Testicular Regression Syndrome and Severe Psychiatric Disorder – a Rare Association Preventing the Optimal Management of the Endocrine Condition

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ABSTRACT

Introduction: Bilateral testicular regression syndrome (TRS) is a very rare condition characterized by the absence of testicular tissue in a genotypic male.

Case report: A 39 years old male with TRS (diagnosed at age 8, during investigation for bilateral cryptorchidism) associating paranoid schizophrenia (diagnosed at the age of 14) is described. The patient received parenteral androgen replacement only for a few months in the pubertal period. After puberty, the psychiatric team strongly advised against the androgen replacement which was stopped and not resumed ever since. At presentation the patient has no subjective complaints but clear signs of hypogonadism. The psychiatric status was stable under neuroleptics. Topical androgen replacement was recommended but it aggravated the psychotic aggressive features so it was stopped.

Conclusion: We present the case of a patient with TRS associating, from early adolescence, a severe psychiatric pathology with aggressive characteristics, which constantly precluded adequate testosterone replacement.

Keywords: testicular regression, vanishing testes, schizophrenia, hypogonadism, replacement.

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INTRODUCTION

Testicular regression syndrome (TRS) or vanishing testis syndrome is a rare condition (less than 5% of all patients with cryptorchidism) (1), defined as the intrauterine disappearance of previously normal testicular tissue in a genetic and phenotypic male. The proof that normal testis initially developed is offered by the presence of identifiable spermatic cord structures and the absence of Mullerian duct derivatives in most patients (2).

Patients with TRS suffer from complete primary gonadal deficiency and have indications for testosterone replacement. Before recommending this therapy, a careful check for possible contraindications should be offered to the patient. Among the well-known possible adverse events or contraindications related to cardiovascular health (3), prostate or breast cancers, erythrocytosis, severe urinary tract symptoms (4), psychiatric reactions also need to be considered. The administration of testosterone esters in normal men leads to an overall increase in manic symptoms but the effects only affect a subset of cases (5). In a sample of patients with schizophrenia, serum testosterone levels were directly correlated with the excitement/hostility levels suggesting that cognitive effects are also manifest in these patients (6). However, in another sample of aggressive patients, no correlation was found between serum testosterone levels and the degree of aggressive symptoms (7).

We report the case of a young patient with TRS associating severe psychiatric pathology, association precluding the adequate replacement of the gonadal deficit. □

CASE REPORT

A 39-years-old male patient with a history of bilateral cryptorchidism, not followed-up since childhood, was referred to our department.

He had initially been evaluated, at the age of eight, for persistent bilateral cryptorchidism. At that time, a laparoscopic exploration of the abdomen and inguinal area was performed. Only a brief description of the surgical procedure was available – no testicular or accessory tissue were found. Due to profound hypogonadism, no spontaneous pubertal development took place

and at around 12 years of age, parenteral androgen replacement was initiated. One year later, a severe schizoaffective disorder (paranoid schizophrenia) was diagnosed and a complex scheme of neuroleptics was instituted. At that time, the psychiatric team strongly advised against androgen replacement therapy, which was stopped and not ever resumed until the initial admission to our department.

At the time of the evaluation in our clinic, the patient had no subjective complaints. On inspection, he was a slightly overweight phenotypic male (182 cm tall, 94 kg of weight), with an eunucoid habitus. No facial or truncal hair were present. The scrotum was completely undeveloped, without rugae, and no testes were palpable in the scrotum or the inguinal canal; micropenis was present. The patient also had moderate gynecomastia, present from at least 5-6 years (Figure 1).

A complete psychiatric evaluation was performed. The patient was characterized as having slight mental retardation, irritability, irascibility, low tolerance to frustration, acting out in anxiogenic context and also dominant ideas of persecution (all compatible with his severe psychotic condition).

The endocrine evaluation revealed severe primary hypogonadism with an undetectable anti-Mullerian hormone (AMH) serum level

FIGURE 1. The patient had no truncal hair and moderate gynecomastia

Test	Value	Normal range
Antimullerian hormone (AMH) (ng/mL)	0.03	0.73-16.05
Testosterone (ng/mL)	0.77 ng/mL	1.75-7.81
Estradiol (pg/mL)	<20 pg/mL	<20-47
FSH (mIU/mL)	66 mIU/mL	1.27-19.26
LH (mIU/mL)	22.19 mIU/mL	1.24-8.62

TABLE 1. The endocrinological evaluation of the patient

(Table 1). The karyotype of the patient was 46, XY.

