Case Report ISSN: 2689-1077

Genetics & Molecular Medicine

Normosmic Hypogonadotropic Hypogonadism, Pituitary Hypoplasia, and Testicular Microlithiasis as Presentation of 45XY Robertsonian Translocation

Eric Baghdasaryan[1,2], Robert Turner[3], Osheen Abnous[4], Yadira Valles-Ayoub[3]* and Michael Robinson[5]

[1]*Touro University Nevada College of Osteopathic Medicine, Henderson, Nevada, USA.*

[2]*University of Southern California, Los Angeles, California, USA.*

[3]*FirmaLab, Los Angeles, California, USA.*

[4]*University of California Los Angeles, Los Angeles, California, USA.*

[5]*Marina Diabetes Center, Diabetes & Endocrinology, Redondo Beach California, USA.*

***Correspondence:**
Yadira Valles-Ayoub, FirmaLab, Los Angeles, California, USA.

Received: 24 Aug 2024; **Accepted:** 27 Sep 2024; **Published:** 04 Oct 2024

Citation: Eric Baghdasaryan, Robert Turner, Osheen Abnous, et al. Normosmic Hypogonadotropic Hypogonadism, Pituitary Hypoplasia, and Testicular Microlithiasis as Presentation of 45XY Robertsonian Translocation. Genet Mol Med. 2024; 5(1): 1-3.

ABSTRACT

Male hypogonadism is characterized by the failure of the testes to produce normal levels of testosterone, sperm, or both. It can manifest as either primary hypogonadism (testicular dysfunction) or secondary hypogonadism (hypothalamic pituitary dysfunction). Testosterone is critical for the development of male physical characteristics and plays an essential role in maintaining muscle mass, bone density, sexual function, and overall mood and energy levels. Hypogonadism, either primary or secondary, can present in various stages of life with different associated symptoms. Most commonly prepubertal age males present with delayed puberty, whereas adult males present with symptoms of decreased libido, erectile dysfunction, fatigue, overall lack of energy and infertility. This report describes a case of hypogonadotropic hypogonadism, testicular microlithiasis, and pituitary hypoplasia associated with a 13;14 Robertsonian translocation, an uncommon and incompletely understood etiology of hormonal dysfunction and infertility.

Keywords

Normosmic Hypogonadotropic Hypogonadism, Pituitary Hypoplasia, Testicular Microlithiasis, 45XY Robertsonian Translocation, Genetic Translocation Disorders

Introduction

Robertsonian translocations (Robs) are a specific type of chromosomal abnormality in which two acrocentric chromosomes fuse at their centromeres to form a single chromosome. Acrocentric chromosomes are notable for having a very short p arm and a long q arm. In humans, chromosomes 13, 14, 15, 21 and 22 are classified as acrocentric. In a Roberstonian translocation, the two long arms of the acrocentric chromosomes join together, while the short arms are typically lost. Despite this loss, the short arms usually contain non-essential genetic material, and individuals with this translocation often exhibit a normal phenotype.

Roberstonian translocations are the most common type of chromosomal translocation, found in approximately 1 in 1,000 births. They are considered "balanced" translocations because the individual typically retains a normal amount of genetic material, although rearranged. Therefore, balanced Roberstonian translocations are generally identified in phenotypically normal adults. Nonetheless, carriers of balanced Robertsonian translocations may face reproductive issues, such as infertility, recurrent miscarriages, or the possibility of having offspring with unbalanced chromosomal abnormalities like Down syndrome.

The most common Robertsonian translocation involves chromosomes 13 and 14, representing about 75% of all Robs [1-4]. The incidence rate of Rob (13;14) is estimated to be 0.97 out of 1000 [5]. Generally, Rob (13;14) translocations are passed on by one of the parents or arise spontaneously during oogenesis. The

rate of spontaneous Rob (13;14) translocations during oogenesis is estimated to be 1.5 x 10 -4 mutations per gamete per generation [4,6]. The most common breakpoints were identified at bands 13q10 and 14q10 in most cases [7,8]. While most Rob (13;14) carriers are phenotypically normal, they are at higher risk for infertility, miscarriages, and offspring with abnormal numbers of chromosomes. Furthermore, Rob (13;14) translocations place carriers at increased risk of having offspring with congenital defects, intellectual development delay, and complications associated with uniparental disomy. Typically, carriers of balanced Rob (13;14) translocations transmit the translocation through multiple generations. Some gametes produced by balanced rob carriers are chromosomally unbalanced, and fertilization of those chromosomally unbalanced gametes results in karyotypically unbalanced zygotes. Within unbalanced zygotes, monosomy of chromosome 13q or 14q, or trisomy of 14q, result in fetal demise. Additionally, trisomy of 13q is typically lethal during early development or shortly after birth [7].

