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ORIGINAL ARTICLE

Occurrence of Hypopituitarism in Tunisian Turner Syndrome patients: familial versus sporadic cases

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ABSTRACT

Objective: To explore unusual association between Turner Syndrome (TS) and Hypopituitarism in a Tunisian cohort.

Methods: We reported 6 patients with TS associated to Hypopituitarism, including three familial cases except the fourth sister who showed only a TS phenotype. Biochemical analysis, resonance magnetic imaging and cytogenetic analyses were performed.

Results: The average age of our patients was 17.2 years (11–31 years). They were all referred for short stature and pubertal delay, except for the fourth sister who presented spontaneous puberty with the integrity of the pituitary axis and the presence of an X ring chromosome. Karyotype analysis showed monosomy in 3 cases and a mosaic TS in the 3 remaining cases, including one patient with abnormal X chromosome structure. Somatotropic and corticotropic deficiencies were confirmed in 2 sporadic cases while the gonadotropic and thyrotropic axes were spared. In contrast; familial cases were consistently affected by the integrity of the corticotropic axis. MRI showed pituitary hypoplasia in all familial cases and pituitary stalk interruption syndrome in only one sporadic case. No correlation was found between the chromosome formula and the anterior pituitary involvement.

Conclusion: Co-segregation of congenital Hypopituitarism with pituitary hypoplasia and X chromosome aberrations could imply a molecular anomaly of transcription factors responsible for the differentiation and development of pituitary cells such as PROP1, POUF1, Hesx1, Lhx3, Lhx4. The etiopathogenic link between X chromosome abnormalities and the occurrence of Hypopituitarism remains unclear; however, the progress of molecular biology may clarify the interrelation between transcription factors and sex chromosome segregation abnormalities.

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Introduction

Turner Syndrome (TS) is a chromosomal condition resulting from a partial or complete absence of one of the two sex chromosomes (the X chromosome) in females. It affects nearly 1 per 2500–4000 female births [1,2]. Females with TS tend to have developmental abnormalities such as short stature, gonadal dysgenesis, and congenital malformations. Hypopituitarism, defined as the complete or partial insufficiency of hormone secretion from the anterior pituitary, has an incidence of approximately 1 in 10,000 individuals. It may result from either genetic conditions or acquired lesions of the hypothalamo-pituitary region. Clinical features may include short stature, impaired sexual maturation, hypothyroidism, and/or hypocortisolism. Association between TS and Hypopituitarism is an unusual finding. Only scarce cases are reported in the literature and pathophysiological mechanisms are still unknown. Thus, it was reported in two cases where a combined growth hormone, gonadotrophin, and thyrotrophin deficiency was confirmed [3]. Recently, we have reported 3 familial cases affected with both TS and Hypopituitarism [4].

In this study, we present an additional series of 3 sporadic patients with this particular and rare association, attaining the largest cohort in literature. This co-segregation has raised an exciting hypothesis which postulates that the interrelation between transcription factors and segregation abnormalities of sex chromosomes could be responsible for a cascade of endocrine pituitary damage.

Patients and methods

We reported 6 patients with TS associated with Hypopituitarism including three sisters [4], who had been referred to the Endocrinology department at Hedi Chaker Hospital, Sfax, Tunisia for statural and pubertal delay. A seventh case, who was a fourth sister to the family cases, showed only a TS phenotype (Figure 1).