The abdominal CT did not reveal any possible intraabdominal gonadal remnant. We also assessed the bone mass by central densitometry and noticed that, despite longstanding untreated hypogonadism, the bone mass was unaffected.

In view of the severe psychiatric disorder, we did not recommend parenteral androgen administration (because of the long half-life of parenteral preparations of testosterone esters). Topical androgen replacement was recommended but it aggravated the psychotic aggressive features in the first month of treatment, which required admission under psychiatric care. The psychiatric reevaluation strongly advised against continuing therapy, and therefore, testosterone replacement was stopped. □

DISCUSSION

Testicular regression syndrome (TRS or 'vanishing testis') is a condition in which testis is thought to have once existed but has atrophied and disappeared during early development.

The absence of testis in a 46XY male can be unilateral or bilateral and the presumed mechanism is represented by *in utero* torsion or infarction of the testis (8). In a large retrospective review of cases with nonpalpable testes 41% of 447 cases had an atrophic remnants or absent testis(9). Therefore, unilateral affection seem to be not so uncommon. Vanishing testis is more common than testicular agenesis in patients with unilateral nonpalpable testis(10). In contrast, bilateral TRS is very rare (11) and a genetic predisposition to the intrauterine destruction of the testes, although not confirmed, cannot be ex-

cluded (12). The majority of cases have normal external genitalia (2).

The absence of testicular remnants at abdominal CT in our case is not entirely surprising. In a large cohort (77 TRS cases) with pathological examination, small remnants of spermatic cord and fibrotic tissue were the typical finding (8). Although no radiological correlation was made, it is highly unlikely that such small remnants can be unequivocally discovered during CT investigation. For the differential diagnosis between TRS and anorchia, the determination of the serum AMH concentration is very useful. AMH is secreted by Sertoli cells and it is essential for the sexual differentiation of the male fetus as it induces the regression of Mullerian ducts. The serum concentration of AMH is used in the differential diagnosis of bilateral cryptorchidism or gonadal dysgenesis. A very low or undetectable level in a genotypically male is suggestive of anorchia (13).

The optimal management is debated. Cryptorchid testicular tissue has long been recognized to be at increased risk of malignancy (14), especially in the intraabdominal location (15). Based on this increased malignant potential of intraabdominal testicular tissue, some advocate surgical excision (16). However, the indication for surgical removal of the rudimentary structures present is less clear than that in bilateral cryptorchidism. In TRS, some histopathological series found no recognizable viable testicular tissue and therefore assumed that the risk of testicular cancer in the rudimentary remnants is almost nil (17, 18). Larger studies reported that in 10% of cases, testicular tissue was present but in all cases this was completely devoid of germ cells leading to an estimated negligible risk of germ-cell cancer in these patients (19). Therefore, many authors advise against surgical intervention (11, 17, 19, 20).

The profound hypogonadism of these patients is a clear indication for replacement therapy. Untreated longstanding hypogonadism can lead to significant morbidity (cardiovascular events, bone loss, diabetes mellitus, metabolic syndrome) and increased mortality (21). Peak bone mass is severely affected if the hypogonadism occurs during puberty and is left untreated (22).

Before initiation of androgen replacement therapy, a careful review of all possible contrain-

dications should be performed. Current guidelines strongly recommend against replacement treatment if breast or prostate cancer are suspected or confirmed, in erythrocytosis, severe obstructive sleep apnea, severe lower urinary tract symptoms, severe heart failure (23). Severe psychiatric disease is not in itself a contraindication for gonadal replacement therapy. The correlation between serum concentrations of testosterone and aggressive symptoms in these patients is inconclusive: some studies reported such an association (6), while others did not (7).

