

# Transient neonatal hypothyroidism in a boy with unbalanced translocation t(8;16)

*Hipotireoidismo neonatal transitório em um menino com translocação não balanceada t(8;16)*

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## SUMMARY

Genetic defects resulting in deficiency of thyroid hormone synthesis can be found in about 10% of the patients with permanent congenital hypothyroidism, but the identification of genetic abnormalities in association with the transient form of the disease is extremely rare. We report the case of a boy with transient neonatal hypothyroidism that was undiagnosed in the neonatal screening, associated with extrathyroid malformations and mental retardation. The boy carries an unbalanced translocation t(8;16), and his maternal uncle had a similar phenotype. Chromosomal analysis defined the patient's karyotype as 46,XY,der(8)t(8;16)(q24.3;q22)mat,16qh+. Array-CGH with patient's DNA revealed a ~80 kb terminal deletion on chromosome 8q24.3qter, and a ~21 Mb duplication on chromosome 16q22qter. *ZNF252* gene, mapped to the deleted region on patient's chromosome 8, is highly expressed in the thyroid, and may be a candidate gene for our patient's transient neonatal thyroid dysfunction. This is the first report on the association of a chromosomal translocation with the transient form of congenital hypothyroidism. This description creates new hypothesis for the physiopathology of transient congenital hypothyroidism, and may also contribute to the definition of the unbalanced translocation t(8;16)(q24.3;q22) phenotype, which has never been described before. *Arq Bras Endocrinol Metab.* 2012;56(8):564-9

## SUMÁRIO

Defeitos genéticos resultando em deficiência hormonal tireoidiana podem ser encontrados em cerca de 10% dos pacientes com hipotireoidismo congênito permanente, porém a identificação de anormalidades genéticas associadas à forma transitória da doença é extremamente rara. Relatamos o caso de um menino com hipotireoidismo neonatal transitório não diagnosticado no teste de triagem neonatal, associado a malformações extratireoidianas e retardo mental. O paciente é portador de translocação não balanceada t(8;16), e seu tio materno tinha fenótipo similar. A análise cromossômica definiu o cariótipo do paciente como 46,XY,der(8)t(8;16)(q24.3;q22)mat,16qh+. A análise cromossômica *array-CGH* com o DNA do paciente revelou deleção terminal de ~80 kb no cromossomo 8q24.3qter, e duplicação de ~21 Mb no cromossomo 16q22qter. O gene *ZNF252*, mapeado na região da deleção no cromossomo 8 do paciente, é altamente expresso na tireoide e pode ser um gene candidato no hipotireoidismo neonatal transitório do paciente. Esse é o primeiro relato de associação de uma translocação cromossômica com a forma transitória do hipotireoidismo congênito. Essa descrição descortina novas hipóteses para a fisiopatologia do hipotireoidismo congênito transitório e também pode contribuir para a definição do fenótipo da translocação não balanceada t(8;16)(q24.3;q22), nunca descrito anteriormente. *Arq Bras Endocrinol Metab.* 2012;56(8):564-9

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## INTRODUCTION

Congenital hypothyroidism (CH), a deficiency of thyroid hormone at birth (1), is the most common congenital endocrine abnormality (2). In general, the condition is permanent; however, some cases are transient – showing a temporary hormonal deficit – and patients do not need lifelong levothyroxine replacement, since recovery of euthyroidism occurs in the first few months or years of life (1,3-5). Since normal thyroid function is essential for development, growth and metabolic homeostasis, transient congenital hypothyroidism (TCH), if not diagnosed or not correctly treated, may cause a deficit in intelligence (6).

TCH can be caused by genetic or non-genetic factors, such as immunologic, environmental or iatrogenic, maternal, or neonatal factors (1,7,8). In the last decade, genetic abnormalities have been identified in some patients, most of them in genes encoding proteins involved in thyroid generation of hydrogen peroxide ( $H_2O_2$ ) – thyroid-oxidase or dual-oxidase 2 (DUOX2), and dual-oxidase maturation factors (DUOXA1 and DUOXA2) (9-13).

Description and genetic analysis of patients with CH may provide important information about the etiology and physiopathology of thyroid diseases, especially in those with syndromic and familial forms of the disorder. We report the case of a boy with TCH associated with extra-thyroid malformations and mental retardation who carries an unbalanced translocation t(8;16), and whose maternal uncle had a similar phenotype.