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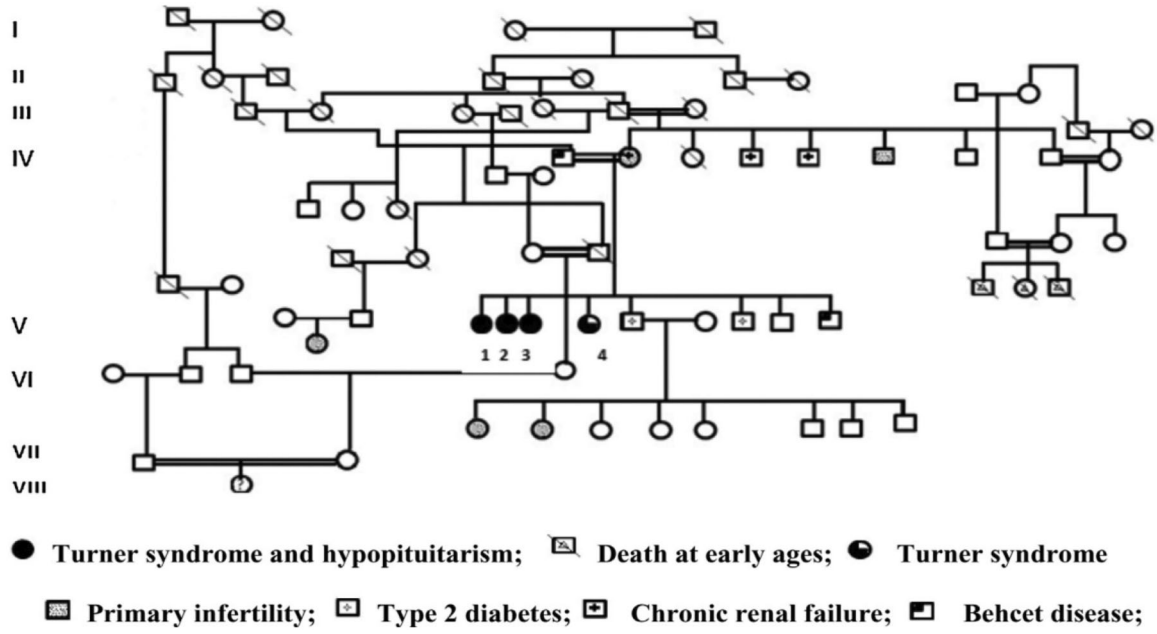

Figure 1. Pedigree of 'F' family.

Biochemical analysis

Hormone dosing was carried out by means of standard Radio Immuno-Assays. ACTH deficiency (ACTH-D) was suspected when the 08 a.m. cortisol level was between 50–180 ng/ml and confirmed by an impaired cortisol response to the stimulation Synactyn test (1 µg tetracosactide) below 180 ng/ml with normal or low basal plasma levels of ACTH [5]. Gonadotropin insufficiency was confirmed when low serum estradiol levels (<40 pmol/l) were associated with inappropriately low serum gonadotropin concentrations. Thyreotrope deficiency was confirmed when inappropriately low serum TSH levels were associated with subnormal serum-free T4 concentrations. Growth hormone deficiency (GH-D) was established by the failure of GH to raise more than 10 ng/ml after a provocative test (insulin tolerance test). All patients were tested for GH after administration of insulin (0.1 U/kg veinously). Blood sample measurements of serum GH were obtained at 0, 30, 60, 90, and 120 min.

Conventional cytogenetic analysis

Routine cytogenetic analysis was carried out with heparinized peripheral blood [6]. More than 30 metaphases were spotted and analyzed through GTG banding with over 550 band resolutions observed. Karyotype was performed in accordance with the ISCN standards [6].

Molecular cytogenetic analysis

Fluorescence *in situ* hybridization (FISH) analysis was performed using SRY and CEPX probe for Y and X chromosomes, respectively. The protocol required direct culture of cells acquired from blood samples. 200 interphase cells were analyzed, and signals were counted accordingly. Images were recorded using an Olympus fluorescence microscope equipped with a CCD camera and analyzed using Cytovision 3.9 V software.

Results

The mean age at diagnosis was 17.2 years (11–31). Patients were referred for delayed puberty (TANNER stage ranging between I and IV) or for short stature (−2 SD and −4 SD), with a height ranging from 123 to 147 cm. All patients exhibited a typical phenotype of TS: a round face with micrognathia, a short neck, pigmented noevi, short fourth metacarp, and low hair implantation. Karyotype analysis confirmed TS with monosomia in 3 cases and mosaicism in 4 cases including one case with structural abnormalities of the X chromosome and one with a ring X chromosome. The growth hormone deficiency (GH-D) was confirmed in three cases based on the insulin tolerance test failure to induce an increase of GH level more than 10 ng/ml.

