Cryptorchidism – Disease or symptom?

Cryptorchidie – maladie ou symptôme ?

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Abstract

Testes descend to the scrotum normally before birth. When they fail to do so, the boy is cryptorchid and has an increased risk for testicular germ cell cancer and subfertility later in life. Early correction of maldescent by orchiopexy operation improves the spermatogenetic capacity of the testis but does not return the testicular cancer risk to the control level. Testicular descent is regulated by testis-derived hormones testosterone and insulin-like peptide 3. Cryptorchidism can therefore be considered a symptom of impaired testicular function that may also be linked to other testicular diseases, such as germ cell cancer and subfertility. Early orchiopexy can alleviate the effects of cryptorchidism on spermatogenesis, but alertness for testicular cancer should be maintained. In searching the genetic and environmental reasons for these diseases, it is useful to consider their connection with each other.

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Keywords: Testis; Reproductive health; Testicular dysgenesis syndrome; Semen; Testicular cancer

Résumé

Les testicules descendent normalement avant la naissance dans le scrotum. Lorsque cette migration ne s’effectue pas, le garçon est cryptorchide et présente un risque accru de cancer testiculaire et d’hypofertilité ultérieure. Une correction précoce de cette anomalie par orchidopexie améliore la spermatogenèse mais n’annule pas le risque de cancer. La migration testiculaire est régulée par les hormones testiculaires, singulièrement la testostérone et le peptide insulin-like 3. Ainsi, la cryptorchidie peut être considérée comme un symptôme de l’altération de la fonction testiculaire qui peut être également lié à d’autres maladies testiculaires comme le cancer des cellules germinales et l’hypofertilité. Une orchidopexie précoce peut corriger les effets de la cryptorchidie sur la spermatogenèse, mais le dépistage du cancer testiculaire doit être maintenu. En recherchant les causes génétiques et environnementales de ces maladies, il est utile de prendre en compte leurs interrelations.

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Mots clés : Testicule ; Reproduction ; Syndrome de dysgénésie testiculaire ; Sperme ; Cancer testiculaire
Testes descend to the scrotum normally during gestational weeks 25–35 [1,2]. If one or both testes remain undescended at birth, the boy is cryptorchid. This occurs in 1–8% of full-term newborn boys [3,4]. Testicular Leydig cell-derived hormones testosterone and insulin-like peptide 3 (INSL3) regulate testicular descent [5]. Gubernaculum is a genitoinguinal ligament that first enlarges and anchors the testis in the inguinal area and then it guides the testis into the scrotum [6]. In the absence of INSL3 action (defect in the hormone or its receptor), gubernaculum fails to show male-like differentiation (at least in mice) [7–9]. A small percentage of cryptorchidism cases have been suggested to have mutations in the genes of INSL3 or its cognate receptor RXFP2 (relaxin family peptide 2) [10]. However, their role in cryptorchidism remains unclear, because only heterozygous changes have been found and for instance, the T222P variant of the RXFP2 gene seems to be a risk factor for cryptorchidism only in some populations [10–13]. The role of testosterone in testicular descent has been known for long, because people with androgen insensitivity have either labioscrotal, inguinal or abdominal testes (most severe grades of androgen insensitivity) [14,15]. Patients with defects in androgen biosynthesis, such as 17-beta hydroxysteroid dehydrogenase 3 and 5-alpha reductase deficiencies have also been described to have inguinal or labioscrotal testes [16,17]. These findings have led to a hypothesis that testicular descent is a two-phase process where INSL3 primarily regulates the first, trans-abdominal phase and testosterone the second, inguinoscrotal phase [6]. However, it is apparent that both hormones are active in the whole process. Cryptorchidism shows familial clustering [18,19], suggesting that genetic reasons could be important. There are several syndromes that include undescended testis as a component pointing also to genetic defects [6,10]. Indeed, we know that all gene defects affecting androgen biosynthesis or action can cause cryptorchidism [4,6]. However, in the large majority of all cases, no genetic defect in androgen signaling or in any other genes can be found [20–24]. Maternal half-brothers have higher concordance rate of cryptorchidism than paternal half-brothers, and monozygotic twins have similar concordance rate as the dizygotic ones [25]. These findings indicate the importance of uterine environment. What is it then in the environment of the fetus that is causing the harm?