## CASE REPORT

A boy born from non-consanguineous parents after an uneventful full-term pregnancy, weighting 2,250 g (< 3<sup>rd</sup> percentile), presented ocular hypertelorism, deviated nasal septum, choanal atresia, umbilical hernia, hypospadias, imperforate anus and bradycardia. In the first day of life, he was submitted to surgical treatment for choanal and anal abnormalities. On 7<sup>th</sup> day of life, neonatal screening for CH was negative, with TSH 7.09  $\mu$ U/mL (cutoff level of TSH used in the screening test was 20  $\mu$ U/mL), and total  $T_4$  16.4 g/dL (reference range 4.5-22.20  $\mu$ g/dL). The presence of dry skin, umbilical hernia, and developmental delay led to clinical suspicion of CH, and when the boy was 3 months old, new thyroid function tests were performed and showed severe thyroid hormone deficiency (undetectable serum free  $T_4$ ) associated with serum TSH of 4.97

$\mu$ U/mL (reference range 0.49-4.67  $\mu$ U/mL). Levothyroxine replacement therapy was started (10.1  $\mu$ g/kg daily) and, six weeks later, thyroid function parameters were normal (serum TSH 0.79  $\mu$ U/mL; serum free  $T_4$  1.18 g/dL, reference range 0.7-1.9).

When the patient was seven months old, his bone age was compatible with that of a one-month-old baby. Two months later, he was referred to an endocrinologist for further investigation. Karyotype was performed and disclosed a chromosome unbalanced translocation (see below). Computed tomography of the central nervous system showed no anatomic abnormalities. Abdominal and pelvic ultrasound and echocardiography were normal.

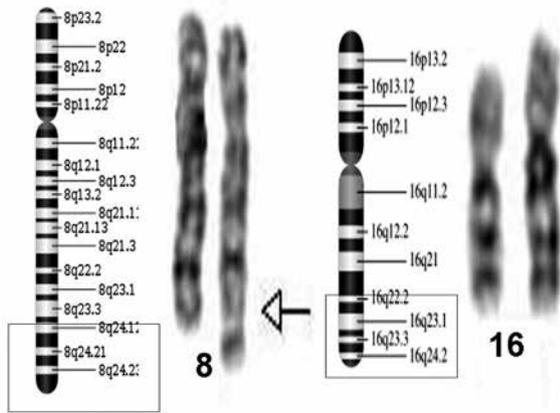
Levothyroxine doses were progressively reduced from 10.1 to 4.9  $\mu$ g/kg/day at eleven months of age. The patient had irregular follow-up from 1 to 4 years old. Nevertheless, all thyroid function tests performed during that period were normal. When the boy reached the age of 3 years and 10 months, levothyroxine dose was 2.5  $\mu$ g/kg/day. Thyroid hormone replacement therapy was then discontinued. Thyroid ultrasound was performed one month later and showed a small-sized gland (0.75 cm<sup>3</sup>) with normal morphology located in the anterior face of the neck. Thyroid scintigraphy confirmed an orthotopic hypoplastic gland. Thyroglobulin serum concentration was normal (17.4 ng/mL, reference range 2.0-60.0 ng/mL), and thyroid autoantibodies were not detected. Since then, the patient remains euthyroid. He had moderate deficit of motor coordination associated with impaired walking due to muscle hypertonia, and delayed speech, but intensive physical and speech therapy since his first years of life have improved his condition significantly. He is able to write his name and read simple words, and has achieved functional independence in self-care. He underwent surgery for hypospadias and deviated nasal septum. In all patient's visits, growth rate was found to be normal, ruling out growth hormone deficiency. The boy, now aged 12, shows the first signs of puberty.

## Genetic analysis

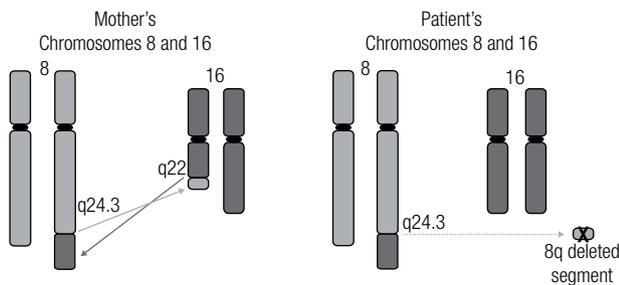
### *Chromosomal analysis after G-banding (550 band resolution) of peripheral blood lymphocytes*

The proband's karyotype showed a derivative chromosome 8 der(8) resulting from a translocation t(8;16) with breakpoints in 8q24.3 and 16q22 inherited from his mother, who carries a balanced reciprocal translocation (Figures 1 and 2). One chromosome 16 pre-

sents large heterochromatin, which represents a polymorphism without clinical significance (16qh+). The proband's karyotype (ISCN 2009) was then defined as 46,XY,der(8)t(8;16)(q24.3;q22)mat,16qh+.

