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Original article

Unusual association of turner syndrome and hypopituitarism in a Tunisian family

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ABSTRACT

Purpose of the study. – Familial occurrence of either Turner syndrome or hypopituitarism is very rare. Particularly, their association is an uncommon finding. In this context, we describe for the first time 4 sisters with Turner syndrome, hypopituitarism was reported in three among them.
Patients and methods. – Our cohort consists of four Tunisian adult sisters belonging to a consanguineous family. Biochemical analysis, resonance magnetic imaging and cytogenetic analyses were performed.
Results. – Turner syndrome was diagnosed at the ages of 14, 17, 31 and 43 years in cases 1, 2, 3 and 4 respectively. They suffered from short stature, dysmorphic syndrome and/or delayed puberty. Interestingly, 3 among them showed also hypopituitarism, hypogonadotrophic hypogonadism and central hypothyroidism. Somatotropic insufficiency was proven in one case. Pituitary MRI has shown an empty sella turcica with hypoplastic pituitary gland in three cases. Their karyotypes were compatible with 45X in one case, 45X/46XX in the second and 45X/46XX/47XXY with x label in two cases.
Conclusion. – Hence, the presence of these familial cases of TS must evoke new etiopathogenetic arguments. Coincidence of hypopituitarism in this family, might suggest common genetic background for the two diseases. This particular family would be a precious tool for an extensive molecular analysis. More attention should be given to other family's members mainly in the presence of delayed puberty and sterility in other members.

1. Introduction

Turner syndrome (TS) is a disease caused by a partial or complete absence of the second X chromosome in women. It affects approximately 1 per 2500–4000 live born females [1,2]. TS is characterized by short stature, gonadal dysgenesia, webbed neck, or cubitus valgus and congenital cardiovascular disease. Familial occurrence of TS is very rare. Thus, the first report of familial Turner syndrome was reported in 1963 in an aunt and niece [3]. But the longest number of cases interested seven women with Turner syndrome in a three generations' family [4–7].

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. The familial incidence of hypopituitarism is rare, accounting for about 10% of cases. While it is a common chromosomal abnormality, the association of TS and hypopituitarism is an uncommon finding. It was reported in two cases where a combined growth hormone, gonadotrophin and thyrotrophin deficiency was confirmed [8,9].

We present herein, for the first time, a multigenerational consanguineous family harboring four adult sisters affected with TS. Interestingly, hypopituitarism was reported in 3 among them.

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2. Patients and methods

2.1. Patients

We considered four sisters who had been referred to the department of endocrinology at the hospital Hedi Chaker, Sfax, Tunisia. All patients belong to a large multigenerational Tunisian family (Fig. 1). On physical examination, it was observed that they had short stature and delayed puberty. The diagnosis of growth hormone deficiency (GH-D) was confirmed by 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). Blood sample measurements of serum GH were obtained at 0, 30, 60, 90, and 120 min. Hypothyroidism was defined as low-normal serum TSH concentration and low serum-free T4 concentrations. Corticotroph deficiency was confirmed by a low plasma ACTH level with low serum cortisol values measured in the morning or an impaired cortisol serum concentration inferior to 20 g/dL (550 nmol/L) during insulin-induced hypoglycemia. Serum FSH and LH were measured before and 30, 60, and 120 min after the administration of 100 g/m^2 of GnRH in all patients. Hypogonadism was confirmed by no increase in FSH and LH in response to GnRH. All hormone measurements were carried out by means of standard RIAs. In the presence of normal or low basal serum levels of ACTH, ACTH deficiency (ACTH-D) had been suspected when the 0800-h cortisol level was below 193 nmol/L and confirmed by an impaired cortisol response to the 1-g tetracosactide test (497 nmol/L). Gonadotropin deficiency had been diagnosed in males when basal testosterone levels were below the normal range (total testosterone 9 nmol/L) in the presence of normal or low gonadotropin levels. A similar diagnosis in females had been supported by serum estradiol levels lower than 40 pmol/L associated with inappropriately low serum gonadotropin concentrations. TSH deficiency had been diagnosed in patients with inappropriately low serum TSH levels in the presence of subnormal serum-free T4 and free T3 concentrations. Posterior pituitary function was studied in all patients. Karyotype analysis confirmed Turner syndrome.

2.2. Methods

2.2.1. Conventional cytogenetic analysis

Routine cytogenetic analysis was performed with 3 mL heparinized peripheral blood using method described earlier [10]. At least 30 metaphases were observed and analysed through GTG banding with over 550 band resolutions observed. Karyotype was designated as per ISCN [10].

