CASE REPORT

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Coexisting diseases modifying each other's presentation - lack of growth failure in Turner syndrome due to the associated pituitary gigantism

Istovremeno postojanje Tarnerovog sindroma i gigantizma: atipična klinička manifestacija bez zastoja u linearnom rastu

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Abstract

Introduction. Turner syndrome presents with one of the most frequent chromosomal aberrations in female, typically presented with growth retardation, ovarian insufficiency, facial dysmorphism, and numerous other somatic stigmata. Gigantism is an extremely rare condition resulting from an excessive growth hormone (GH) secretion that occurs during childhood before the fusion of epiphyseal growth plates. The major clinical feature of gigantism is growth acceleration, although these patients also suffer from hypogonadism and soft tissue hypertrophy. **Case report.** We presented a girl with mosaic Turner syndrome, delayed puberty and normal linear growth for the sex and age, due to the simultaneous GH hypersecretion by pituitary tumor. In the presented case all the typical phenotypic stigmata related to Turner syndrome were missing. Due to excessive pituitary GH secretion during the period while the epiphyseal growth plates of the long bones are still open, characteristic stagnation in longitudinal growth has not been demonstrated. The patient presented with delayed puberty and primary amenorrhea along with a sudden appearance of clinical signs of hypersomatotropinism, which were the reasons for seeking medical help at the age of 16. **Conclusion.** Physical examination of children presenting with delayed puberty but without growth arrest must include an overall hormonal and genetic testing even in the cases when typical clinical presentations of genetic disorder are absent. To the best of our knowledge, this is the first reported case of simultaneous presence of Turner syndrome and gigantism in the literature.

Key words:
turner syndrome; gigantism; pituitary neoplasms; adolescent; women; puberty; growth hormone; insulin-like growth factor I.

Apstrakt

Uvod. Tarnerov sindrom je jedna od najčešćih hromozomskih aberacija kod osoba ženskog pola, koja se tipično manifestuje zaostajanjem u rastu, insuficijencijom jajnika, karakterističnim crtama lica i drugim različitim somatskim poremećajima. Gigantizam je izrazito retko oboljenje koje nastaje kao posledica pojačane sekrecije hormona rasta (HR) tokom detinjstva, a pre srastanja epifiznih zona rasta dugih kostiju. Osnovna klinička karakteristika obolelih od gigantizma je visok rast, mada ove osobe tipično imaju i hipertrofiju mekih tkiva i hipogonadizam. **Prikaz bolesnika.** Prikazali smo bolesnicu sa Tarnerovim sindromom, zakasnelim pubertetom i normalnim linearnim rastom, nastalim zbog istovremenog postojanja hipersekrecije HR iz pituitarnog tumora. U tom slučaju, izostajale su sve fenotipske karakteristike tipične za Tarnerov sindrom. Usled pojačane sekrecije HR koji je delovao na otvorene epifizne ploče dugih kostiju, izostao je karakterističan zastoj u longitudinalnom rastu. Bolesnica je razvila sliku zakasnelog puberteta i primarne amenoreje, uz nagli razvoj kliničkih pokazatelja hipersomatotropinizma, što je i bio razlog za obraćanje lekaru u 16. godini života. **Zaključak.** Svi slučajevi zakasnelog puberteta koji se manifestuju bez zastoja u rastu, zahtevaju detaljno hormonsko i genetsko ispitivanje, čak i kada ne postoji tipična klinička manifestacija genetskog obolenja. Prema nama dostupnim podacima, ovo je prvi opisani slučaj istovremenog postojanja Tarnerovog sindroma i gigantizma u literaturi.

Ključne reči:
tarnerov sindrom; gigantizam; hipofiza, neoplazme; adolescenti; žene; pubertet; somatotropin; iGF1.

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Introduction

Turner syndrome presents with one of the most frequent chromosomal aberrations in female that occurs in about 1 *per* 2,500 newborn girls. For the diagnosis of this syndrome the presence of characteristic somatic stigmata in phenotypic females, is coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism [1]. Typical clinical features are growth retardation, gonadal dysgenesis and numerous congenital somatic stigmata. In those cases, in which the diagnosis was not made at birth, it was determined during childhood or puberty, due to the growth retardation or primary amenorrhea [2].