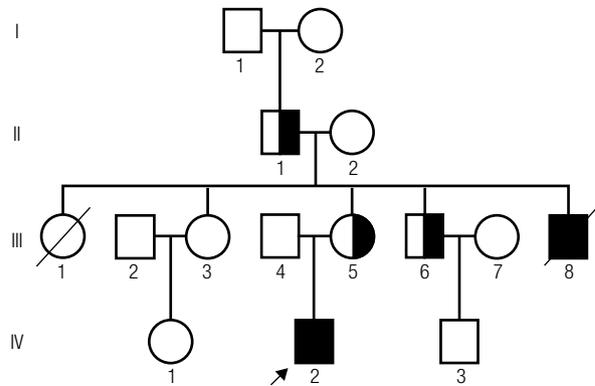


**Figure 1.** Translocated chromosomes 8 and 16 from the patient's karyotype.



**Figure 2.** Schematic representation of patient's mother's (balanced) and patient's (unbalanced) translocation t(8;16). Balanced translocation: genetic material was transferred from chromosome 8 long arm (8q24.3qter) to chromosome 16 long arm (16q), and from 16q (16q22qter) to 8q. Unbalanced translocation: the patient inherited normal chromosomes from his father, an abnormal chromosome 8 from the mother, and one normal chromosome 16 from the mother, resulting in terminal deletion in one chromosome 8, and partial trisomy of chromosome 16.

We also analyzed the chromosomes of other 21 out of 37 family members spanning four generations, and a balanced translocation t(8;16) was found in other three phenotypically normal family members (the patient's mother, one maternal uncle, and the maternal grandfather) (Figure 3). All of them are asymptomatic, and no thyroid dysfunction or autoimmune thyroid diseases were detected. The patient's mother and her brother inherited the balanced translocation from their father, whose parents are still alive and have normal karyotypes. Mental retardation is present in six other family members who do not have any chromosome abnormalities and reported other causes for their deficits.



**Figure 3.** Family pedigree. Black and white individuals (II1, III5 and III6) have a balanced translocation t(8;16). Individuals in black have an abnormal phenotype, including hypothyroidism. Chromosomal analysis was performed on individuals I1, I2, II1, II2, III3, III4, III5, III6, IV2, and IV3, as well as in 12 other family members not shown in the pedigree.

### Array-CGH

For further mapping of the rearrangement, copy number variations of DNA segments (CNV) were investigated in the patient using the Human Genome Comparative Genomic Hybridization (CGH) microarray 60K (Agilent Technologies, Santa Clara, CA). The statistical algorithm ADM-2 was used with a 6.7 sensitivity threshold, and the minimum number of consecutive aberrant probes was set at three to determine an abnormality. The average size for CNV detection was 300 Kb.

Array-CGH with proband's DNA revealed a ~80 kb terminal deletion on chromosome 8q24.3qter (chr8: 146164694-146245835 Build 36/Hg18) and a ~21 Mb duplication on chromosome 16q22qter (chr16: 67957802-88893296 Build 36/Hg18). The genome browsers UCSC (<http://genome.ucsc.edu>) and Ensembl (<http://www.ensembl.org>) were used to assess the known genes mapped to the involved segments. The deletion on chromosome 8 includes only two known genes, *ZNF252* and *C8ORF77*, and a putative pseudogene, all with unknown function. The duplication on chromosome 16 extend from band q22.1qter and includes approximately 283 genes (NCBI build 36.3 September 15<sup>th</sup> 2011). No genes mapped to this segment have been previously related to hypothyroidism.

### Patient's maternal uncle

We accessed the medical records of the patient's maternal uncle, a boy born at full-term in pelvipodal presentation, small for gestational age (1,900 g; < 3<sup>rd</sup>

percentile), with persistent neonatal jaundice. At the time when he was born (22 years ago) screening test for CH was not yet being performed routinely in his area. At the age of four months, he was diagnosed with severe hypothyroidism, and was promptly treated. At eight months of age he was admitted to the hospital because of tracheobronchitis. His weight was 4,780 g (3 kg below -2 SD), and height was 64 cm (-2 SD). He presented syndromic features – a wide anterior fontanel, oblique palpebral fissures, ocular hypertelorism, ogival palate, micrognathia, microstomia, and retractile testes. He also was hypoactive and presented psychomotor delay, not being able to sit or hold objects. Despite receiving levothyroxine therapy (9.15 mcg/kg daily), the patient was still hypothyroid (TSH 12.97  $\mu$ U/mL – normal range for the method was < 7.0  $\mu$ U/mL; T4 5.3  $\mu$ g/dL – reference range 6-16.5  $\mu$ g/dL). Thyroid hormone replacement dose was adjusted, tracheobronchitis was treated, and the patient was discharged from the hospital. He died two months later (at the age of ten months). No further information was found, and the patient's karyotype was not studied.

## DISCUSSION

One of the remaining challenges in thyroid disease physiopathology is the etiologic diagnosis of CH. Genetic causes are rarely identified (2).

