Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/21669
DOI URL: http://dx.doi.org/10.21474/IJAR01/21669

RESEARCH ARTICLE

HYPOGONADOTROPIC HYPOGONADISM IN MOSAIC TURNER SYNDROME: A RARE AND ATYPICAL PRESENTATION

H. Bouaichi[1], S. Habibi[1], G. Bourkadi[1], Z. El Azime[123], M.-A. Essafi[123], H. Aynaou[123] and H. Salhi[123]

1. Department of Endocrinology, Diabetology, Metabolic Diseases and Nutrition, University Hospital Hassan II, Fez, Morocco.
2. Faculty of Medicine, Pharmacy, and Dentistry, Fez, Morocco.
3. Laboratory of Epidemiology and Health Sciences Research.

Manuscript Info

Manuscript History
Received: 20 June 2025
Final Accepted: 23 July 2025
Published: August 2025

Key words:-
Turner syndrome; Mosaicism; Central hypogonadism; Hypogonadotropic hypogonadism; Delayed puberty; Pituitary hypoplasia; Short stature.

Abstract

Turner syndrome is the most common sex chromosome abnormality in girls, typically resulting from complete or partial monosomy of the X chromosome. It is typically associated with short stature and hypergonadotropichypogonadism, due to gonadal dysgenesis and defective ovarian feedback on the hypothalamic-pituitary axis. In this context, elevated levels of follicle stimulating hormone (FSH) and luteinizing hormone(LH)are expected during puberty.The occurrence of hypogonadotropichypogonadism in a patient with Turner syndrome is highly unusual and may lead to diagnostic confusion, as it contradicts the expected endocrine pattern.We report a rare case of a 13 year and 9 month old girl referred for evaluation of delayedpubertyandshortstature,with no dysmorphic features.Hormonal analysis revealed low gonadotropin levels. Cytogenetictestingshowedamosaickaryotype(45, X/46, XX), and pituitaryMRIrevealed anterior pituitaryhypoplasia, consistent with central hypogonadism, the evaluation of the remaining pituitary axes, including the thyrotropic,corticotropic, and somatotropic axes, revealed preserved endocrine function.This case highlights the diagnostic challenges posed by atypical presentations of Turner syndrome. Although hypergonadotropic hypogonadism is the norm, the coexistence of central hypogonadism especially in mosaic cases should be considered. Clinicians must remain vigilant for hypothalamic or pituitary dysfunction in Turner patients with unexpected hormonal findings to ensure accurate diagnosis and optimal management.

"© 2025 by the Author(s). Published by IJAR under CC BY 4.0. Unrestricted use allowed with credit to the author."

Introduction:-

Turner syndrome (TS) is a chromosomal disorder affecting approximately 1 in 2,000 to 2,500 live births assigned female**(1).** It is characterized by complete or partial monosomy of the X chromosome and is associated with a well-recognized spectrum of clinical manifestations, including short stature, congenital anomalies, and endocrine dysfunctions. The most consistent endocrine abnormality is hypergonadotropic hypogonadism, secondary to ovarian

Corresponding Author:-H. Bouaichi
Address:-Department of Endocrinology, Diabetology, Metabolic Diseases and Nutrition, University Hospital Hassan II, Fez, Morocco.

dysgenesis and consequent absence of negative feedback on the hypothalamic-pituitary axis. The clinical presentation of TS varies significantly across different stages of life. In the neonatal period, it may include lymphedema or congenital heart defects; during childhood, short stature and growth failure are prominent features; while in adolescence, delayed puberty and gonadal insufficiency become the main clinical concern.

Although uncommon, hypogonadotropic hypogonadism may coexist with TS, particularly in individuals with mosaic karyotypes. This atypical association can be clinically misleading, as it deviates from the classical endocrine phenotype of TS. The underlying pathophysiology remains poorly understood but may involve congenital anomalies of the hypothalamus or pituitary gland, such as anterior pituitary hypoplasia, or genetic defects impacting pituitary development. In such cases, gonadotropin secretion (FSH and LH) may be impaired irrespective of gonadal status, complicating both the diagnostic process and therapeutic decision-making.

We report the case of a girl with mosaic Turner syndrome and hypogonadotropic hypogonadism, associated with anterior pituitary hypoplasia. This rare clinical presentation underscores the importance of investigating central causes of hypogonadism when hormonal findings are inconsistent with the established clinical or cytogenetic context.

Case report:

We report the case of a 13-year-and-9-month-old girl admitted to our department for the investigation and management of short stature and delayed puberty. She was the first child of healthy parents with a first-degree consanguineous relationship. Pregnancy and delivery were uneventful, and she was born at term. There was no relevant personal or familial medical history.