Rob (13;14) carriers, along with other Robertsonian translocation carriers, are also at increased risk for uniparental disomy [9]. Reports have consistently shown uniparental disomy to be associated with a Robertsonian translocation involving chromosome 14. Similarly, Rob (13;14) is believed to be associated with trisomy 13, 18, 21, and Turner Syndrome (X chromosome monosomy). A study performed on 1987 Robertsonian translocation carriers revealed a higher risk of breast cancer among Rob (13;14) carriers [10]. Together, these studies highlight the expansive potential clinical sequelae associated with Roberstonian (13;14) translocations.

Various factors are thought to play a role in the development of such clinical outcomes including the precise location of breakpoints, inheritance pattern, and effects on other chromosomes, both near and distant to the translocation location. As such, genetic counseling is becoming increasingly relevant for individuals found to be balanced carriers. This report highlights a unique scenario involving a 20 year old male patient who presented with symptoms of fatigue and difficulty concentrating at school. Work up ultimately revealed low testosterone and gonadotropin levels. Chromosome analysis revealed a 45XY rob (13;14) translocation carrier.

Case Report

A 20-year-old male was referred for endocrine evaluation by his primary care physician with a history of fatigue, lethargy, and difficulty concentrating at school. He had no past medical illnesses, other than some history of delayed pubertal development in his early teenage years. He had no history of cryptorchidism or mumps orchitis. He had no history of disturbance in smell or taste. He was the product of a normal pregnancy and full-term delivery without complications and had no history of delayed intellectual development. He was a college student, focusing on pre-law. His Initial laboratory studies showed a total testosterone of 36.4 ng/dl (264-916) with a free testosterone of 0.9 pg/ml (9.3-26.5). LH and FSH levels were 1.9 mIU/ml (1.7-8.6) and 1.2 mIU/ml (1.5-12.4) respectively. The serum prolactin was 11.9 ng/ml (3.6–31.5).

Additional hormone studies were obtained showing a free T4 of 1.4 ng/dl with a TSH of 0.719 uIU/ml (0.450–4.50). The growth hormone was 1.2 ng/ml (0–10.0) with an IGF-1 of 328 ng/ml (116 to 410). A morning serum cortisol was 18.3 µg per deciliter (6.2 to 19.4) with a plasma ACTH 36.2 pg/ml (7.2–63.3). A Ferritin level was 119 ng/mL (30–400). On physical examination, His height was 5‘7’ and weighed 132 pounds. He had a normal body habitus. There was no skeletal deformity evident. The head was normocephalic but with mandibular prognathism, malocclusion, and dental disarray. He had scant axillary and pubic hair present. There was no gynecomastia or nipple hypoplasia. The testes were small in size and on scrotal ultrasound measured 3.0 x 1.6 x 2.8 cm with 7.0 cc volume on the right and 2.8 x 1.4 x 1.9 cm with 4.0 cc volume on the left. There were numerous punctate, high-level echoes scattered throughout the parenchyma of both testes consistent with microlithiasis.

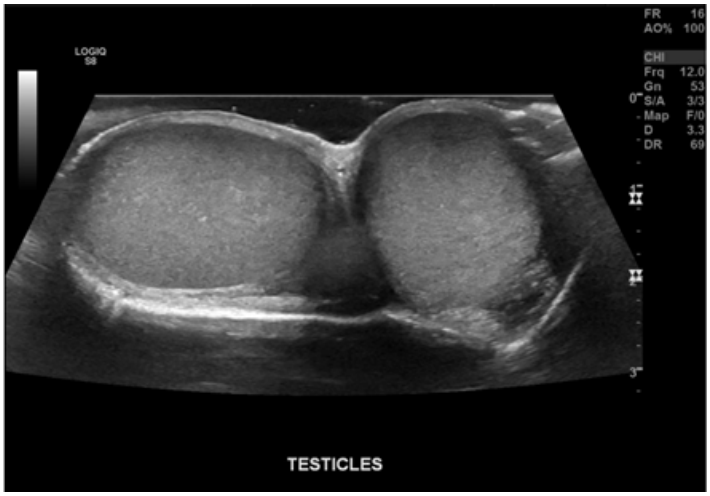
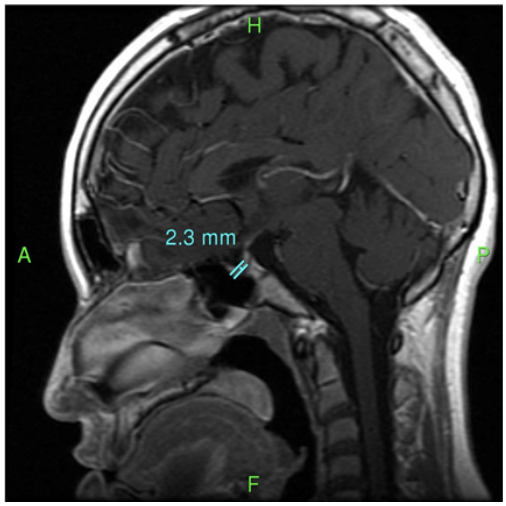


