CASE REPORT

46,XY Hypergonadotropic hypogonadism and myasthenia gravis

CORINA LICHIARDOPOL[1)], V. HERLEA[2)], VIRGINIA IOAN[2)],
V. TOMULESCU[2)], F. MIXICH[3)]

[1)]*Department of Endocrinology,*
University of Medicine and Pharmacy of Craiova
[2)]*Fundeni Institute, Bucharest*
[3)]*Department of Genetics,*
University of Medicine and Pharmacy of Craiova

Abstract

Both hypergonadotropic hypogonadism and myasthenia gravis can be parts of type II autoimmune polyendocrine syndrome and association between the two disorders has been reported in few cases. A 14 year old male patient with a personal history of bilateral cryptorchidism and ptosis was referred for delayed puberty. Clinical examination revealed eunuchoid habitus, small, soft testes, gynecomastia, ptosis, a myasthenic deficit score of 22.5 points and an IQ of 84 points. Decreased testosterone (0.064 ng/mL) and elevated LH (64.5 mUI/mL) were consistent with hypergonadotropic hypogonadism and karyotype was normal: 46,XY. Thyroid function, haematologic evaluation, BUN, elecrolytes, and glycemia were in the normal range. Therapy consisted of anticholinesterase inhibitors, immunosuppressants, corticotherapy, testosterone; thoracoscopic thymectomy was performed showing thymic lymphoid hyperplasia on histopathologic examination. Myasthenic score improved (12.5 points), progressive virilization occurred, and a year later the patient presented with cushingoid features and obesity.

***Keywords*:** hypergonadotropic hypogonadism, cryptorchidism, myasthenia gravis.

Introduction

46,XY hypergonadotropic hypogonadism may be the result of congenital disorders that affect testicular organogenesis (Klinefelter syndrome, X chromatin – negative variants of gonadal dysgenesis, complete and incomplete forms of testicular dysgenesis, testicular regression, plurimalformative syndromes, maternal ingestion of progestins, exposure to endocrine disrupters, testicular unresponsiveness to LH – hCG/LH receptor defect, testosterone biosynthesis (enzyme deficits impairing both adrenal and testicular steroidogenesis as StAR, CYP11A1, HSD3B2, CYP17, DHCR7 or impairing primarily testicular steroidogenesis as CYP17 [17,20 lyase], HSD17B3), testosterone action (complete and incomplete androgen resistance) and testosterone metabolism (SRD5A2 deficiency).

Phenotypic spectrum ranges from complete XY sex reversal to minor undervirilization. Acquired 46,XY hypergonadotropic hypogonadism may emerge from orchitis, infiltrative, autoimmune disorders, trauma, irradiation, toxins and drugs. Appearance of these disorders before puberty impairs the acquisition of normal secondary sex characteristics [1, 2].

Myasthenia gravis (MG) is a neuromuscular disorder usually due to an autoimmune attack that decrease the number of available acetylcholine receptors (AchR) at the neuromuscular junction level. Transient neonatal MG occurs in 10–20% of infants born to myasthenic mothers.

In rare instances myasthenia is congenital, being the result of mutations of genes coding for the five subunits of the acetylcholine receptor or for acetylcholinesterase (AchE). Myasthenia gravis affects 1 : 7500 individuals and clinical features are represented by weakness and fatigability of skeletal muscles, particularly the cranial muscles with diplopia and ptosis.

Autoimmune MG is associated with thymic abnormalities in 75% of patients and with other autoimmune disorders such as hyperthyroidism (3–8% of patients), rheumatoid arthritis, scleroderma and lupus [3].

There are few reported cases with associated myasthenia gravis and hypergonadotropic hypogonadism [4–8].

The pathogenetic link between the two disorders is autoimmunity, since both can be parts of type II autoimmune polyendocrine syndrome, defined by the occurrence in the same individual of two or more of the following: primary adrenal insufficiency, Graves disease, autoimmune thyroiditis, type 1A diabetes mellitus, primary hypogonadism, myasthenia gravis, celiac disease, vitiligo, alopecia, serositis and pernicious anemia. Of note that circulating organ-specific autoantibodies are present before overt clinical disease [9].

