years and exhibited a further increase in thyroid gland volume shown by ultrasound (Table 1). Bone age was measured twice more at 21 months and 25 months and continued to increase disproportionately to chronological age (Table 2). No clinical or biochemical adverse events were observed during the treatment period.

Genomic DNA was extracted from EDTA blood samples obtained from the index patient (child) and her parents. High resolution melting PCR [45] followed by Sanger sequencing detected a c.1895C >T mutation leading to threonine being substituted by isoleucine (p.T632I) in the index patient but not in the parents; therefore, this mutation is categorized as a sporadic germline mutation.

During the course of her treatment, the patient remained within the normal range for weight, height and head circumference according to the Polish guidelines [46] (Table 1; (Supplementary Figures1-3); mid-parental height/target height for the patient is 169 cm, 75th percentile). As the patient's psycho-physical development is normal thus far, the parents and treating physician agreed to delay total thyroidectomy and continue to discuss the patient's parents' concerns regarding anesthesia and post-operative complications. The primary physician continues to monitor the patient's psychological,

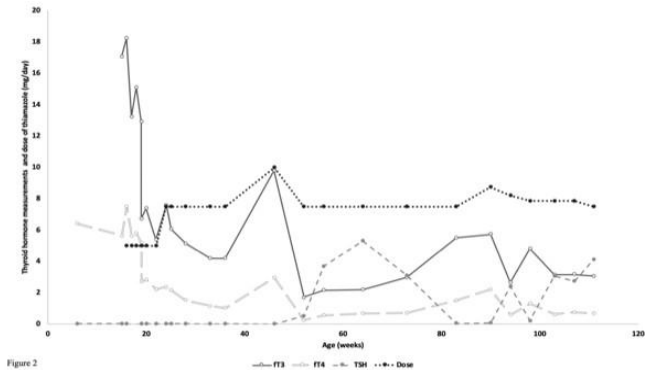

Figure 2: Patient thyroid hormone measurements and thiamazole dose following diagnosis and onset of treatment at 6 and 16 weeks of age respectively. Units of measurement are as follows: fT4 [ng/dl]; fT3 [pg/ml]; TSH [uIU/ml].

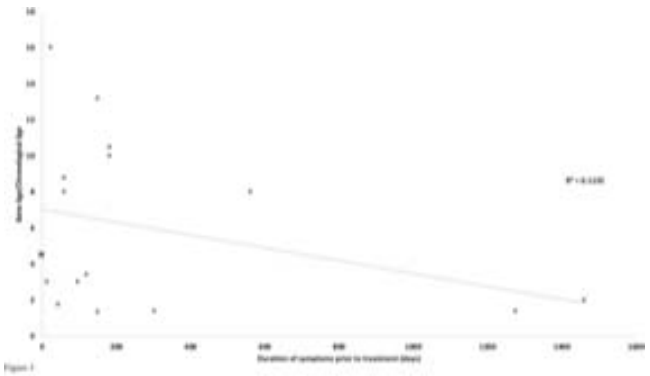

Figure 3: Linear regression analysis of bone age/chronological age and duration of symptoms of patients from Table 1 including present case (represented as a square) with correlation coefficient of 0.1135.

neurological and anthropometrical state and treat with antithyroid drugs.

Discussion/Conclusion

In this study, we describe the case of an asymptomatic neonate with biochemical hyperthyroidism where molecular analysis revealed a sporadic gain-of function TSHR mutation, p.T632I. This mutation has previously been described as a somatic mutation in hot thyroid nodules as well as in both a hot follicular thyroid carcinoma and a hot papillary thyroid carcinoma [45,47,49].

The same nucleotide substitution has been previously described in a case of SNAH with a severe phenotype [2]. However, at variance with the case described by Kopp et al. (1), here we describe a patient with the same TSHR mutation in whom hyperthyroidism was diagnosed without any symptoms. Very different clinical manifestations with regards to severity of symptoms and age of onset for hyperthyroidism have previously been described for the same TSHR germline mutations causing neonatal NAH [8,25,26].

This case is distinguished from all other cases of neonatal NAH by the documented presence of advanced bone age before onset of symptoms. In previously documented cases of neonatal NAH, patients presented with a spectrum of symptoms, the most common of which were tachycardia, restlessness, poor weight gain and diarrhea. Children with biochemical hyperthyroidism are nearly always frankly symptomatic, especially with adrenergic symptoms [50,51]. Had her mother not been treated with levothyroxine during her pregnancy, our asymptomatic patient would not have been evaluated for hyperthyroidism based on heart rate (within normal range) and lack of other symptoms of hyperthyroidism, despite her advanced bone age, which may have gone undetected.

Advanced bone age is thought to be characteristic of children with untreated hyperthyroidism. Advanced bone age is an important concern for children with hyperthyroidism as it impacts adult height and the effects of untreated SNAH hyperthyroidism are not reversible [52-54]. It is not known if the induction of advanced bone age or the induction of craniosynostosis is dependent on the duration of hyperthyroidism.

There are 26 published cases of children with NAH and advanced bone age in 10 families and 13 sporadic cases. Only 15 cases have quantified advanced bone age and documented time of symptoms prior to treatment (Table 2). The correlation coefficient of symptom duration before the start of antithyroid treatment and bone age/chronological age, excluding patients untreated for >1 year, is 0.1135. Although these data are anecdotal, this suggests an absence of correlation between these variables shown in (Figure 3).

Although there is considerable inter and intra-rater variability in bone age determination and different methods for the evaluation of bone age were used, these findings argue that neither the duration of symptoms prior to treatment nor the age at onset of symptoms, two factors which are likely to be the best possible indicators for the duration of untreated hyperthyroidism, explain the degree to which advanced bone age is present. These findings are in line with the finding of this case report with advanced bone age despite a presumed short duration of hyperthyroidism.

TSHR has been demonstrated to be expressed in both osteoblasts and osteoclasts, albeit with cAMP independent pathways [55]. While some studies have proposed that the effect of thyrotoxicosis on the bone is due to increased thyroid hormone rather than decreased TSH, the role of the TSHR in bone is still uncertain [56-58]. The degree of hyperthyroidism may be indicative of one aspect of TSHR signaling whereas the advanced bone age/bone phenotype could also be the result of an alternative pathway based on coupling of TSHR to all four G protein subfamilies [59], some of which are yet to be fully explored, particularly in bone.

NAH patients do not respond well to antithyroid drug treatment and remission of hyperthyroidism is rarely achieved. This was demonstrated early in our case as the patient needed several dose increases which resulted only in transient periods of normalization of thyroid function. For this reason, thyroidectomy is the treatment of choice for NAH [60]. Detection of a TSHR germline mutation and verification of the diagnosis of NAH provides a justification for early total thyroidectomy. Less complete surgeries are associated with frequent relapses [60].

In summary, we report a case of SNAH due to a previously characterized constitutively activating TSHR mutation. This case is unique in that NAH was detected prior to the onset of symptoms, yet bone age was already advanced. Our report demonstrates the importance of early detection and treatment of NAH as hyperthyroidism can impact bone development very early and even before the onset of symptoms.

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