Gigantism is an extremely rare condition with approximately 100 reported cases altogether. Gigantism results from an excessive secretion of growth hormone (GH) that occurs during childhood, while the epiphyseal growth plates of the long bones are still open. Cases of GH hypersecretion could originate from a primary pituitary source like somatotroph adenomas, or could be caused by disturbed regulation or an increase of growth hormone-releasing hormone (GHRH) secretion followed by pituitary hyperplasia. The major clinical feature of gigantism is growth acceleration. Those patients often suffer from hypogonadism or delayed puberty, macrocephaly and soft tissue hypertrophy, hyperhidrosis, headache or weakness [3].

Coexistence of Turner syndrome with pituitary tumors is extremely rare. As an example of coexisting diseases modifying each other's presentation, we presented a girl with delayed puberty due to the Turner syndrome but with normal linear growth, for sex and age, due to the simultaneous GH hypersecretion by pituitary tumor. According to a standard procedure, written informed consent for diagnostic procedures, as well as for publishing a case was obtained from the patient.

Case report

A 16-year-old female with a 2-year history of rapid linear growth, soft tissue hypertrophy, hyperhidrosis, weakness and primary amenorrhea was referred to our Clinic. She was full term born, with weight of 2.500 g and length of 51 cm. Her growth velocity was practically normal until 14 years of age, when marked growth acceleration (15 cm/year) was noticed with increasing size of hands and feet. Menarche was absent. Mental development was quite normal. There was no family history of tall stature.

Physical examination revealed enlarged hands and feet, coarse facial features, discrete frontal bossing, mild prognathism and macroglossia. Her height was 171 cm [(height score + 1.75 standard deviation (SD); 90th for-age percentiles)], while her weight was 74 kg, with body mass index (BMI) of 25.4 kg/m^2. She was normotensive, with heart rate of 80 beats per minute, without signs of organomegaly. She was in Tanner stage III of puberty with the normal appearance of external genitalia.

Laboratory data listed in Table 1 revealed increased GH and insulin-like growth factor-I (IGF-1) levels, according to the age-adjusted reference range, and prepubertal serum concentrations of sex steroids and gonadotropins. The patient was eucortisolemic and euthyroid with negative thyroid peroxidase antibody titer. There was no other functional abnormality of the anterior pituitary. The increased serum phosphate level of 2.25 mmol/L (the age-adjusted reference range being 0.97–1.81 mmol/L) was observed. Genetic analysis pointed at a mosaic karyotype 46,X,der(X)/45,XO (45/55%) suggestive of Turner syndrome.

Magnetic resonance imaging (MRI) pituitary scans revealed a hypodense microadenoma of the pituitary gland, on the right side within the sellar region, with dimensions of 7 × 6.5 × 8.5 mm (Figure 1). Pelvic ultrasonography revealed normal dimensions of the uterus and ovaries, with thin endometrium and absent ovarian follicles. Ulnar epiphyseal growth plates appeared open on MRI. Echocardiography showed normokinetic left ventricle with mild mitral valve prolapse (MVP). Her bone mineral density was normal. She was short-sighted. No other endocrine, cardiovascular, renal, intestinal, hearing or mental disorder could be detected.

The patient underwent transsphenoidal surgery but with pituitary tumor only partly removed. Postoperative MRI showed reduced dimensions of previously described pituitary microadenoma with the rest tissue of 3 mm in diameter. The-

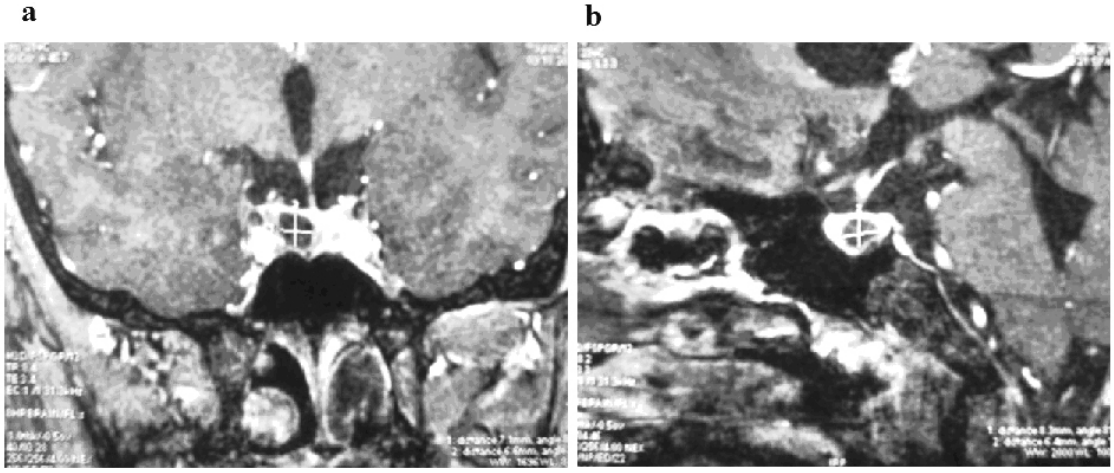

Fig. 1 – Magnetic resonance imaging (MRI) pituitary scans with a hypodense intrasellar tumor on the right side of the fossa sugesting pituitary adenoma (a – coronal section; b –sagittal section)