Patient and method

We present the case of a 14 year old male patient referred for delayed puberty, with a personal history of

psychomotor delay (he was able to speak and walk at the age of two years), bilateral cryptorchidism diagnosed at the age of six years, iterative orchiopexy at the age of six, seven, nine and 10 years, and ptosis that occurred after the first orchipexy.

He was born after an uneventful pregnancy at 40 weeks gestational age by cesarean section, with a birth weight of 2 800 g.

Physical examination findings (Figure 1) were: height 171 cm, (75 percentiles for age), weight 46 kg (25 percentiles for age), body mass index 15.7 kg/m^2 (3 percentiles for age), eunuchoid habitus with upper segment smaller than lower segment and biacromial diameter smaller than bitrochanterian diameter, horizontal smile, ptosis with impairement of horizontal movements and convergence, absent facial hair, scarce axillary hair, pubic hair stage 3 Tanner, small (1/1.5 cm), soft testes palpable in the scrotum, near the external inguinal ring, gynecomastia, normal blood pressure, normal thyroid on palpation, hypoplastic muscles with proximal weakness, a myasthenic score (QMG) of 22.5 points which decreased to 12 points after Mestinon administration, normal tendon reflexes, high-pitched voice, acatisia and multifocal tics. Psychological evaluation established an IQ of 84 points.

Visual field and pulmonary vital capacity were normal and also skull X-ray (Figure 2), hand X-ray (Figure 3).

Abdominal ultrasound was normal and excluded the presence of mullerian derivatives. Testicular volume estimated by ultrasound was 1 mL each. Breast ultrasonography was consistent with Tanner stage 2 with width of the mammary tissue of 5.8 mm on the left and 9.4 mm on the right. Thyroid echogenicity and volume (11.5 ml) were normal. MRI was performed and revealed a tissular mass of 6/2.5 cm in the anterior mediastinum contrast head MRI was normal including a normal sized pituitary (7/8 mm) with present posterior bright spot on T1 weighted images.

Hormonologic evaluation showed: low testosterone 0.064 ng/mL, high LH 64.5 mUI/mL, a slightly increased prolactin level 536 µUI/mL, normal TSH 3 µUI/mL and free T4 13.41 pmol/L. Other laboratory findings (blood smears, CBC, haemoglobin, BUN, electrolytes, glycemia) were in the normal range. The tests for antistriated muscle and anti-acetylcholin receptor antibodies were not available. Karyotype was normal, 46,XY.

The patient started therapy with anticholinesterase inhibitors immunosuppressants and corticosteroids with reduction of QMG at 8 points, and then underwent thoracoscopic thymectomy.

Macroscopic examination of the surgical specimen of 12/7/3 cm identified no tumors or adenopathies and histopathologic examination revealed thymic lymphoid hyperplasia (Figure 4).

Preoperatively neurological evaluation established a QMG of 11.5 points and vital capacity of 70%. Postoperatively QMG was 12.5 points and androgenic therapy was added to medication, with progressive virilization. After 1 year the patient had a cushingoid appearance and obesity (Figure 5).

Discussions

The presence of a low testosterone level in the context of a high LH level establishes the diagnosis of hypergonadotopic hypogonadism.

Pubic hair was present because adrenarche depends on adrenal androgens and gynecomastia reflects a high estradiol/testosterone ratio because of decreased testosterone.

The normal karyotype 46,XY excluded Klinefelter syndrome or X chromatin variants of gonadal dysgenesis as possible causes of hypergonadotropic hypogonadism in our patient.

Genetic disorders responsible for male hypergonadotropic hypogonadism affecting testicular organogenesis, testicular responsiveness to LH, testosterone biosynthesis, action and metabolism are shown in Table 1 [1, 2].

