Journal of Pediatric Endocrinology

Open Access

Austin Publishing Group

Case Presentation

A Mutation in PAX8 Presenting as Congenital Hypothyroidism with Incomplete TSH Response to Levothyroxine Treatment

Reinauer C[1]*, Hermanns P[2], Mayatepek E[1], Klee D[3], Pohlenz J[2], Meissner T[1] and Kummer S[1]

[1]Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, 40225 Duesseldorf, Germany

[2]Department of Pediatrics, Johannes Gutenberg University Medical School, 55101 Mainz, Germany

[3]Department of Diagnostic and Interventional Radiology, Medical Faculty, University Hospital, 40225 Dusseldorf, Germany

***Corresponding author:** Christina Reinauer, Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Moorenstr. 5, 40225 Duesseldorf, Germany

Received: August 20, 2018; **Accepted:** October 01, 2018; **Published:** October 08, 2018

Abstract

Mutations in the PAX8 gene can cause Congenital Hypothyroidism (CH) due to thyroid dysgenesis. Diagnosing PAX8 gene mutations may be challenging due to broad phenotypic variability but can be confirmed by sequence analysis. We report the follow-up of a girl with CH due to a heterozygous PAX8 mutation (p.S54G). She showed an incomplete suppression of serum TSH levels despite adequate doses of levothyroxine and thyroid hormone levels in the upper reference range during follow-up. Her case is one of the rare reports worldwide that show incomplete TSH normalization based on a PAX8 mutation despite free T4 levels being in the target range. Supraphysiological free T4 levels can be avoided by aiming to maintain free T4 levels in the upper normal range and observing the clinical follow-up rather than aiming at normalizing TSH levels.

Keywords: Congenital hypothyroidism; PAX8; Neonatal hyperthyrotropinemia; Thyroid dysgenesis

Abbreviations

TSH: Thyroid Stimulating Hormone; PAX: Paired Domain Transcription Factor; TSHR: TSH Receptor; TPO: Thyroid Peroxidase; TG: Thyroglobulin

Introduction

The Pax8 protein (paired domain transcription factor) is involved in thyroid development and Thyroid Peroxidase (TPO) and Thyroglobulin (TG) gene expression [1]. PAX8 mutations are a rare cause of Congenital Hypothyroidism (CH) with thyroid dysgenesis (OMIM #167415) affecting less than 3% of cases [2,3]. Other transcription factors involved in disorders of thyroid differentiation include NKX2.1, FOXE1, the TSH Receptor (TSHR), NKX2.5, and GLIS3 [4,5]. To date, approximately 80 cases of congenital hypothyroidism due to PAX8 mutations have been reported worldwide [2,6,7]. Some PAX8 mutations are also associated with urogenital malformations [8] or CNS abnormalities [9].

Here we report the genetic cause of hypothyroidism in a child diagnosed with CH during routine newborn screening, who had persistently elevated TSH despite high-normal free T4 levels with levothyroxine treatment, and report the clinical course after identifying the PAX8 mutation.

Case Presentation

A female neonate was delivered at 38 weeks of gestation by Caesarean section due to maternal HELLP syndrome after an otherwise uneventful pregnancy. She was the first child of non-consanguineous German parents. Postnatal adaptation was uncomplicated, and she was fully breastfed with good postnatal weight gain. Routine newborn screening on the second day of life showed a significantly increased TSH level of 93 µU/ml. Treatment was started with 40 µg/d of levothyroxine (11.7 µg/kg bw/d) after confirmation on the fourth day of life. At that time, both free T4 at 21.9 pmol/l (n 12-22) and T3 levels at 1.6 ng/ml (n 0.8-3.3) were normal. Thyroid autoantibodies were negative, TG levels were found in the normal range (44.7 ng/ml [n <60.0]). All other laboratory findings were unremarkable. Ultrasound revealed an orthotopic, hypoplastic thyroid gland with a small 2 mm nodule in the left lobe with otherwise homogeneous parenchyma.

