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Cryptorchidism and its long-term complications

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Abstract. – Cryptorchidism is the most frequent defect of the male urogenital tract at birth. It represents a risk factor for primitive testiculopathy associated with long-term complications (infertility, testicular neoplasia, and hormonal changes). An only consensus exists: "children with bilateral cryptorchidism who are not treated in early age are certainly set to become infertile". The majority of Authors agrees that the cryptorchid testicle will be in for structural and functional alterations and the rate of infertility is inversely proportional to the age at the time of orchidopexy. Cryptorchidism causes secretory primitive testicular pathology responsible for infertility. It is correlated to a non-specific severe histopathological pattern that can be useful to predict future infertility at the moment of orchidopexy. Also cryptorchidism represents the major risk factor associated with germ cell testicular neoplasia (5-10 times more probably than a normal testicle) due to genetic, hormonal, environmental factors.

Key Words:

Cryptorchidism, Male infertility, Testicular neoplasia.

Introduction

Non syndromic (simple) cryptorchidism is the most frequent defect of the male urogenital tract at birth. It occurs when the testicle fails to descend from the lumbar region to the scrotum during natural migration: in 2-4% of full-term and in 20-30% of premature births. The estimated need for orchidopexy concerns about 27,000 cases per year in the US[1]. Simple and syndromic cryptorchidism have several causes (Table I e II). Although cryptorchidism is considered a "modest malformation", it represents a well-characterized risk factor for primitive testiculopathy, showing a potential wide frame of altered spermatogenesis, associated with long-term functional-like complications (infertility), and/or degenerative-organic ones (testicular neoplasia). Since Charny[2] underlined that "orchidopexy techniques have registered a progressive and satisfying improvement of the cosmetic result, but testicular functional result has not reached the target which has been set", few achievements have been made during the years. As matter of fact, although the effects of spermatogenesis and the future fertility of the patient with a history of cryptorchidism have been studied in an extensive way, scientific opinion has reached *an only consensus*: "children with bilateral cryptorchidism who are not treated in early age are certainly set to become infertile". The *majority of the Authors agree on two other aspects*[3-5]: a) the cryptorchid testicle will be in for structural and functional alterations; b) the rate of infertility is inversely proportional to the age of the patient at the time of orchidopexy. The logical conclusion to this point of view is believing that problems due to infertility, secondary and cryptorchidism, could have been simply managed by anticipating orchidopexy before the age of 2. Unfortunately, after 30 years since results on fertility following early age orchidopexy are available, the therapeutic strategy for operating before the age of 2 has not reached an unanimous consensus. The follow-up results have registered a wide range infertility rate, correlated to the past of both bilateral (28.5-82%) and monolateral (62-74%) cryptorchidism[3,4], and to the complications due to long-term cryptorchidism (fertility and testicular neoplasia) based on the region, side and age at the time of orchidopexy[6]. It is estimated that about 20% of the patients who have undergone orchidopexy at puberty are at risk for future paternity even after TESE-ICSI, due to a "real testicular azoospermia"[7]. Cryp-

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Table I. Causes of non syndromic cryptorchidism.

Mechanical factors	Endocrine factors
Inguinal canal obliteration	Low/absent GnRH
Inguinal hernia	Hypopituitarism
Fibrous septum between internal inguinal ring and scrotum	Dysgenesis/anorchia
Brevity of spermatic funicle elements	Testosterone biosynthetic problems
	MIF deficiency/persistent Mullerian ducts
	5 α reductase deficiency
	Androgen resistance

torchidism pathogenesis is still uncertain, but it's supported by one or more of the following factors: *anatomical* (peritoneal adhesions, mesorchium brevity, spermatic vessels and deferent duct brevity, tight inguinal canal, external inguinal ring obstruction), *hormonal* (hypothalamus-pituitary deficiency) and *dysgenic primitive testicular*. Pathogenesis affects the hormonal balance (FSH, LH, androgens), which mediate testicular migration during gestational age by the anti-Müllerian hormone and the androgen dependent factors, such as the insulin like 3 (INSL3) produced by the Leydig cells. INSL3 acts through a G-protein coupled receptor, LGR8 (leucine-rich repeat-containing G protein-coupled receptor 8), stimulating gubernaculum growth[8] and/or direct or indirect androgenic action through calcitonin gene-related peptide release from genito-femoral nerve (during the trans-inguinal phase: from seventh gestational month to birth or shortly after)[9]. During the first year of life, cryptorchid child don't show functional deficiency relating to hypothalamus-pituitary-testicular axis nor changes in testosterone biosynthesis[10]. In pre-pubertal and, especially, in post-pubertal age FSH ed LH levels depend on testicular hormones production (testosterone and inhibin B), reflecting testicular hystopathology. Plasma FSH levels generally increase in those men with severe oligospermia and mycro-orchidism (testicular size <12 ml). Plasma LH and testosterone levels are usually normal, but mean basal and peak GnRH-stimulated LH levels are slightly higher than normal, suggesting subtle Leydig cell dysfunction[11]. Syndromic cryptorchidism represents an aspect of hereditary syndromes characterized by hormonal changes, such as constant or occasional hypogonadism (hypogonadotropic or hypergonadotropic) and/or

Table II. Syndromic Cryptorchidism.