The spectrum of genital anomalies ranges from complete XY sex reversal to minor undervirilization or infertility. Undescended testes are the most common genital anomaly which can be isolated, or occurs in association with other anomalies in many genetic disorders.

Simple cryptorchidism is common in premature and low-birth-weight children and is related to maternal obesity, cesarean section delivery and the existence of other affected family members [10].

Testosterone level appears to have an important role during the transinguinal phase of testicular descent [11].

Transabdominal descent seems to be controlled by *INSL-3* and its receptor *LGR8* [12], through mutations of these genes were identified only in a minority of cases with isolated cryptorchidism, and homeobox containing genes that play a central role in the sequential morphogenesis of segmental structure along the body axis, as *HOXA10*, may be implied, too [13].

Association of testicular maldescent with hypospadias and the severity of each of these conditions predict the likelihood of an intersex state [11].

It was suggested that cryptorchidism, reduced fertility and testicular malignancy are interrelated and represent the spectrum of the testicular dysgenesis syndrome caused by both genetic defects and antenatal intervention of endocrine disruptors [14].

In cases with simple cryptorchidism testicular histology is normal in the first 12–18 months, then a reduction in germ cell population ensues, and similar histological changes occur in the contra-lateral descended testis after two years, which suggests that the undescended and scrotal testes share a common intrinsic abnormality; clinically they are softer and smaller than normal [15].

Even after orchipexy, fertility is impaired in 50–70% of boys born with one undescended testis and up to 75% of subjects with bilateral undescended testes [11].

Approximately 10% of testis tumors develop in individuals with a history of cryptorchidism and the risk is proportional with the severity of cryptorchidism; 10–20% of tumors occur in the contra-lateral descended testis if cryptorchidism is unilateral [16].