Experiments in several animal models have shown that many environmental chemicals can cause cryptorchidism [26]. These compounds are called endocrine disruptors, because they affect hormone production, metabolism or signaling [27]. Anti-androgens are the best-characterized compounds that cause cryptorchidism by interfering with androgen synthesis or receptor transactivation [28,29]. Potent estrogens have been shown to affect INSL3 expression and also androgen receptor expression [30–32]. Dioxins act via aryl hydrocarbon receptors (AhR) [33] and can also induce cryptorchidism and delayed testicular descent [34,35], although the mechanism is not as well characterized as that for anti-androgens and estrogens. During the last ten years, reproductive toxicologists have carried out mixture studies showing dose-additive effects of anti-androgens [36]. These studies indicate that the no adverse effect levels (NOAELs) are true only when the chemical is tested alone. When agents are combined together at doses way below their NOAELs, they can together cause severe adverse outcome [37]. With mathematical modelling, we can predict the combined effects of similarly acting agents when individual compounds and the dose-responses are well characterized [38]. This will bring novel information for risk assessment of chemicals.

Cryptorchidism could be considered rather harmless birth defect unless it was linked to other reproductive health problems. It is a well-known risk factor for germ cell cancer and impaired semen quality [39,40]. Only minority of testicular cancer patients have had the history of cryptorchidism, but the cryptorchid boys do have a 4–6-fold testicular cancer risk compared to non-cryptorchid boys [40]. There is strong evidence that testicular cancer has its origin already in utero when germ cell development is misguided and carcinoma in situ – cells are formed inside seminiferous tubules [41]. These cells start to proliferate at puberty and appear as gross cancer in young men [41]. Therefore, it is not surprising that treatment of cryptorchidism does not really influence the risk of testicular cancer. There are reports suggesting that treatment of cryptorchidism before puberty would be beneficial compared to post-pubertal surgery [42,43], but even the small benefit was challenged in a large registry study [44]. As the testicular cancer risk seems to be similar notwithstanding the treatment, spermatogenic potential is greatly influenced by correction of testicular location [39]. Spermatogenesis requires cooler temperature than elsewhere in the body, and in cryptorchid testis sperm production is impossible. Therefore, the testes have to be brought into the scrotum to allow effective physiological cooling mechanisms. There is ample evidence that germ cell number decreases fast after the first year of life in undescended testes [45–47]. This came apparent even in testicular size when cryptorchid boys who had been treated with orchiopexy either at 9 months or at 3 years were compared in longitudinal follow-up [45]. Histological analysis confirmed the massive germ cell loss in the testes of the late-operated group [45]. These and other previous similar studies have been the basis of the recommendation to treat cryptorchidism before the age of one year to preserve the spermatogenic potential as good as possible [48]. Unfortunately, some boys who have cryptorchidism may already have such a spermatogenic defect that orchiopexy does not help [49]. Cryptorchidism is also sometimes associated with hypospadias. Urethral development is under androgen regulation, and therefore, it is easy to understand that these two birth defects can be tightly linked. Since testicular cancer also has a fetal origin and its risk is increased by both cryptorchidism and hypospadias, all these disorders may share etiological factors [50]. Biological plausibility would suggest that those factors should have something to do with androgen signalling. Indeed, genetic defects of androgen synthesis and partial androgen insensitivity typically cause both of these birth defects and increase the risk of germ cell cancer greatly. In addition, they severely compromise spermatogenesis. Poor semen quality may therefore also stem from the same problems as genital abnormalities and testicular cancer. Realizing these connections led to the testicular dysgenesis syndrome (TDS) hypothesis, a concept suggesting that
Cryptorchidism, hypospadias, testicular germ cell cancer, and impaired semen quality share etiology in part of the cases [50,51]. This can be genetic, such as mutations in NR5A1 (SF-1) or androgen receptor, or environmental, such as exposure to anti-androgens (e.g. fungicides vinclozolin and procymidone). Shared genetic risk factors between different TDS phenotypes were observed in a study combining genome-wide association study and systems biology approaches [52].