2.2.2. Molecular cytogenetic analysis

Fluorescence in situ hybridization (FISH) analysis was performed using SRY and CEPX probe for Y and X chromosomes respectively. The protocol involved direct culture of cells obtained from the blood sample. Two hundred interphase cells were analyzed and signals were counted accordingly. Images were recorded using Olympus fluorescence microscope equipped with a CCD camera and analyzed using Cytovision 3.9 V software.

3. Results

3.1. Clinical data

Patients' history began in 1991 when the case index (case 1) was addressed to the Endocrinology department (CHU Hedi Chaker in Sfax, Tunisia), for short stature and delayed puberty. Interestingly, the interview of this affected woman indicated that all her sisters (3) suffered also from TS. These patients belong to an 8 generations extended Tunisian family (Fig. 1). This latter is characterized by a high rate of consanguinity (≈30%). Interestingly, clinical follow up has showed that in addition to TS, three patients suffered from hypopituitarism. Clinical and hormonal characteristics of patients are illustrated in Table 1. Ages of the 4 patients ranged between 14 and 53 years. In this particular family, there is aggregation of other autoimmune (Behcet) and non-autoimmune diseases (chronic renal failure, chronic coronary failure and primary infertility).

3.1.1. Case 1

The older sister (V-1), a 53-year-old woman, was first examined at the age of 31 years. She presented a typical picture of turner syndrome (height: 134 cm, weight: 45 kg). She had a round face with micrognathia and her neck was short. A number of pigmented noevi were observed in her face and body. She had also short fourth metacarp and low hair implantation. Secondary, sex characteristics were absent with amenorrhea. The rest of the clinical examination was normal. Hormonal analyses were carried out at this time and objected hypogonadotrophic hypogonadism and thyrotrophin deficiency. She had hypoplasic uterus and streak ovaries in ultrasonography. Evaluation of hypothalamic pituitary axis was performed. The insulin tolerance test confirmed growth hormone deficiency. Indeed, the peak of GH was 0.27 μu/mL after insulin-induced hypoglycemia (Table 1). Whereas, a sufficient response of cortisol suggested intact function of adrenocorticotroph cells (Table 1). Prolactine concentration was normal (7.5 ng/mL). Magnetic resonance imaging (MRI) of the pituitary axis revealed empty sella turcica. The pituitary stalk was in the median line but it was very thin. The optic chiasm and cavernous sinuses were normal (Fig. 2a).

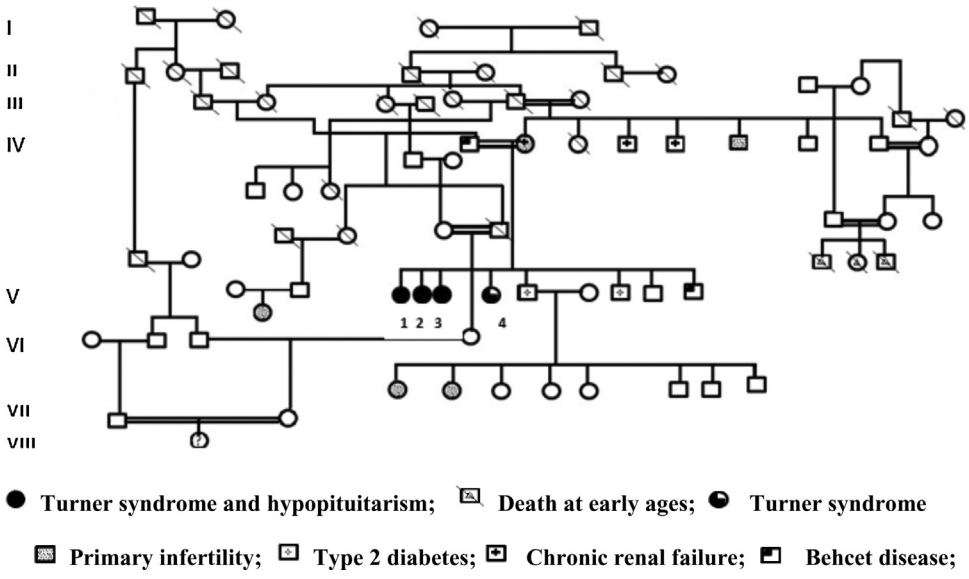

Fig. 1. Pedigree of the studied family.