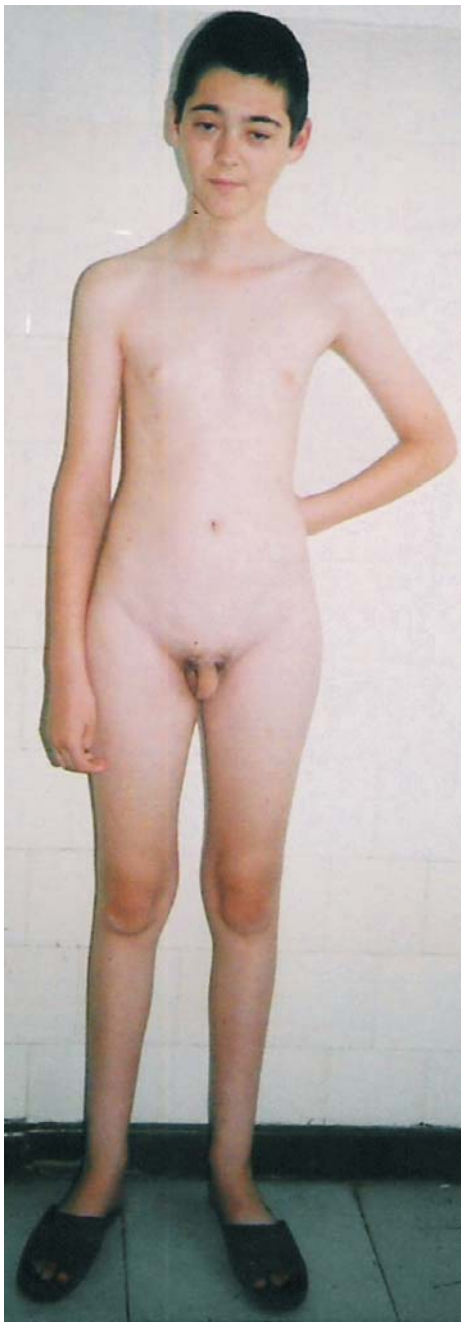

Figure 1 – ***Phenotypic aspect at presentation***

Figure 2 – ***Skull X-ray***

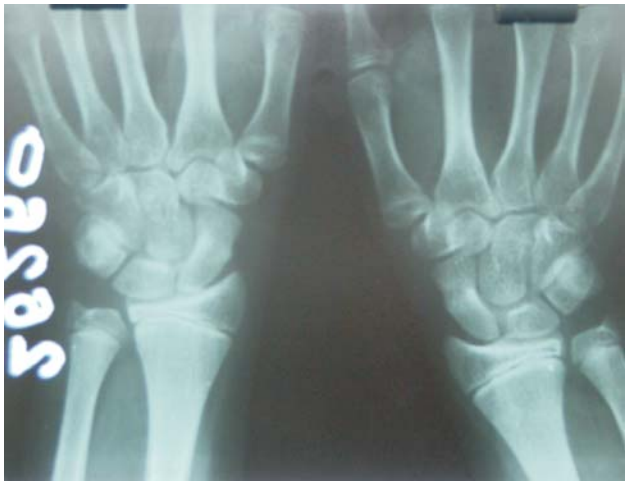

Figure 3 – ***Hand X-ray***

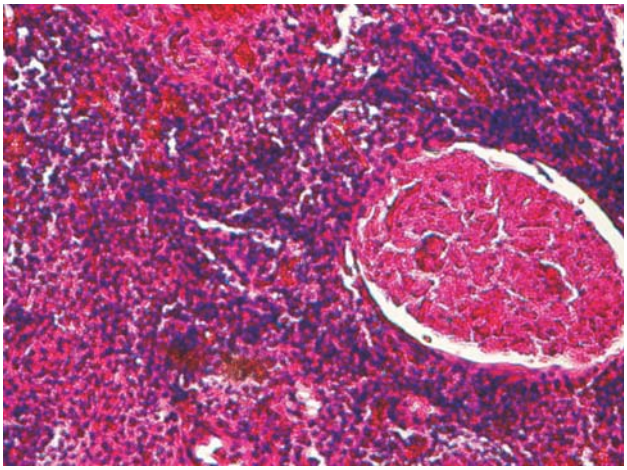

Figure 4 – ***Thymic lymphoid hyperplasia***

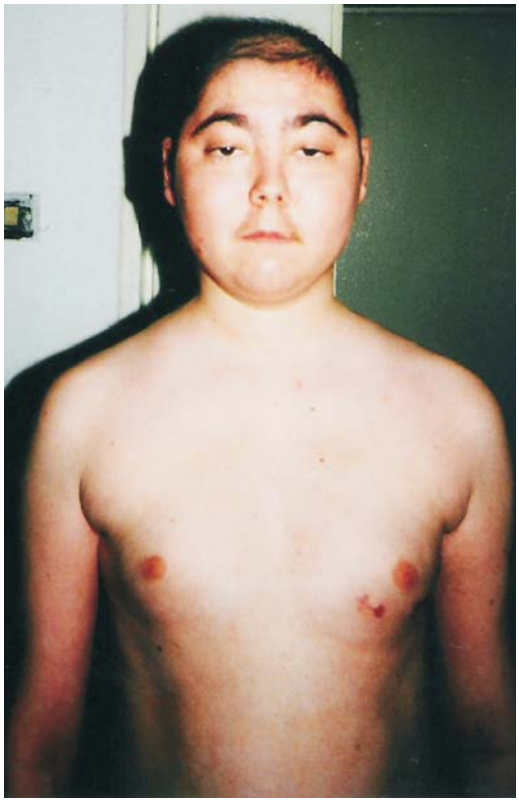

Figure 5 – ***Constitutional aspect after one year***

All these facts support the hypothesis that an undescended testis is an abnormal testis but in the majority of cases the underlying defect remains unrecognized. Probably this is due to the fact that many aspects of the testicular differentiation and descent are incompletely understood.

Another hypothesis could be that testicular defects may be induced by cryptorchidism itself (residence in a higher temperature environment) or its therapeutic approaches (surgical manipulation of the testis, surgical injury of the vasculature or to the vas deferens may result in autoimmune orchitis [17] and hCG treatment may increase apoptotic loss of spermatogonia [18]).