Cryptorchidism presents usually as an isolated disease without hypospadias, and problems in sperm production or testicular cancer would appear two to three decades later if ever. We should, however, be alert of these later risks. As mentioned in the beginning, Leydig cell-derived hormones regulate testicular descent, i.e. the testis is regulating its own descent, and the failure suggests that there is something wrong in the testis itself. INS13 levels in cord blood of persistently cryptorchid boys were somewhat lower than those of healthy boys [53]. At three months of age, during the mini-puberty, the boys with severe cryptorchidism had immeasurable levels of bioactive testosterone [54]. Furthermore, gonadotropin levels at this age were elevated in cryptorchid boys as a sign of compensation attempt [55]. All these findings point to a primary testicular defect as a cause of cryptorchidism. This does not exclude the well-known fact that in hypogonadotropic hypogonadism, cryptorchidism is a part of the phenotype, because of lacking testosterone production in the late phase of gestation and in mini-puberty. However, hypogonadotropic hypogonadism is a rare disease and only seldom found behind cryptorchidism [24]. In this sense, cryptorchidism can be considered a symptom of a testicular defect.

Cryptorchidism has been treated with hormonal medication or with surgery (orchiopexy). Human chorionic gonadotropin has been used since the 1930s with the logic that increasing testosterone levels could induce the inguinoscrotal descent. Similar logic is behind the GnRH agonist treatment that became popular in the 1980s when favorable reports of its efficacy in open-label studies were published. However, several studies in the last century showed that the efficacy of hormone treatment was not good and the risk of secondary testicular ascent to cryptorchid position was also substantial [56,57]. Strong gonadotropin stimulation was found to cause leakage of both erythrocytes and leukocytes in testicular interstitium [58,59], and increased post-treatment apoptosis of the germ cells [60], resulting even to smaller testis size in adults compared to surgically treated men [61]. Surgery is not without risks either, but they are usually limited to the most difficult cases of cryptorchidism where the testes are located in the abdomen and the funicle containing the spermatic cord and blood vessels is short, making it difficult to move the testes down to the scrotum [62]. Compromised testicular circulation may lead to testicular atrophy after the operation.

Practical approach to cryptorchidism is rather simple. Most of the cryptorchid cases are unilateral, and 50–75% of the testes that are not fully descended at birth, do so during the first three months after birth, after which the likelihood of spontaneous cure is small [63]. Thus, the boy should be re-examined between 3–6 months after birth and referred to paediatric surgery if cryptorchidism prevails [48]. Orchiopexy should be scheduled before the age of one year. If both testes are non-palpable, diagnostics of disorders of sex development (DSD) should be considered [48]. The first thing is to exclude salt-wasting 21-hydroxylase defect (congenital virilizing adrenal hyperplasia) that may masculinize a girl so badly that she can be considered a cryptorchid boy at birth. After correct diagnosis, she will then be treated with hydrocortisone and fludrocortisone [64]. In DSD diagnostic work-up karyotype, endocrine evaluation, and imaging of the internal genital organs will reveal whether the child has testes or not [65]. Follow-up and treatment will then be similar as that of unilateral cryptorchidism. However, the paediatric urologist may perform orchiopexies in two separate operations in cases where there is a high risk for testicular atrophy to make sure that both testes are not lost. If postoperative atrophy appears there is a possibility for minimal surgery on the other side, to bring the contralateral testis to a palpable position. This can preserve the endocrine function of the testis, although spermatogenesis in this still suprascrotal testis is likely to be compromised [48].

In addition to congenital cryptorchidism, there is a big group of children with acquired cryptorchidism, i.e., they have ascended testes either the first time or after temporary descent of congenital cryptorchid testis [66]. The reasons for testicular ascent are not known, but the ascended position inhibits spermatogenesis. In Dutch longitudinal follow-up studies, the rate of spontaneous descent during puberty is high in this group of boys [67,68], and in the Netherlands, wait-and-see policy has been tried to avoid unnecessary surgery [69]. However, approximately one fifth of acquired undescended testes ended up to surgery [67,68], and we cannot be sure how much damage waiting may cause in the testis. Semen studies from Holland with small patient groups of acquired cryptorchidism suggest that orchiopexy at diagnosis may not improve future fertility potential as compared to wait-and-see policy [68]. Nevertheless, in Nordic countries, we have followed a precautionary principle by suggesting that also acquired cryptorchidism should be treated surgically without long delays [48].

In the large majority of cryptorchid cases, etiology remains unknown. This presents a great challenge for clinical and basic scientists and requires a multidisciplinary approach combining information from epidemiology, endocrinology, genetics, toxicology and environmental sciences. The small defect can be a sign of a big problem that requires diagnosis and treatment. Ultimately we want to prevent these reproductive health problems altogether.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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