On clinical examination, her weight was 25 kg (−5 SD), height 132 cm (<−4 SD), and BMI was 14.3 kg/m², consistent with underweight. Her target height was within the −4 SD range. No dysmorphic features were noted, specifically no pterygiumcolli, cubitus valgus, low posterior hairline, or other physical signs suggestive of Turner syndrome. There were no clinical signs of pituitary tumor syndrome. Tanner staging showed breast and pubic hair development at stage I, with underdeveloped external genitalia, consistent with delayed puberty.

Bone age, assessed by the Greulich and Pyle method, was 10 years, reflecting a delay of 3 years and 9 months compared to her chronological age.Given the short stature and delayed bone age, a cytogenetic analysis was performed and revealed a mosaic Turner syndrome (45,X (CEPXx1,SRYx0)[5] / 46,XX (CEPXx2,SRYx0)[95]) with no SRY gene detected. A representative karyotype image is shown in Figure 1.

Given the delayed puberty, a hormonal workup was conducted. Gonadotropin levels revealed hypogonadotropic hypogonadism: FSH was 1.35 mIU/mL and LH was 0.13 mIU/mL. According to Tanner stage I reference ranges (FSH: 0.3–3.8 mIU/mL; LH: 0.1–1.0 mIU/mL), Estradiol was undetectable (<5 pg/mL).

These values were within prepubertal limits but were considered inappropriately low for her chronological age, indicating insufficient activation of the hypothalamic–pituitary–gonadal axis. Other pituitary hormones were within normal ranges: prolactin 8.4 ng/mL, TSH 2.102 µIU/mL (0.340–5.6), free thyroxine (FT4) 0.87 ng/dL (0.61–1.12), and morning cortisol (measured at 08:00 AM) 12 µg/dL, indicating normal function of the thyrotropic, corticotropic, and somatotropic axes.

Pelvic ultrasound revealed a prepubertal uterus measuring 22 x 7 mm, with a globular shape and no visible endometrial line. The ovaries were small, measuring 10 x 6 mm on the right and 9 x 5 mm on the left, with no identifiable follicles. These findings are consistent with a hypogonadal state.

Magnetic resonance imaging (MRI) of the hypothalamic–pituitary region, using sagittal and coronal T1- and T2-weighted sequences, revealed anterior pituitary hypoplasia, with a height of 3.9 mm, consistent with an age-inappropriately small pituitary gland. No additional midline or structural anomalies were identified.