Diagnosis of central hypothyroidism was established in three cases as they showed low serum free T4 concentrations (pmol/L) (mean value: 4.7; extremes: 4.2) concomitant with low-normal serum TSH (mUI/L) (mean value: 1.5; extremes: 1.2–2).

Corticotropin deficiency was confirmed in two cases as they had low serum cortisol (mean value: 75.75 [ng/ml], extremes: 0.5–151) concomitant with low plasma ACTH (mean value: 8.5 [pg/ml], extremes: 4–13).

Hypogonadism was confirmed in three cases as no raise in FSH and LH levels concomitant with low serum estradiol levels.

Posterior pituitary function explored in all patients was normal. The MRI showed an empty sella in two cases, pituitary hypoplasia in one case, an interruption of the pituitary stem in one case, and no anatomic abnormalities in the other two cases (Figure 2). The diagnosed features of patients are illustrated in Tables 1 and 2.

Discussion

TS is known to be associated with congenital abnormalities, yet association with Hypopituitarism is an unfamiliar finding. The first case of a pituitary deficiency co-occurring with gonadal dysgenesis owing to a TS was described by Efstathiadou in 2000 [7]. At the onset, the patient was diagnosed with somatotropin, thyrotropin, and gonadotropin deficiencies. Afterward, with the

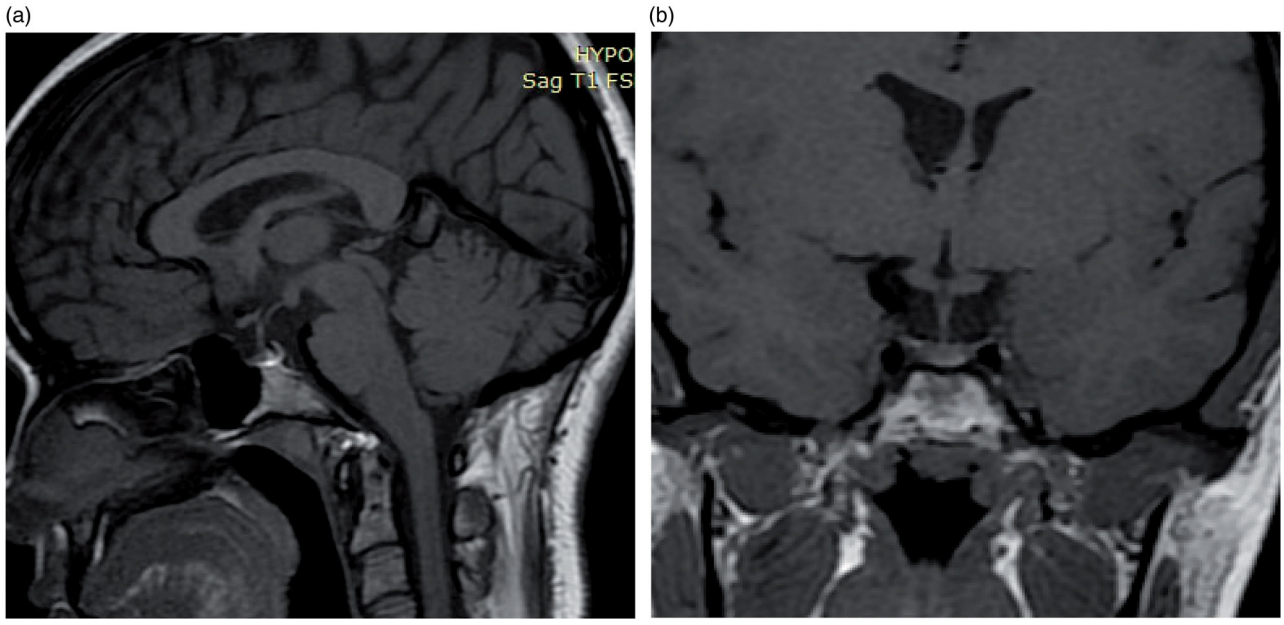

Figure 2. Pituitary sagittal (a) and coronal (b) magnetic resonance imaging scans showing hypoplastic adenohypophysis for patient case 6 (V3).