Figure 1: Scrotal ultrasound revealed characteristic “starry sky” appearance: The testes are diminished in size 7.0 cc on the right and 4.0 cc on the left. Testicular microlithiasis is present greater on the right.

A subsequent MRI of the pituitary with and without contrast showed a hypoplastic homogeneous appearing pituitary gland with a height of 2 mm and showing no focal abnormal area of increased or decreased enhancement.



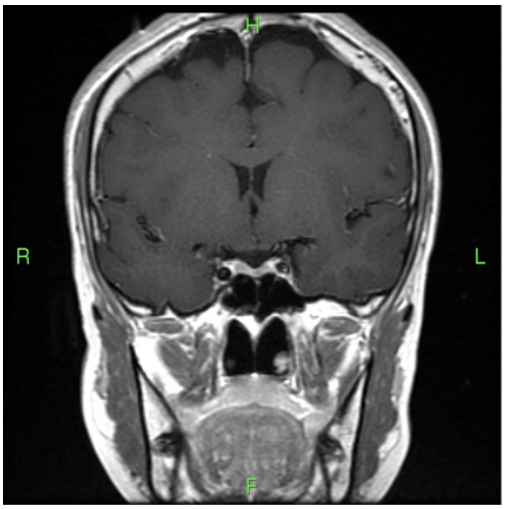


Figure 2: MRI pituitary without and with contrast: Significantly diminished height of the pituitary gland may be based on hypofunction or hyperstimulation. In addition, exogenous administration of hormones could result in a similar appearance.

A chromosome analysis revealed 45XY karyotype with a Robertson translocation between chromosomes 13 and 14 in all cells.

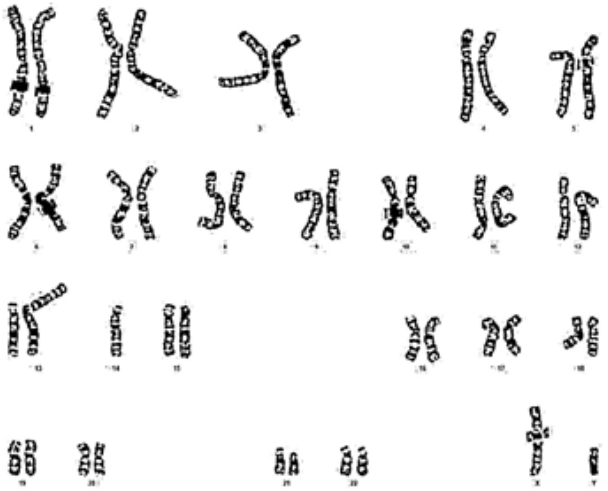


Figure 3: Chromosome, blood, routine. Cells Counted: 20. Cells Analyzed: 20. Cells Karyotyped: 2. Band Resolution: 500. Cytogenetic result: 45, XY, der (13,14)(q10;q10). Interpretation: Robertsonian Translocation Carrier.

Conclusion

To our knowledge, this is the first reported case of a Robertson translocation with this presentation. The association of normosmic hypogonadotropic hypogonadism, pituitary hypoplasia and testicular microlithiasis with this condition has not been previously described. While testicular microlithiasis can be associated with hypogonadism and infertility, the risk for development of testicular cancer is controversial [11,12] and unknown in this population. Affected patients may be candidates for periodic testicular surveillance. Clinical follow-up and genetic counseling is becoming increasingly important in this category of patients.

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