Table 1 – ***Genetic disorders causing male hypergonadotropic hypogonadism***

Gene	Locus	Inheritance	Associated features
		1. Impaired testicular organogenesis	
WT1	11p13	AD deletions	Denys Drash syndrome: diffuse mesangial sclerosis, Wilm tumor Frasier syndrome*: renal sclerosis, gonadoblastoma WAGR: Wilms tumor, aniridia, genitourinary anomalies, mental retardation
[a]*SF1*	9p33	AD/AR	± adrenal insufficiency
SRY	Yp11.3	Y	–
*SOX9**	17q24.3–25.1	AD	- camptomelic dysplasia
DHH	12q13.1	AR	± minifascicular neuropathy
$10q^{-}(?)$	$10q25–q^{ter}$	-	- renal anomalies, dysmorphia
*DMRT1**	9p24.3	deletions	- mental retardation, craniofacial anomalies
*WNT4**	1p31	duplications	–
*DAX1**	Xp21.3	duplications	–
ATRX	Xq13.3	X-linked	mental retardation ± α-thalassemia
		2. Impaired testosterone synthesis	
LHR	2p21	AR	–
*StAR**	8p11.2	AR	- adrenal insufficiency
CYP11A1	15q23–24	AD	- adrenal insufficiency
HSD3B2	1p13.1	AR	- adrenal insufficiency
CYP17	10q24–25	AR	- hypertension
HSD17B3	9q22	AR	–
[a]*DHCR7*	11q12–13	AR	microcephaly, $2^{nd}–3^{rd}$ toe syndactyly, cleft palate, mental retardation, dysmorphic facies
		3. Defects in androgen dependent tissues	
androgen receptor	Xq11–12	X-linked	–
SRD5A2	2p23	AR	–

*disorders with complete XY sex reversal; [a]disorders that affect both testicular organogenesis and steroidogenesis

In our patient the severity of cryptorchidism imposed iterative orchipexy. The absence of mullerian derivatives excluded a severe form of testicular dysgenesis or true hermaphroditism, the low testosterone level excluded incomplete androgen resistance (in which testosterone is elevated), 5α-reductase deficiency (normal testosterone level).

A possible etiology for hypergonatropic hypogonadism in the presented case could be incomplete testicular dysgenesis, LH resistance, a defect in testosterone biosynthesis or could be the consequence of orchipexy.

The low normal IQ associated with cryptorchidism would suggest a mutation in the *ATRX* gene because there are reported cases without α thalassemia, but additional features such as deafness, renal anomalies, dysmorphic facies and mild skeletal defects [19] are lacking; mental retardation is usually severe in *ATRX* mutations. In our patient the association of hypergonadotropic hypogonadism with myasthenia gravis is probably coincidental, because the presence of cryptorchidism suggests the antenatal nature of the testicular defect. Nevertheless, an additional testicular autoimmune disease was not excluded.

Myasthenia gravis is more frequent in women than men, in a ratio of 3 : 2 and its incidence peaks in women in their twenties and thirties and in men in their fifties and sixties [3].

In our patient symptoms appeared at six years, after the first orchipexy, related to surgical stress and anesthetic drugs, was generalized at 14 years and associated thymus hyperplastia. It was shown that in myasthenic patients with thymic hyperplasia, in women and in patients with early onset of the disease there is linkage with the extended haplotype A1–B8–DR3 which is associated with a high prevalence of autoimmune disorders and with a locus on chromosome 6p21.3, MYAS1 [20].

Thymic hyperplasia is found in 65% of myasthenic patients and is not necessarily associated with thymus enlargement [3]. In these patients thymectomy has a beneficial effect, which was also the case in the presented patient.

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Corresponding author
Corina Lichiardopol, University Assistant, MD, Department of Endocrinology, University of Medicine and Pharmacy, Emergency County Hospital, 1 Tabaci Street, Craiova, Romania; Phone +40251–502 130, E-mail: corinalich@gmail.com

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