The father's sister had a mildly elevated TSH (5.6 µU/ml), the paternal grandfather had struma nodosa, and the paternal grandmother was diagnosed with mild autoimmune thyroid disorder, both with normal thyroid function test. The mother had euthyroid transient TSH-receptor antibody elevation during pregnancy. Otherwise, no abnormalities were noted in the family history.

Thyroid hormone concentrations showed an initial TSH decrease to 0.6 µlU/ml at 2 weeks of age (n 0.5-16, Figure 1). Levothyroxine dosage was therefore gradually reduced, as free T4 levels were elevated to 35.0 pg/ml (n 10.8-20.3) at this time. Treatment with a dosage of levothyroxine 15 µg/d resulted in elevated TSH levels at 3 weeks of age. Subsequently 25 µg (5.2 µg/kg bw/d) of levothyroxine per day was started at 5 weeks of age, resulting in free T4 levels in the upper normal range (Figure 1).

On follow-up, TSH levels were persistently elevated from 6 months of age onwards (from 9.5-52.6 µU/ml) on 25-50 µg/d of levothyroxine, while free T4 was maintained at the upper limit of normal or even above the age-adjusted normal range (upper limit of normal 20.3 pg/ml until 12 months of age or 17.1 pg/ml age 1-6 years). The parents of the patient credibly assured optimal treatment adherence. Notably, serum TSH levels declined only with a short course of increased levothyroxine dosage, leading to elevated free T4 levels. Figure 1 shows the clinical course of the patient from birth to

Citation: Reinauer C, Hermanns P, Mayatepek E, Klee D, Pohlenz J, Meissner T, et al. A Mutation in PAX8 Presenting as Congenital Hypothyroidism with Incomplete TSH Response to Levothyroxine Treatment. J Pediatri Endocrinol. 2018; 3(1): 1024.

5 years of age.

Periodic ultrasound controls revealed unremarkable parenchymal structures and a mildly hypotrophic gland (at age 2.5 years lobes were each 0.2 ml, norm 1.1-4.7 ml).

Persistently elevated TSH levels despite high free T4 and normal T3 levels prompted to screen for TSHR and PAX8 gene mutations by Sanger sequencing. Molecular genetic studies were conducted after written informed consent. While the molecular analysis of the TSHR gene was normal, a single heterozygous mutation was found in exon 3 of the PAX8 gene (c.160A>G, p.S54G, Figure 2). This mutation was previously described in association with nongoitrous CH [10]. It leads to an exchange of a highly conserved serine at position 54 in the DNA-binding domain, which occurred de novo in the patient, as both parents were unaffected.

To prevent overtreatment/supraphysiological free T4 levels, we aimed at maintaining free T4 levels within the upper normal range and observed the clinical follow-ups rather than attempting to normalize TSH. Discontinuation of therapy was waived due to consistently elevated TSH levels mainly >40 µmol/l. Kidney malformations were ruled out by normal ultrasound in this patient. We did not see any evidence for impaired lipid metabolism or extrathyroidal symptoms. In particular, there was no evidence for CNS involvement, as psychomotor development was age-appropriate, all developmental milestones were attained adequately, and the girl thrived well. After the age of 12 months, growth, weight, and body mass index resumed parallel to the 25th WHO percentile, with head circumference on the 90th percentile.

Discussion

To date, the detailed pathophysiologic mechanism of PAX8 mutations leading to hypothyroidism remains largely unknown. Being a transcription factor, PAX8 could relate to dysregulation of transcriptional processes as well as the functional differentiation of thyroid cells [9]. In 2004, Meeus et al. described the same heterozygous mutation (p.S54G) in two Belgian siblings and their father with congenital hypothyroidism and hypotrophic thyroid glands [10].

Functional analyses detected a loss of the DNA-binding ability in the mutant Pax8 protein and an inability to act synergistically with TTF1 (NKX2.1) [5,10]. Similar to our case, both reported children had elevated TSH levels at ages 3.5 and 9 years regardless of adequate levothyroxine doses (3.2-3.9 µg/kg bw/d), clinical euthyroidism, and high-normal free T4 levels [10]. TSH levels could not be persistently normalized. Although PAX8 mutations show a high clinical variability, only very few reports exist worldwide that show incomplete TSH normalization despite free T4 levels being in the target range based on a PAX8 mutation [3,10,11]. Therefore, PAX8 mutations - besides TSHR mutations - should be considered in patients with persistently elevated TSH despite free T4 being well within the normal range.