Our patient had a syndromic form of transient hypothyroidism associated with mental retardation and an unbalanced translocation inherited from his mother. His maternal uncle presented common phenotypic features, suggesting a similar chromosome abnormality inherited from his father. From all the 23 family members who were studied, the proband and his deceased maternal uncle were the only ones who had confirmed hypothyroidism. All the family members with balanced translocation t(8;16) are asymptomatic and euthyroid.

Oakley and cols. documented much higher prevalence of extrathyroid malformations in patients with transient (14.8%) than in those with permanent CH (5.4%). Nevertheless, of their 344 patients, a chromosomal imbalance – t(14;15) – was diagnosed in only one patient with permanent CH, even though it was not clear how many patients underwent chromosomal analysis (14).

Interestingly, some of the extrathyroid malformations found in our patient, such as hypospadias (15,16), choanal atresia, and anal stenosis (17) have already

been described in association with terminal duplications of chromosome 16 overlapping with the region duplicated in the proband. However, none of these patients presented hypothyroidism.

A complex clinical syndrome involving permanent hypothyroidism, tuberous sclerosis, sclerosis complex, adult polycystic kidney disease, and hypomelanosis of Ito has been associated to an unbalanced translocation t(8;16)(q24.3;p13.3)pat. Nevertheless, different from our case, the patient's family members had already been diagnosed with thyroid diseases (18). Our case report is, to the best of our knowledge, the first to describe a patient with TCH and t(8;16).

Genetic mutations or partial deletion in patients with TCH were described in genes encoding DUOX2, and/or DUOXA1 and DUOX2 (9-13). In spite of this, none of the known candidate genes involved in the thyroid hormone synthesis have been mapped to the deleted segment on our patient's chromosome 8, or to the duplicated segment on chromosome 16. Even the thyroglobulin gene (*TG*), mapped to the long arm of chromosome 8, is out of the deleted region (~12 Mb from breakpoint).

The patient's thyroid phenotype seems to be related to his unbalanced translocation t(8;16), since the balanced translocation observed in his relatives is not associated with any dysfunction. Considering the size of the chromosome 16 duplicated segment, it is possible that the partial trisomy 16q is involved with the patient's syndromic phenotype.

Notwithstanding, we cannot exclude the fact that the partial deletion of the chromosome 8 can participate on the physiopathology of the transient hypothyroidism observed in our patient, mainly because of the *ZNF252* gene, which belongs to the zinc finger genes, one of the largest transcriptional gene regulation family. Although its function is still unknown, *ZNF252* is highly expressed in the thyroid, suggesting a prominent role of the gene in that tissue (19). Consequently, haploinsufficiency of *ZNF252* may be involved in our patient's TCH. Nonetheless, new studies reporting the association of mutations in this gene with CH patients and knockout animals should address the role of *ZNF252* in thyroid function. A case report recently published described *ZNF764* (mapped to chromosome 16q) haploinsufficiency in a patient with mental retardation, hypospadias, and thyroid hormone resistance (20).

Our patient had transient severe hypothyroidism with undetectable serum T4 in his third month of life, but

with inappropriately normal serum TSH for the severity of thyroid hormone deprivation, suggesting central nervous system involvement. At the time of diagnosis, the patient was not assisted by endocrinologists and a dose-response curve with TRH stimulus had not been performed. In the beginning of our study, the patient was euthyroid and on thyroid hormone reposition; therefore, TRH testing was not considered at that time. After levothyroxine discontinuation, we decided not to carry out the TRH test because the probability of a positive test was extremely remote and there were ethical concerns.

Indeed, the patient presented normal growth, normal puberty, and no signs of combined pituitary deficiency. None of the known genes related to development of the thyroid regulatory system or TSH synthesis, including *TRH*, *TSH $\beta$* , and *TRH-R*, are mapped to chromosomal regions affected in our patient's unbalanced translocation.

Regardless of the possible misdiagnosis of CH in the patient's first week of life, it is difficult to explain why he had TSH levels over 7  $\mu$ U/mL on the 7<sup>th</sup> day and not later, when T4 levels were undetectable, but serum TSH concentration remained under 5  $\mu$ U/mL. It is also possible that initial thyroid hormone levels would have reflected an euthyroid state that dramatically changed later on, as he presented hypothyroidism with features of central involvement.

We believe that this description creates new hypothesis for the physiopathology of transient congenital hypothyroidism. Moreover, our case report may also contribute to genetic counseling, and to the definition of the phenotype of the unbalanced translocation t(8;16) (q24.3;q22), which has never been described before.

Consent: this study was approved by the Research Ethics Committee of UNIGRAN – Centro Universitário da Grande Dourados, Brazil. Written informed consents for publication of this case report and any accompanying images were obtained from proband's parents and from all other individuals (from parents of those who were underage) who had their karyotypes studied. A copy of the written consents for the study and for the publication of the data is available for review by the editors of this journal.

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