In our patient, the association of severe hypogonadism due to TRS and psychiatric disease, despite not formally contraindicating testosterone replacement, made it impossible to ade-

quately correct the gonadal deficit. This suggests that the decision to initiate gonadal replacement therapy also needs to be carefully weighed in certain patients with severe psychiatric diseases. □

CONCLUSIONS

Severe psychiatric pathology with aggressive tendencies can be aggravated by testosterone replacement. The association of severe hypogonadism with severe psychopathology sometimes precludes adequate testosterone replacement. □

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REFERENCES

1. Spires SE, Woolums CS, Pulito AR, Spires SM. Testicular regression syndrome: a clinical and pathologic study of 11 cases. *Arch Pathol Lab Med* 2000;124:694-698.
2. Pirgon O, Dundar BN. Vanishing testes: a literature review. *J Clin Res Pediatr Endocrinol* 2012;4:116-120.
3. Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol* 2016.
4. Basaria S. Male hypogonadism. *Lancet* 2014;383:1250-1263.
5. Pope HG, Jr., Kouri EM, Hudson JI. Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. *Archives of General Psychiatry* 2000;57:133-140; discussion 155-136.
6. Moore L, Kyaw M, Vercammen A, Lenroot R, Kulkarni J, Curtis J, et al. Serum testosterone levels are related to cognitive function in men with schizophrenia. *Psychoneuroendocrinology* 2013;38:1717-1728.
7. Sisek-Sprem M, Krizaj A, Jukic V, Milosevic M, Petrovic Z, Herceg M. Testosterone levels and clinical features of schizophrenia with emphasis on negative symptoms and aggression. *Nordic Journal of Psychiatry* 2015;69:102-109.
8. Smith NM, Byard RW, Bourne AJ. Testicular regression syndrome—a pathological study of 77 cases. *Histopathology* 1991;19:269-272.
9. Kirsch AJ, Escala J, Duckett JW, Smith GH, Zderic SA, Canning DA, Snyder HM 3rd. Surgical management of the nonpalpable testis: the Children's Hospital of Philadelphia experience. *J Urol* 1998;159:1340-1343.
10. Merry C, Sweeney B, Puri P. The vanishing testis: anatomical and histological findings. *Eur Urol* 1997;31:65-67.
11. Nishizawa S, Suzuki K, Tachikawa N, Nukui A, Kumamaru T, Shioji Y, et al. [The vanishing testis: diagnosis and histological findings]. *Nihon Hinyokika Gakkai Zasshi* 2000;91:537-541.
12. Ambulkar PS, Waghmare JE, Tarnekar AM, Shende MR, Ghosh SK, Pal AK. SRY-positive 46, XY male with vanishing testis syndrome, feminization and gynecomastia. *Nepal Med Coll J* 2012;14:1-4.
13. Matuszczak E, Hermanowicz A, Komarowska M, Debek W. Serum AMH in Physiology and Pathology of Male Gonads. *Int J Endocrinol* 2013;2013:128907.
14. Campbell HE. The incidence of malignant growth of the undescended testicle: a reply and re-evaluation. *J Urol* 1959; 81:663-668.
15. Emir H, Ayik B, Elicevik M, Buyukunal C, Danismend N, Dervisoglu S, Soylet Y. Histological evaluation of the testicular nubbins in patients with nonpalpable testis: assessment of etiology and surgical approach. *Pediatr Surg Int* 2007;23:41-44.
16. Antic T, Hyjek EM, Taxy JB. The vanishing testis: a histomorphologic and clinical assessment. *Am J Clin Pathol* 2011;136:872-880.
17. Cendron M, Schned AR, Ellsworth PI. Histological evaluation of the testicular nubbin in the vanishing testis syndrome. *J Urol* 1998; 160:1161-1162; discussion 1163.
18. Dhandore P, Hombalkar NN, Gurav PD, Ahmed MH. Vanishing testis syndrome: report of two cases. *J Clin Diagn Res* 2014;8:ND03-04.
19. Hegarty PK, Mushtaq I, Sebire NJ. Natural history of testicular regression syndrome and consequences for clinical management. *J Pediatr Urol* 2007;3:206-208.
20. Grady RW, Mitchell ME, Carr MC. Laparoscopic and histologic evaluation of the inguinal vanishing testis. *Urology* 1998;52:866-869.
21. Zarotsky V, Huang MY, Carman W, Morgentaler A, Singhal PK, Coffin D, Jones TH. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology* 2014;2:819-834.
22. Carsote M, Capatina C, Valea A, Dumitrascu A. Vanishing testes syndrome-related osteoporosis and high cardio-metabolic risk in an adult male with long term untreated hypergonadotropic hypogonadism. *Arch Endocrinol Metab* 2016;60:79-84.
23. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM, Task Force ES. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536-2559.