Table 1. Clinical characteristics of studied patients according to karyotype analysis.

	Case 1	Case 2	Case 3	Case 4 (V1)	Case 5 (V2)	Case 6 (V3)	(V4)
Age (years)	20	20	21	57	40	46	47
Age at diagnostic (years)	14	11	16	31	14	17	43
Height [cm (SD)]	123 (−4 SD)	125 (−4SD)	135 (−4SD)	136 (−4 SD)	144 (−3SD)	147 (−2SD)	156
BMI (kg/m^2)	17.18	16	19.2	25	18	22	26
Bone age (years)	10	09	12	-	12	-	-
Dysmorphyic syndrome	Micrognathia pigmented noevi Short fourth metacarp Low hair implantation	Short neck pigmented noevi Short fourth metacarp Low hair implantation	Micrognathia Short neck Pigmented noevi Low hair implantation	Micrognathia short neck Pigmented noevi Short fourth metacarp Low hair implantation round face	Short neck pigmented Noevi Short fourth Metacarp Low hair implantation	Micrognathia Short neck Short fourth metacarp Low hair implantation	Cubitus valgus Short neck Low hair implantation
TANNER stage	I	I	III	IV	III	IV	V
Karyotype	45X0	45X/46XX	Mos45, X[15]/46, X, i(X)(q10)[10]/ 46, XX[5]	45X0 (8%)/46XX	45X0 (23%)/46XX/ 47XXX (3%)	45X0	45X0 (13%)/46XX/ 47XXX (4%) + r(X)

ascertainment of several clinical characteristics and the absence of ovarian tissue on ultrasound, karyotype was carried out. Results revealed concrete gonadal dysgenesis secondary to TS with no evidence of mosaicism. MRI showed a hypoplastic pituitary gland and an ectopic localization of neuro-hypophysis. So far, only nine cases of TS associated with Hypopituitarism have been reported in the literature (Table 3). Three congenital cases with such an association were already reported in 2016 by our team, as described in Table 1 (cases 4, 5, and 6) [4]. Up to date, only 12 cases with Hypopituitarism associated with TS are described (half of them are reported in our series). Interestingly, the familial occurrence of this association is seen in 5 out of 12 patients.

The mean age at Hypopituitarism diagnosis in our cases was 17.2 years (11–31); which was later in adulthood as compared to literature. In fact, some of the clinical features of Hypopituitarism, such as short stature and impaired sexual maturation, are similar to those of TS. As the association between TS and Hypopituitarism is rare and misunderstood, Hypopituitarism could remain undiagnosed for many years. In order to comfort the interpretation of the results obtained in our clinical investigation, we combined them with the already reported cases in the literature (Table 3).

The somatotropic axis was preserved in only one sporadic case, among all explored patients. However, the gonadotropin and thyreotropin axes were deficient in all familial cases and only in 2/7 sporadic patients; suggesting a co-segregation with a gene implied in gonadotropin and thyrotropin cell differentiation and development. It is worth mentioning that in our series, unlike familial cases aged between 40 and 57 years, sporadic patients are still young (20 years) to be definitively evaluated for their gonadotropin function. A regular follow-up would be necessary.

Correlation between sexual chromosome abnormalities and the occurrence of pituitary deficiency was not detected. As for

Table 2. Results of hormonal and imagery investigation according to karyotype analysis.