re was also a newly visualized hypodense mass, on the left side of the pituitary fossa, with dimensions of 3 × 7 mm, suggesting possible pituitary hyperplasia or multiple adenomas (Figures 2). Unfortunately, this speculation could not be histologically proven due to the insufficient amount of tissue material provided at surgery.

Two months after the surgery the patient's condition subjectively improved, but with the clinical evidence of moderate hypersomatotropism still present. Circulating levels of GH and IGF-1 were reduced, but remained above normal and without suppressibility in oral glucose tolerance test (OGTT) (Table 1).

Further treatment of Turner syndrome included sex hormone replacement therapy which was followed with the occurrence of regular menstrual bleeding. The patient was also treated with the long-acting release somatostatin analogue, intramuscularly at monthly intervals over an 18 months period with the ensuing normalization of biochemical parameters of GH secretion and clinical remission. However, as there were no reductions of the size of intrasellar masses the patient was preparing for stereotactic radiosurgery.

Discussion

Observation that coexisting disorders could influence each other's clinical presentations is not unusual. However, it rarely concerns major clinical signs and symptoms.

Cases of Turner syndrome accompanied by pituitary adenomas are very rare. The search of the MEDLINE database retrieved only two cases of Turner syndrome accompanied by acromegaly [4, 5]. The association of Turner syndrome with pituitary hyperplasia verified by histological examination, unfortunately at autopsy, was published in one case [6], with nonfunctioning pituitary microadenoma in two cases [7, 8], while in two more casesthe presence of prolactinoma was demonstrated [9, 10]. To the best of our knowledge no case of Turner syndrome associated with gigantism was reported until now.

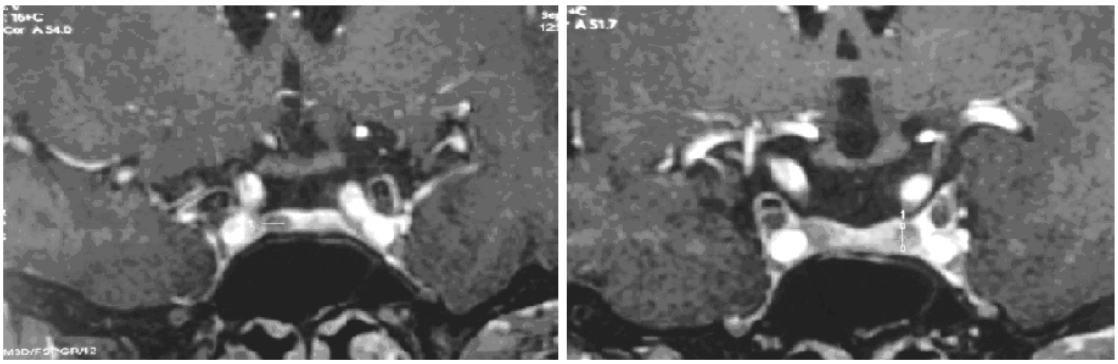

Fig. 2 – Postoperative control. Magnetic resonance imaging (MRI) of the pituitary showing reduced intrasellar tumor on the right side and hypodense mass on the left side of the fossa suggesting possible pituitary hyperplasia or multiple adenomas.

Table 1

Endocrine data in patient before and 2 months after pituitary tumor surgery

Parameter	Values		
	preoperative	postoperative	normal range
GH (ng/mL)	34.3	12.6	< 11.4
IGF-1 (mU/L)	1388.0	1141.0	193–731
LH (U/L)	20.9	12.2	5 – 20
FSH (U/L)	59.84	44.0	5 – 20
Estradiol (pmol-L)	68.4	70.6	95.5–704.8
Testosteron (nmol/L)	0.66	0.7	< 0.922
FT4 (pmol/L)	14.65	20.41	11.5–22.7
TSH (mU/L)	5.29	2.875	035–5.5
TPO-Ab (U/mL)	51.7	50	o-eo
Prolactin (mU/L)	195	137	< 380
Cortisol (nm.ol/L)	498.0	515.5	853–459.6
0800 h			
1600 h	292.7	323.2	64–327.2
ACTH (pmol/L), 0800 h	10.7	5.2	1.6–13.9
GH (ng/mL), nadir during OGTT	-	6.9	0–1

GH – growth hormone; iGF-1 – insulin-like growth factor; LH – luteinizing hormone; FSH – follicle-stimulating hormone; FT4 – free thyroxine; TSH – thyroid stimulating hormone; TPO-Ab – thyroid peroxidase autoantibodies; ACTH –adrenocorticotropic hormone; OGTT – oral glucose tolerance test.