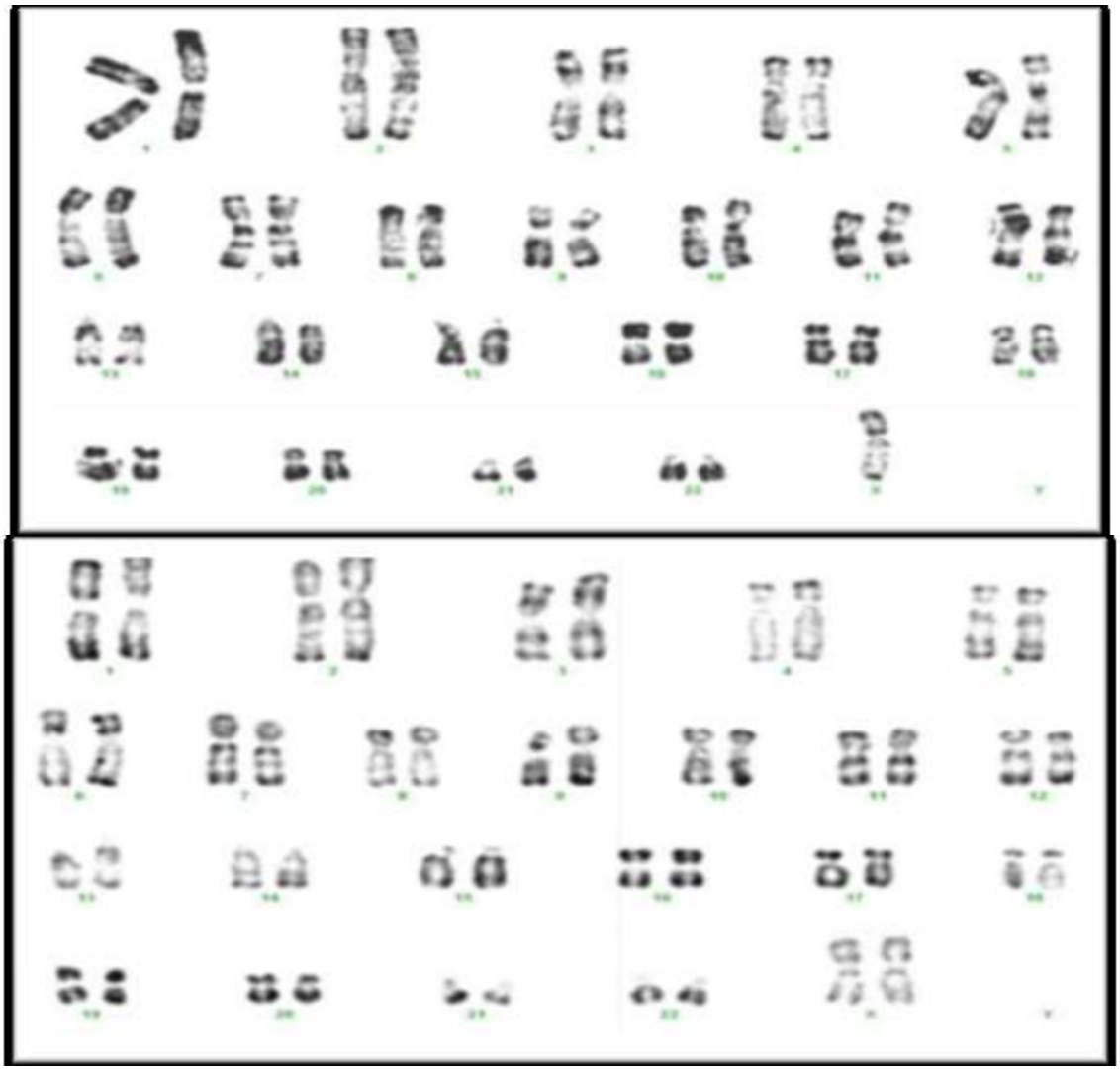

Figure 1. **Karyotype image of our patient**

Following the diagnosis, a complementary assessment was initiated to screen for Turner Syndrome–related complications. The patient was referred for cardiac, renal, and audiological evaluations, as well as for thyroid, glucose, and lipid testing all of which returned normal findings.

The therapeutic decision was to initiate treatment with recombinant growth hormone (rGH), with low-dose estrogen therapy planned to allow for optimal prepubertal growth before inducing puberty

Discussion:-

Turner syndrome (TS) is a rare chromosomal disorder resulting from complete or partial monosomy of the X chromosome, with an estimated prevalence of 1 in 2,500 live female births **(1).** It is characterized by short stature, gonadal dysgenesis leading to hypergonadotropic hypogonadism, and various systemic manifestations, including cardiac, renal, and skeletal anomalies **(2,3).** The typical hormonal profile involves elevated FSH and LH due to impaired ovarian feedback on the hypothalamic-pituitary axis.

The coexistence of TS with hypogonadotropic hypogonadism is extremely rare. To our knowledge, there have been 13 documented cases of Turner syndrome associated with hypogonadotropic hypogonadism, including four familial cases and nine sporadic cases. This rare association presents a diagnostic challenge due to the paradoxical hormonal profile and overlapping clinical features. A comparative summary of reported cases is provided in Table 1.

Our case illustrates this unusual association in a mosaic TS patient with pituitary hypoplasia. The diagnosis was based on the presence of short stature, delayed puberty, and the identification of a 45, X0/46, XX karyotype. Hormonal evaluation showed inappropriately low gonadotropin levels for chronological age, and MRI confirmed pituitary hypoplasia.

Previous case reports have proposed several mechanisms to explain this association. Valenta et al. (1984) described two cases potentially linked to autoimmune hypophysitis or arachnoidocele**(4)**. Donti et al. (1989) reported a patient with combined immune deficiency **(5).** In other cases, iron overload from chronic transfusions (thalassemia major) was implicated **(6).**These conditions differ significantly from our patient, who showed no signs of autoimmunity, immune deficiency, or chronic transfusions.

Congenital pituitary malformations, such as hypoplasia or empty sella, were identified in several reports (**7,8).** Some authors also suggested a genetic predisposition, particularly in familial forms **(11).**

Table 1. Summary of reported cases of Turner syndrome associated with hypogonadotropic hypogonadism