	Case 1		Case 2		Case 3		Case 4 (V1)		Case 5 (V2)		Case 6 (V3)		(V4)
	Congenital Turner: Family 'F'												
Age at diagnosis/Current age (years)	14	20	11	20	16	21	31	57	14	40	17	46	43
Gonadotropic Axis													
FSH (mU/l)	-	66	70	-	120	-	0.2	-	2	2.3	1	-	30
LH (mU/l)	-	12	7.1	-	13	-	9	-	-	0.9	5	-	23
E2 (ng/ml)	-	<5	12	-	9	-	-	-	1	7	9	-	11
PRL (ng/ml)	-	14	-	-	9	-	0.2	-	8	<9	-	-	<9
Corticotropic Axis													
Cortisol(ng/ml)			***		**		***	***	***	***	***		***
Basal	201	0.5	117	184	151	-	198	221	189	201	125	-	144
Peak	-	-	201	-	128	-	312	203	241	192	251	-	202
ACTH (pg/ml)	-	4	-	-	13	-	-	-	-	36	-	-	-
Thyreotrope Axis													
TSH (mU/l)	8.5	6	2.6	2.4	4.4	-	1.5	-	2.06	-	1.2	-	2.7
FT4 (pmol/l)	16	15.5*	12.6	16.3	17.4	-	4.2	15*	5.9	11*	4.2	-	13
Somatotrope Axis													
GH(ng/ml)	**		**		**								**
Basal	0.21	-	0.043	-	0.28	-	0.01	-	-	-	-	-	2.8
Peak	17	-	0.02	-	1	-	0.27	-	-	-	-	-	22.4
IGF1(ng/ml)	103	-	-	-	-	-	-	-	-	-	-	-	107
Pituitary deficiency	Corticotropin		Somatotrope		Corticotropin somatotrope		Gonadotropin Thyreotrope somatotrope		Gonadotropin thyreotrope		Gonadotropin thyreotrope		
Pituitary MRI	Normal		Normal		Interruption of the pituitary stem		Empty sella		Empty sella		Hypoplastic pituitary		Normal
Karyotype	45 × 0		45X/46XX		45X0 [15]/46, X, i(X)(q10) [10]/ 46, XX [5]		45X0 (8%)/46XX		45X0 (23%)/46XX/ 47XXX (3%)		45X0		45X0 (13%)/46XX/ 47XXX + r(X)

*L-Thyroxine treatment; **test for insulin hypoglycemia; ***Synactyn test; - not determined.

Table 3. Literature review of published cases of coexisting Turner Syndrome and Hypopituitarism.

Number of cases	Gonadotropic deficit	Somatotrope deficit	Thyreotropic deficiency	Corticotropic deficit	Karyotype	MRI	Reference
1^S	+	+	+	−	45X0	Hypoplastic pituitary, Ectopic posthypophysis	[7]
1^S	+	+	+	−	45X0/46XX		[10]
2^F	+	+	+	−	45X0/46XX/47XXX	Hypoplastic pituitary Empty sella	[11]
1^S	−	+	−	−	45, X/46, XY	Normal	[12]
1^S	−	+	−	+	45, X/46, XY	Normal	[13]
3^F	+	+	+	−	45X0 (8%)/46XX.	Empty sella	[4]
	+	−	+	−	45XO (23%)/ 46XX/ 47XXX(3%)	Hypoplastic pituitary	
	+	−	+	−	45X0	Empty sella	
V4 patient	−	−	−	−	45X0 (13%)/46XX/ 47XXX + r (X)	Normal	
$6^{3F/3S}$	+ (3^F)	+ (2^S, 1^F)	+ (3^F)	+ (2^S)	See Table 1	See Table 2	Our series

F: familial cases; S: sporadic cases.

patients (V4) belonging to familial cases of TS, the presence of the ring chromosome on FISH analysis may explain the absence of pituitary deficiency. In our opinion, these congenital cases of pituitary insufficiency imply that transcription factors play a key role in a genetic cascade of cell differentiation and proliferation in the anterior pituitary [8].

Corticotropin deficiency was present in 3/7sporadic cases and absent in all familial cases, suggesting a role of some transcription factors such as mutations of PROP1, POUF1, Hesx1, Lhx3, Lhx4, and Ptx2 genes [8].

It is worth noting that MRI of the pituitary region revealed a normal aspect of pituitary sella in 4/7 sporadic cases and a

hypoplastic pituitary in all familial cases. No correlation was found between chromosomal formula and MRI findings. Interestingly, an interruption of the pituitary stalk was present in only one sporadic patient having mosaicism with an abnormality of chromosome X structure.