Frequent in syndromes (s)	Occasional in syndromes (s)
Aarskog's	Cockayne's
Carpenter's	Coffin-siris'
Fraser's (cryptophthalmos)	Cri-du-chat's.
Nevoid basal cell carcinoma syndrome (Gorlin's)	Achondroplastic dwarfism
Lowe's	Down's
Meckel-Gruber's	Fanconi's
Noonan's	Femoral hypoplasia-unusual facies's.
Opitz's	Hallermann-Streiff's.
Roberts's	Steinert myotonic dystrophy
Robinow's	Prader-Willi's.
Rubinstein-Taybi's	Saethre-Chotzen's.
Seckel's	Trisomy 8 s.
Smith-Lemli-Opitz's	XXY s.
Triploidy s.	XYY s.
Trisomy 13 s.	Zellweger's.
Trisomy 18 s.	–21q s.
–4p s.	
–13q s.	
–18q s.	

testosterone biosynthesis or androgenic action defect, and more or less complex genetic alterations. All these factors accounts for the frequent or occasional occurrence of cryptorchidism always due to multiple congenital alteration both somatic and nervous (CNS) (Table II).

Complications after long-term cryptorchidism

Infertility

Cryptorchidism is included among the causes of secretory kind primitive testicular pathologies which are responsible for infertility due to a "male factor". The predisposing factors seem to be due genetic, hormonal (testosterone, genetic alterations of the insulin-like factor 3) and/or environmental purposes[12].

Although there is no specific cryptorchidism pathognomonic histopathological pattern existing, the factor discriminating future fertility is the presence of Ad spermatogonia at the time of orchidopexy[4]. Therefore, testicular biopsy histopathology when performing orchidopexy can show useful information to predict future fertility[13].

As a matter of fact, future infertility of the cryptorchid is associated with a particular severe anatomopathological testicular secretory frame which can already be observed in a young cryptorchid[3,4,14]: 0 Ad spermatogonia (dark), and <0.2 germ cells/transverse tubular section (v.n. >2/transverse tubular section). Then, according to some studies[4,14], the above-mentioned severe anatomopathological testicular secretory frame is significantly correlated (p<0.001) in time with: a) a reduced nemaspermatic production (average: 8.9×10^6 spermatozoons /ejaculated), 25 times less compared to the group of controlled cryptorchids (showing Ad spermatogonia in both testicles during biopsy performed at the time of orchidopexy); b) azoospermia in 20%. Moreover, since 70% of the patients with monolateral cryptorchidism shows an improper transformation of Ad spermatogonia, some Authors classify cryptorchidism as a bilateral disease[4,14].

Another histo-pathological pattern which can frequently be observed in biopsies regarding crypthorchid testicles is *mixed testicular atrophy*, defined as "synchronous, contemporary and of variable proportions, a presence of seminiferous tubules including both a normal progressive spermatogenetic maturation of the germ cells and tubules having a Sertoli cell-only syndrome". According to a recent study[15] carried out on 18 patients who underwent testicular biopsy during orchidopexy and then again in adulthood aimed at expanding on infertility, the alterations of spermatogenesis observed in *prepubertal* biopsies were generally classified as type I (modest alterations), II (marked germinal hypoplasia), and III (severe germinal hypoplasia).

Instead, the alterations of spermatogenesis in biopsies carried out in *adulthood* where divided into lesions of the adluminal compartment or of the basal compartment of seminiferous tubules, by comparing the prepubertal biopsy frame of each patient versus the postpubertal one. The Authors noticed that the recurrent frame (responsible for infertility) of mixed testicular atrophy was that of type III with incomplete spermatogenesis (p<0.0001) and more severe lesions of the germinal epithelium (p=0.049). Type III lesions correlated with a frame of mixed testicular atrophy also conferred the worst prognosis in the programs of assisted reproductive technology (ART)[15]. On the other hand, a diametrically opposed histopathological situation to the ones described[3,4,14,15] and less severe one, already witnessed by Bergada et al[16] and verified in another subgroup of patients with previous cryptorchidism, would justify the results of a recent retrospective study[17], carried out on 142 azoospermic patients and previously suffering cryptorchidism (71.8% treated with orchidopexy before the age of 10), who underwent TESE (testicular sperm extraction) between 1995-2005, during medical assisted procreation (PMA) through ICSI (intracytoplasmic sperm injection). In this study, the prognosis of nemaspermatic recovery is considered good, since all together it is equal to 65%, and in particular, 63% (55/87) of patients with a history of bilateral cryptorchidism, and 61.9% (36/42) of patients with a history of monolateral cryptorchidism. The Authors of this study have asserted that a predictive value for the recovery was represented by normal FSH values and testicular volume >10 ml[17].