Authors (Year)	Age	Karyotype	PituitaryFindings	Hormonal Profile	Associated Conditions
Valenta et al. (1984) [4]	20 & 25 yrs	45,X / ?	Arachnoidocele	Lowgonadotropins	Autoimmunitysuspected
Donti et al. (1989) [5]	13 yrs	X-ring	Normal MRI	Lowgonadotropins	Combined immune deficiency
Afonso Lopes et al. (1995) [6]	14 yrs	45,X / ?	Pituitaryironoverload (hemochromatosis)	Panhypopituitarism	Thalassemia major
Gallicchio et al. (2003) [8]	14 yrs	45,X	Empty sella	Panhypopituitarism	–
Efstathiadou et al. (2000) [9]	27 yrs	45,X / 46,XX	Hypoplasticpituitary	Panhypopituitarism	–
Pakpahan et al. (2020) [10]	27 yrs	Mosaic 45,X0/46,XX	Not specified	Hypogonadotropichypogonadism	–
Bougacha-Elleuch et al. (2016) [11]	4 sisters (adults)	45,X / 46,XX (familial)	Hypopituitarismin 3 sisters	Central hypogonadism	Parental consanguinity, suspectedrecessive traits
Cucu et al. (2011) [7]	13 yrs	45,X	Pituitaryhypoplasia	Panhypopituitarism	–

The clinical relevance of this association lies in its misleading presentation. The absence of the expected hypergonadotropic profile may delay the diagnosis of TS, particularly in mosaic forms without typical phenotypic features. In our case, the absence of dysmorphic signs and the presence of low gonadotropins prompted a broader diagnostic workup, including karyotyping and MRI.

While our patient had a normal thyroid axis, as reported in several similar cases **(9-10**), this finding alone does not rule out other central endocrine deficits. A limitation of our case is the absence of dynamic pituitary testing to explore potential additional hormonal deficiencies.

Clinically, this case highlights the importance of suspecting central hypogonadism in patients with TS and atypical presentations. It reinforces the need for multidisciplinary evaluation, including endocrine, genetic, and radiological assessments. Early identification of pituitary anomalies may influence both diagnostic and therapeutic strategies.

Conclusion:-

This case highlights the need for thorough investigation of atypical presentations of Turner syndrome, particularly when the expected hypergonadotropic profile is absent. Recognizing the possible coexistence of central hypogonadism is essential for accurate diagnosis and appropriate management. A multidisciplinary approach involving endocrinological, genetic, and radiological evaluation is crucial to guide both the diagnostic process and therapeutic decisions in such complex presentations.

References:-

1-Syndrome de Turner Protocole national de diagnostic et de soins Centre de Référence des maladies endocriniennes rares de la croissance et du développement / Octobre 2021
2- Ranke MB, Saenger P. Turner's syndrome. Lancet. 2001 Jul 28;358(9278):309-14. doi: 10.1016/S0140-6736(01)05487-3. PMID: 11498234.
3. Sybert VP, McCauley E. N Engl J Turner's syndrome Med. 2004;351:1227–1238.
4 - Valenta LJ, Elias AN, Bocian M. Atypical biochemical findings in Turner's syndrome: identification of a possible subset. FertilSteril. 1984 Nov;42(5):798-802. doi: 10.1016/s0015-0282(16)48211-7. PMID: 6436075.
5- Donti E, Nicoletti I, Venti G, Filipponi P, Gerli R, Spinozzi F, Cernetti C, Rambotti P. X-ring Turner's syndrome with combined immunodeficiency and selective gonadotropin defect. J Endocrinol Invest. 1989 Apr;12(4):257-63. doi: 10.1007/BF03349979. PMID: 2745937.
6- Afonso Lopes, A., Benador, D., Wacker, P. et al. (1995) Turner's syndrome and hypogonadotrophic hypogonadism: thalassemia major and hemochromatosis.
J. Pediatr. Endocrinol. Metab., 8,73–77.
7- C Cucu , C Poiana , D Hortopan , A Dumitrascu.al Unexpected association: Turner syndrome and hypopituitarism: a case report (2011) Presented at Society for Endocrinology, Endocrine Abstracts (2011) 26 P629
8 -Gallicchio CT, Alves ST, Ramos HI, Llerena JC, Guimarães MM. Association of Turner's syndrome and hypopituitarism: a patient report. J PediatrEndocrinolMetab. 2003 Jul-Aug;16(6):901-5. doi: 10.1515/jpem.2003.16.6.901. PMID: 12948305.
9- Zoe Efstathiadou, Agathocles Tsatsoulis, Turner's syndrome with concomitant hypopituitarism: Case report, Human Reproduction, Volume 15, Issue 11, November 2000, Pages 2388–2389, https://doi.org/10.1093/humrep/15.11.2388
10 - Cennikon Pakpahanet.al–Case Report : A Woman 27 Year Old with Mosaic Turner Syndrome Associate Hypogonadotropic Hypogonadism Indonesian Andrology and Biomedical Journal –Vol.1 No. 2 December 2020
11- N. Bougacha-Elleuch , M. Elleuch , N. Charfi , et al. Association inhabituelle du syndrome de Turner et de l'hypopituitarisme dans une famille tunisienne CurrResTransl Med. , 64 (1) (2016) , pages 9 à 13 ,10.1016/j.retram.2016.01.003