Acquired Cryptorchidism: What Should We Know? The Results of a Systematic Review

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1. Introduction

Cryptorchidism or undescended testis (UDT) is the most common genital abnormality seen at term in boys (Meij-de Vries A et al 2010, Topari & Kalieva 1999). Traditionally, UDT was thought to be a congenital disease, with a prevalence of about 0.8-1% by 1 year of age (Berkowitz G Set al 1993). The term acquired UDT was introduced in the last few decades, after well-documented clinical observations in individuals and groups of patients that many boys continue to be diagnosed and treated later in childhood (Myers NA & Officer CB 1975, Atwell JD 1985, Clarnette TD et al 1977, Schiffer KA et al 1987, Robertson JF & Azmy AF 1988, Wright JE 1989, Fenton EJM et al 1990, Mayr J et al 1995) despite the recommendations for early surgical treatment by orchidopexy (Ritzén M et al 2007). Today, acquired UDT is a recognized separate entity, and after a new clinical classification in 2003, UDT is categorized into two forms: congenital UDT and acquired UDT (Hack WW et al 2003a).

Although the pathogenesis of congenital UDT is considered multifactorial including hormonal, genetic, and environmental influences (Ghacko JK & Barthold JS 2009, Barthold JS 2008), the exact etiology of acquired UDT remains unclear (Meijer RW 2004). Furthermore, while surgical treatment is recommended for congenital UDT patients as young as 6 months (Ritzén M, 2007), to reduce the increased risks of progressive infertility, testicular malignancy, torsion, associated inguinal hernia, and because of cosmetic and psychological aspects (Ashley RA et al 2010, Lamah M et al 2001) there is much controversy in the management of acquired UDT (Hack WW et al 2010).

In this article, we present the current data of the literature of this distinct entity in a concise but comprehensive review.

2. Patients and methods

A systematic review of the literature was performed focusing on the diverse aspects of the epidemiology, pathogenesis, diagnosis and management of acquired UDT. Data were

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extracted from Medline database form inception to October 2011. A UDT was defined as a non-palpable testis inside the scrotum and for which further traction on cord traction was painful (Meij-de Vries A et al 2010). A congenital UDT was defined as a testis which had not previously descended (Meij-de Vries A et al 2010, Hack WW et al 2003b), whereas an acquired UDT was defined as an UDT in which a previous scrotal position was documented on at least one occasion (Barthold JS & González R 2003). This does not include testes identified as being cryptorchid after inguinal surgery.

3. Epidemiology

Although the incidence of congenital UDT in full term males remains constant in the last few decades (Barthold JS & González R 2003), the true incidence of acquired UDT remains unknown, because of the lack of studies documenting the prevalence of this condition (Hack et al 2010) First Villumsen et al (Villumsen AL & Zachau-Christianssen B 1966) in 1966, reported that 69/4300 boys, (84 testes), had 2%, either unilateral or bilateral ascending testes from a normal position at birth to a higher position by the age of 3 years. In 1975, Myers et al (Myers NA & Officer CB 1975) reported a study of two families in whom all nine boys had normal descended testes documented as infants, but four in one family and three in the other required surgery for UDT before their teenage years. Wyllie in 1984, (Willye GG 1984) reported a study of 100 boys with retractile testes in whom 42% had testes at a higher level after a 5-year observation. Atwell in his paper, (Atwell JD 1985) reported an incidence of 1% acquired UDTs of all orchipexies undertaken in his unit. In a study from Oxford (John Radcliffe Hospital Cryptorchidism Study Group 1986)) was found that 40% of boys whose testicles had not descent at birth but had done so by 3 months became undescended by the age of 1 year. Since then, others have given various rates, with ascending testes comprise 16% (Fenton EJM et al 1990), 2.3% (Gracia J et al. 1997), 5% (Eardley I et al 1994), 20% (Rabinowitz R & Hulbert WC, Jr 1997 ), and 73% (Hack WW et al 2003b) of all orchipexies. In a cross sectional Dutch study, Hack et al (Hack et al 2007a) found a prevalence of acquired UDT up to 2.2% among 6-13 year old boys. Acerini et al (Acerini CL et al 2009), in a UK infant cohort study observed a cumulative incidence up to 7% at the age of 24 months (0.7%, 4%, 1.3% , and 1% at ages 3 months, 12 months, 18 months , and 24 months respectively). More recently, Wohlfahrt- Veje et al (Wohlfahrt-Veje C et al 2009) reported that acquired UDTs account for 58% of all cases of cryptorchidism (congenital and acquired) at 18 months, 71% at 36 months and 69% thereafter.

Although estimates regarding the true incidence of testicular ascent vary considerably, orchidopexy rates and higher than expected mean age of orchidopexy suggest that acquired UDT is more common than indicated by the number of detailed case reports. Most authors agree that acquired UDTs is a common phenomenon outnumbering congenital UDTs by a factor of two to three (Hack WW et al 2003b, Hack WW et al 2007a) 1, Agarwal PK et al 2006. This could mean that the pathogenesis of AUDTs, as in congenital forms, is multifactorial also.