Gigantism results from GH excess that occurs during childhood when open epiphyseal growth plates allow excessive linear growth. Hypothalamic GHRH excess or dysregulation has been considered to be the most common cause of GH hypersecretion affecting the pediatric population [3].

Due to the small number of affected patients, there are no clearly defined signs and symptoms typical for gigantism. Nevertheless, the major clinical feature of gigantism is growth acceleration; these patients can also have coarse facial features, soft tissue enlargement and disproportionately large hands and feet. Those people also suffer from delayed puberty or hypogonadism, menstrual irregularity, headache, weakness, peripheral neuropathy or joint pain [3, 11].

The genetic background for Turner syndrome is highly variable and includes numerous anomalies of the sex chromosomes. Most of the female patients with Turner syndrome are the carriers of the "typical" karyotype of 45X; in 10% of all cases there is a karyotype with isochromosome X [i(Xq) or i(Xp)], while the rest of the patients are individuals with mosaic karyotype of 45,X/46,XX [12]. The most common clinical features are short stature, gonadal dysgenesis and insufficiency. Facial dysmorphism, webbed neck, cardiovascular and kidney malformations as well as lymphedema could also be present. Some patients suffer from cognitive disorders and behavior issues. The absence of puberty with primary amenorrhea represents one of the most frequent symptoms of Turner syndrome, although those patients exhibit spontaneous puberty in 30% and spontaneous pregnancy in 2–5% of cases. However, the major clinical sign of the patients suffering from Turner syndrome remains short stature [1, 12].

In the presented case all the typical phenotypic stigmata related to Turner syndrome were missing. Beside the discrete MVP, we were not able to discover any other systemic malformations or anomalies. Also, due to excessive pituitary GH secretion during the period while the epiphyseal growth plates of the long bones are still open, characteristic stagnation in longitudinal growth has not been demonstrated. The patient presented with delayed puberty and primary amenorrhea along with a sudden appearance of clinical signs of hypersomatotropinism, which were the reasons for seeking medical help at the age of 16. Low serum estrogen levels, increased gonadotropins and karyotype analysis confirmed the existence of Turner syndrome. Biohumoral markers of hypersomatotropinism, in the presence of pituitary microadenoma and still open epiphyseal growth plates, revealed by MRI, confirmed the diagnosis of associated gigantism. Simultaneous occurrence of Turner syndrome and gigantism abolished major clinical sign from both conditions – short stature from Turner syndrome and pronounced growth acceleration from gigantism. This could be the reason for relative delay in diagnosis of these coexisting diseases in our case.

Girls born with Turner syndrome have intrauterine growth retardation and exhibit growth failure during early childhood. Slowdown of growth becomes more pronounced during puberty due to the absence of characteristic peak in pulsatile secretion of GH and IGF-1. Previously, it was considered that short stature represents the consequence of reduced spontaneous GH secretion [12, 13]. Thereafter, it was concluded that estradiol is necessary for the neuroendocrine regulation of pulsatile GH secretion during normal puberty, and became evident that low daily concentrations of GH in patients with Turner syndrome was the result of estradiol deficiency [5, 14]. However, although estrogen replacement therapy applied in girls with Turner syndrome during puberty normalizes daily level of GH in serum, the growth deficit remains. Therefore, it is concluded that growth defect in the majority of patients with Turner syndrome is not solely the result of classical GH deficit [12].

Pathogenesis of growth failure in patients with Turner syndrome is not still completely understood. Most of the authors consider longitudinal growth retardation as the consequence of GH/IGF-1 resistance, particularly on the epiphyseal growth-plate level [2, 15].

Firstly, GH/IGF-1 insensitivity in Turner syndrome was demonstrated on molecular level. Monocyte-macrophage cells in peripheral blood of patients with Turner syndrome expressed lower values of LDL degradation, compared to healthy controls, alongside with the reduced monocyte-stimulated T-lymphocyte proliferation and IL-2 secretion. This indirectly showed lower GH/IGF-1 sensitivity of these cells [16]. Similarly, skin fibroblasts from girls with Turner syndrome release significantly lower amount of IGF-1 and IGF-2 compared to normal fibroblasts [17]. However, female patients with Turner syndrome treated with GH alone or in combination with estradiol, have supraphysiological IGF-1 levels, suggesting the presence of the mechanism that overcomes IGF-1 resistance [18].