Pathogenetic Mechanisms Responsible for Infertility Correlated to Cryptorchidism

It is believed that infertility induced by cryptorchidism is an endocrinopathy whose main cause is recognized as an *"impaired"* mini-puberty[18], defined as a hormonal risk factor peak period of gonadotropin occurring during early

childhood, which is necessary and important to induce the development and transformation of gonocytes into Ad spermatogonia[3,5,14,18-21]. As a matter of fact, this period is insufficient and inadequate in about 50% of the testicles of cryptorchid subjects in the inguinal region and in 90% of the testicles situated in the intra-abdominal region[18]. In order to correct this mini-puberty imperfection, some Authors have shown that a 5 month alternate-day medication before the age of six immediately following orchidopexy of LH-RH analogue (Buserelin) does not inhibit gonadotropin secretion and assures higher LH values at the end of treatment[21], but above all it determines an increase in the number of spermatogenetic germ cells (versus a control group undergoing orchidopexy only)[3,5,14,18-20].

Neoplastic Degeneration (Testicular Neoplasia)

Cryptorchidism represents the major risk factor associated with germ cell testicular neoplasia (seminomatous, SEM; non seminomatous, NSEM). These types of neoplasia have a 5-10 times more probability of outbreak in the cryptorchid testicle compared to a normal one. This risk becomes higher the higher the region of testicle descent is (abdominal vs. inguinal)[22]. The wide range as a risk factor (OR 2.9-11) for testicular neoplasia of cryptorchidism depends on the multiple pathogenetic mechanisms (genetic, hormonal, environmental ones) which are responsible for a certain kind of cryptorchidism. The major degenerative risk factors can be found in TDS (testicular dysgenesis syndrome)[23] presenting some of the peculiar common features: pathogenetic hypothesis [disturbed gonadal development in fetal age by one or more: genetic factors (family OR = 3.8 with a testicular neoplasia carrying father; OR = 7.6 with a testicular neoplasia carrying brother)[24]; subjection to *endocrine disruptors*, such as constant polluting organics, pesticides, phthalates); motherly life style (smoking), phenotype at birth (cryptorchidism, hypospadias), long-term complications such as infertility, and/or testicular neoplasia (in more severe forms)][25]. The different final testicular expression resulting is due to the different interaction between the altered/destroyed scheduling of embryo-foetal development regarding the male gonad and to the adverse pre- or post-natal gonadotropic environmental influences. On the other hand, foetal origin testicular neoplasia is supported by the association with some clinical and biological risk factors (low weight at birth; urogenital congenital deformity: cryptorchidism, hypospadias)[25-27]. As the precursor of seminomatous neoplasia (SEM), nonseminomatous germ cell testicular neoplasia (NSEM), as well as certain types of germ cell neoplasia in the extragenital region (retroperitoneal, mediastinic, CNS), carcinoma *in situ* or CIS has several cytological features in common with foetal germ cells[28,29]. Therefore, from a clinical point of view, in post-orchidopexy follow-up, besides clinical evaluation another important adjuvant role is played by diagnosis through diagnostic imaging with scrotal ultrasonography. Apart from providing information on echo-sounding and reduced echostructure of the previous cryptorchid testicle, it may reveal the presence of areas of microlithiasis which should not be considered as a rare report but rather deserves being monitored since the risk of turning itself into a carcinoma affecting these areas is significant[30,31]. According to what has been said, testicular biopsy is the only diagnostic procedure to identify patients at risk of future infertility, and/or candidates in line for treatment with GnRH analogue following orchidopexy. Unfortunately, material regarding biopsy which is studied and published in literature is influenced by a selection bias, since it derives from:

a) cryptorchid testicles which are non responsive to hormonal therapy, and therefore subjected later on to orchidopexy;
b) cryptorchid testicles which have never been treated with hormonal therapy, and directly treated with surgery.

As a matter of fact, there is no possibility to carry out a quantitative analysis of spermatogenesis directly on those subjects who have reached testicular descent after medical treatment. Therefore, it is not possible to obtain any results on functionality in this group since the clinical-anatomical result which has been reached is not simply cosmetic, like that following orchidopexy. At this point it is possible to understand how long-term results only, by using the seminologic analysis combined with second level evaluations (chromatin compaction, fragmentation of spermatic DNA, early apoptosis markers) besides echographic monitoring, based on the age of the patient at the time of treatment (hormonal and/or surgical). These exams are able to indicate if and how some factors (such

as age, kind of treatment) are really important in order maintain the fertility of patients with cryptorchidism in the future.

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