Learning Points

CH with persistently elevated TSH and high-normal free T4 levels despite levothyroxine treatment should prompt genetic testing for candidate genes affecting thyroid dysgenesis.

Treatment should aim at maintaining free T4 levels within the upper normal range and observing the clinical follow-ups rather than aiming at normalizing TSH levels.

Acknowledgment

We would like to thank the family members for their valuable cooperation and participation, providing written and informed consent to be included in this case report.

Author Contributions

All the authors gave their consent for the entire content of this submitted manuscript and approved submission.

References

1. Macchia PE, Lapi P, Krude H, Pirro MT, Missero C, Chiovato L, et al. PAX8 mutations associated with congenital hypothyroidism caused by thyroid dysgenesis. Nat Genet. 1998; 19: 83-86.
2. Narumi S, Araki S, Hori N, Muroya K, Yamamoto Y, Asakura Y, et al. Functional characterization of four novel PAX8 mutations causing congenital hypothyroidism: new evidence for haploinsufficiency as a disease mechanism. Eur J Endocrinol. 2012; 167: 625-632.
3. Kumorowicz-Czoch M, Madetko-Talowska A, Dudek A, Tylek-Lemanska D. Genetic analysis of the paired box transcription factor (PAX8) gene in a cohort of Polish patients with primary congenital hypothyroidism and dysgenetic thyroid glands. J Pediatr Endocrinol Metab. 2015; 28: 735-743.
4. Pohlenz J, Van Vliet G, Deladoey J. Developmental abnormalities of the thyroid. Genetic Diagnosis of Endocrine Disorders. Academic Press, London, 2016; 127–136.
5. Hermanns P, Grasberger H, Cohen R, Freiberg C, Dörr HG, Refetoff S, et al. Two cases of thyroid dysgenesis caused by different novel PAX8 mutations in the DNA-binding region: in vitro studies reveal different pathogenic mechanisms. Thyroid. 2013; 23: 791-796.
6. Srichomkwun P, Admoni O, Refetoff S, de Vries L. A Novel Mutation (S54C) of the PAX8 Gene in a Family with Congenital Hypothyroidism and a High Proportion of Affected Individuals. Horm Res Paediatr. 2016; 86: 137-142.
7. Montanelli L, Tonacchera M. Genetics and phenomics of hypothyroidism and thyroid dys- and agenesis due to PAX8 and TTF1 mutations. Mol Cell Endocrinol. 2010; 322: 64-71.
8. Carvalho A, Hermanns P, Rodrigues AL, Sousa I, Anselmo J, Bikker H, et al. A new PAX8 mutation causing congenital hypothyroidism in three generations of a family is associated with abnormalities in the urogenital tract. Thyroid. 2013; 23: 1074-1078.
9. Hermanns P, Kumorowicz-Czoch M, Grasberger H, Refetoff S, Pohlenz J. Novel Mutations in the NKX2.1 gene and the PAX8 gene in a Boy with Brain-Lung-Thyroid Syndrome. Exp Clin Endocrinol Diabetes. 2018; 126: 85-90.
10. Meeus L, Gilbert B, Rydlewski C, Parma J, Roussie AL, Abramowicz M, et al. Characterization of a novel loss of function mutation of PAX8 in a familial case of congenital hypothyroidism with in-place, normal-sized thyroid. J Clin Endocrinol Metab. 2004; 89: 4285-4291.
11. Wang F, Liu C, Jia X, Liu X, Xu Y, Yan S, et al. Next-generation sequencing of NKX2.1, FOXE1, PAX8, NKX2.5, and TSHR in 100 Chinese patients with congenital hypothyroidism and athyreosis. Clin Chim Acta. 2017; 470: 36-41.