On the other hand, GH/IGF-1 resistance may contribute to the explanation of pituitary tumorigenesis in Turner syndrome.

Pituitary function is under tight hypothalamic control, mediated by the effects of releasing and inhibiting hormones. It has been proposed that pituitary tumors are derived from an intrinsic pituitary cell defect leading to monoclonal expansion of a single transformed cell [19]. Hypothalamic hormones may have an important role in promoting the growth of already transformed cell clones and expansion of small adenomas into large tumors. However, it is important that chronic GH excess may be capable to overcome the functional GH resistance causing increase in circulating IGF-1. Induction of GH-secreting pituitary adenomas could be the result of GHRH hypersecretion or decreased somatostatin control [20].

IGF-1 is peripheral hormone helping GH to produce numerous physiological effects on peripheral tissues, including longitudinal growth. Circulating IGF-1 acts as a negative feedback regulator of the GH-gene expression. It inhibits hypothalamic GHRH secretion and acts directly on somatotrophs abolishing stimulatory action of GHRH [21]. Increased need of peripheral tissues for larger amount of IGF-1 could link GH/IGF-1 resistance and GHRH hypersecretion. Similar mechanism could explain the occurrence of acromegaly in patient with anorexia nervosa, a psychosomatic disorder characterized by functional GH resistance [19].

Experimental data on transgenic mice demonstrated that GHRH hyperstimulation resulted primary in somatotroph hyperplasia and, after 8–10 months, in multifocal somatotroph

adenomas. Clinical confirmation of this phenomenon occurs in the development of acromegaly or gigantism in patients with ectopic secretion of GHRH, such as neuroendocrine tumors [22].

It is well-known that target gland hormones (adrenal, thyroid and sex hormones) have strong negative feedback on transcription of genes that encode synthesis of trophic hormones and their secretion. Failure of target gland is accompanied with the loss of negative feedback inhibition and consequent compensatory hyperplasia of respective pituitary trophic hormone cells. Consequently, longstanding primary target gland failure may be associated with pituitary enlargement, as frequently seen on MRI [20].

Although gonadotroph adenomas could also be expected in patients with Turner syndrome, literature data revealed no association among these two conditions. Histochemical and immunochemical studies, conducted on pituitary tissue of four autopsies of cases with Turner syndrome, showed neither gonadotroph hyperplasia nor adenoma. In these cases only corticotroph hyperplasia and adrenocorticotropic hormone (ACTH) immunoreactive adenoma have been perceived [23]. Also, it has to be mentioned that gonadotropin-releasing hormone (GnRH) receptor expression has been documented in the different types of pituitary adenomas [22, 23]. Therefore, the authors speculated that corticotroph cells have expressed GnRH receptors during the time they were exposed to chronic follicle-stimulating hormone (FSH) or luteinizing hormone (LH) hyperstimulation [23].

Thus, we can assume that the GH/IGF resistance, potentially already existing in the presented patient due to the Turner syndrome, has caused hypersecretion of GHRH with ensuing somatotroph hyperplasia and consecutive GH hypersecretion. We could also speculate that somatotroph cells exposed to GnRH and GHRH hyperstimulation, accompanying primary ovarian insufficiency characteristic for Turner syndrome, would express GnRH receptor during the time course. The drawback of our case presentation was the absence of conclusive histological verification of pituitary adenomas or hyperplasia visualized by MRI before and after transsphenoidal surgery. So, definite histological and immunohistochemical confirmation for the existence of acidophilic adenoma, hyperplasia and/or possibly accompanying gonadotroph adenoma was lacking due to the insufficient amount of tissue material provided at surgery. Obviously, autonomic hypersecretion of GH during puberty was sufficient to overcome potential GH/IGF resistance at the level of epiphyseal growth plates and provide accelerated linear growth in our patient. Ensuing lack of growth failure has caused the late detection and postponed treatment of gonadal dysgenesis.

Conclusion

Physical examination of children presenting with delayed puberty but without growth arrest must include an overall hormonal and genetic testing even in the cases when typical clinical presentations of genetic disorder are absent. Authors also believe that this unique case of gigantism coexisting with Turner syndrome threw some more light on still not completely elucidated mechanisms of tumorigenesis in Turner syndrome and possible role of GH/IGF-1 axis in this process.

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