Finally, we can assume that a complex genetic cascade dictates organ commitment, cell differentiation, and cell proliferation within the anterior pituitary. Mutations in genes encoding both signaling molecules and transcription factors have been implicated in the etiology of Hypopituitarism in humans. These include HESX1, LHX3, LHX4, PROP1, POUF1, and more recently, SOX3 and SOX2. Mutations within these genes are associated with a recessive phenotype characterized by deficiencies in GH, thyroid-stimulating hormone, luteinizing hormone, and follicle-stimulating hormone with a sparing of the corticotrophs. Recently, in a pilot study focusing on global gene expression analysis in TS, XIST was significantly down-regulated ($p < .0001$) among 470 expressed genes identified [9].

To our knowledge, this is the largest study describing co-segregation of pituitary deficiency and TS in both familial and sporadic cases. Our results could suggest that familial occurrence of such association involves a more severe hormonal and neuropituitary anatomic defect, but a protector effect except for the preservation of the corticotrophin lineage.

According to our findings, we can postulate a possible correlation between structural aberration of sex chromosomes and pituitary determinism and differentiation. This correlation had never been described in the literature.

Certainly, advances in molecular sequencing of genes playing a key role in pituitary development and interplaying with sexual chromosomes will illuminate our comprehension of mechanisms of such an association.

Conclusion

The association between TS and anterior pituitary deficiency is a very rare occurrence. In this co-occurrence, the clinical aspect is dominated by signs of Hypopituitarism and moderate dysmorphic syndrome. Unfortunately, it is common for TS to go undiagnosed for years, typically until puberty, thus a karyotype should be performed for the slightest suspicion of TS. The diagnosis of this syndrome is important so as not to misinterpret the pathologies which may be associated with it and for a better evaluation of the prognosis of fertility.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Gravholt CH. Epidemiological, endocrine and metabolic features in Turner syndrome. Eur J Endocrinol. 2004;151(6):657–687.
[2] Bondy CA. Turner's syndrome and X chromosome-based differences in disease susceptibility. Gend Med. 2006;3(1):18–30.
[3] Gallicchio CT, Alves ST, Ramos HI, et al. Association of Turner's syndrome and Hypopituitarism: a patient report. J Pediatr Endocrinol Metab. 2003;16:901–905.
[4] Bougacha-Elleuch N, Elleuch M, Charfi N, et al. Unusual association of Turner syndrome and Hypopituitarism in a Tunisian family. Curr Res Trans Med. 2016;64(1):9–13.
[5] Jublanc C, Bruckert E. Adrenal insufficiency of the adult. Rev Med Interne. 2016;37(12):820–826. French.
[6] Elleuch M, Mnif Feki M, Kammoun M, et al. Descriptive analyses of Turner syndrome: 49 cases in Tunisia. Ann Endocrinol. 2010;71(2):111–116.
[7] Efstathiadou Z, Tsatsoulis A. Turner's syndrome with concomitant Hypopituitarism: case report. Hum Reprod. 2000;15(11):2388–2389.
[8] Reynaud R, Saveanu A, Barlier A, et al. Pituitary hormone deficiencies due to transcription factor gene alterations. Growth Horm IGF Res. 2004;14(6):442–448.
[9] Massingham LJ, Johnson KL, Scholl TM, et al. Amniotic fluid RNA gene expression profiling provides insights into the phenotype of Turner syndrome. Hum Genet. 2014;133(9):1075–1082.
[10] Gallicchio CT, Alves ST, Ramos HI, et al. Association of Turner's syndrome and Hypopituitarism: a patient report. J Ped Endocrinol Metab. 2003;16(6):901–906.
[11] Lomna-Bogdanov E, Bolanowski M, Slezak R, et al. Familial Hypopituitarism associated with mosaic form of Turner syndrome. Gynecol Endocrinol. 2005;20(1):22–25.
[12] Oueslati I, Khiari K, Ali IH, et al. Coexisting Turner's syndrome, Hashimoto's thyroiditis, and growth hormone deficiency. Indian J Endocrinol Metab. 2016;20(4):573–574.
[13] Oueslati I, Kraoua L, Khiari K, et al. Partial Hypopituitarism in a female patient with a 45, X/46, XY mosaicism. Annal Endocrinol. 2017;78(1):56–58.