3.1 Pathogenesis

The pathogenesis of acquired UDT is not fully clarified, since several mechanisms have been proposed to elucidate the testicular ascent. Essentially, 4 major theories have been described
to explain the process of secondary ascent (excluding that for iatrogenic reasons). The first theory is based on surgical findings during orchidopexies. Atwell (Atwell JD 1985) noted the presence of a persistent processus vaginalis (PV) in 9/10 of his patients. He proposed that the acquired malposition of the testis is due to partial absorption of the PV into the parietal peritoneum, and this alteration in the distribution of the peritoneal lining of the abdominal cavity leads to traction of the spermatic cord and ascent of the testis. Clarnette et al (Clarnette et al 1977, Clarnette et al 1997) reported the presence of a fibrous structure extending with the cord structures, which on immunohistochemistry showed the characteristics of a remnant of the PV. Other studies found the presence of PV or hernia sac in 23%-76% of orchiopexies for acquired UDT (Robertson JF & Azmy AF 1988, Wright JE 1989, Meijer RW 2004, Gracia J et al 1997, Eardley I et al 1994, Hack WW 2003b, Redman JF 2005). Based on these findings, it was suggested that the persistence of a patent PV or its remnants is responsible for tethering the testis in a static position during a period of somatic growth. However, recently Meij-De Vries et al (Meij-de Vries A et al 2010), studying the perioperative surgical findings in congenital UDTs and acquired UDTs, found that acquired UDTs are more likely to have a closed PV, and a normal insertion of the gubernaculum. The conflicts seems to be continued, after the current findings of Mirillas et al (Mirillas et al 2010) who studied the sonographic pattern of the PV in children with acquired UDTs and found that PV is patent in a manner similar to the inguinal hernia and hydrocele. They suggested that a scrotal testis could be retracted through the PV to a higher position with contraction of the cremaster muscle.

The second theory speculates an association between retractile testes and acquired UDTs. Agarwal et al (Agarwal PK et al 2006) reported an incidence of 32% of retractile testes which became ascending during of about 3-year follow-up period. Willie (Willye GG 1984) reported an incidence of 42% of retractile testis to become ascending. Stec et al (Stec AA et al 1987) noted an incidence of 3.2% (21 of 666 retractile testes) underwent secondary ascent and orchidopexy. They stated that the majority of retractile testes resolve without surgical intervention. Eardlay et al (Eardley I et al 1994) found that 27% of ascending testes were previously retractile. Smith et al (Smith JA et al 1989) reported an increased secondary ascent of the testes in boys with cerebral palsy, where an increased cremasteric muscle hypertonicity is noted. These findings show that about a third of ascending testes may be passing through a retractile phase through the transition from the scrotum to an extrascotal position (Hack ww et al 2003c). Natural course of acquired undescended testis in boys. Brit J Surg, 90, pp.728-31). The following mechanisms have been proposed to clarify the possible causes of retractile testes to become ascended: a) Smith et al (Smith JA et al 1989), speculated that cremaster muscle spasticity may be a possible cause of acquired UDT in patients with cerebral palsy. However, the proposed etiology in otherwise normal boys is not clear (Barthold JS & González R. 2003), b) The cremaster muscle is androgen sensitive and exhibits decreased activity, resulting in decreased testicular retractility, during periods of high androgen production, specifically in infancy and puberty. It has been shown, that target disruption of estrogen receptors in mice produces cremasteric hypotrophy and testicular retraction (Bartlett JE et al 2008). Theoretically, environmental chemicals that influence sex steroid production or action could exaggerate the physiological hyperactivity of the cremaster muscle in young boys and increase the risk of testicular ascent (Gray LE & Osthy 2001). However, reproductive hormone activity is low during mid childhood, and
the association between ascent testis and these substances is theoretical, and c) Robertson et al (Robertson JF & Azmy AF 1988) suggested that peri-testicular adhesions might be responsible for retaining the retractile testis in an inguinal position but this association has not been proved yet.

A third hypothesis proposed by Rusnack et al (Rusnack SL et al 2002) who found that primary undescended testes, ascending testes and the contralateral descended testes share the same histopathology concerning the total and differential germ cell counts per tubule. These findings suggest that an endocrine defect could be the cause of acquired UDT, since no thermal effect can be blamed for the decreased germ cell count in the descent testes. A further implication of an endocrine defect in the pathogenesis of acquired UDT is derived from recent reports which found an increased risk of AUDTs with proximal hypospadias (Tasian GE et al 2010, Itesako T et al 2011). The authors suggest that the role of prenatal and postnatal androgen disruption may link these conditions.

Finally, the fourth theory speculates the role of genitofemoral nerve (GFN) as a factor in testicular ascent. Hutson et al (Hutson JM & Hasthorpe S 2005) found that the GFN acts as second messenger for androgen by release calcitonin gene related peptide (CGRP) to control descent of the testis. They proposed the following mechanism by which the influence of the GFN is implicated: at birth the spermatic cord is 4 to 5 cm in length, but by the 10th year, it is 8-10 cm. This doubling in length is inhibited if there is a residual fibrous remnant of the PV, which may caused by deficient CGRP release from the GFN postnatally. Shono et al (Shono T et al 1999) reported that the proximal division of the GFN in neonatal rats causes testicular maldescent and may also induce testicular ascent in adulthood. They proposed that some intrauterine disorders of the GFN may cause testicular ascent.

The perception of acquired UDT has not been widely accepted. Rabinowitz et al (Rabinowitz R & Hulbert WC, Jr. et al 1997) studied 21 patients (23 undescended testis) and found that the gubernaculum attachment in half of the cases was abnormal. They stated that “this condition is ought to a missed diagnosis at a younger age. The testis is undescended, but almost completely descended. With somatic growth the distance between the terminal portion of the gubernaculum and the scrotum increases, making the diagnosis more obvious”. Furthermore, Redman in his paper (Redman JF 2005) challenged the concept of acquired UDT, arguing for “abandoning the concept and diagnosis of the ascending testis and embracing the phenomenon that the examination of the testis in infants and boys is an inexact process”.

### 3.2 Natural history

The assessment of the natural history of acquired UDT is complicated by the difficulty in differentiating between “high retractile” testes and testes that have ascended from a normal descended position in the scrotum (Taghizadeh AK & Thomas DF 2008). However, some conclusions concerning the natural history are extracted by three long-term prospective studies performed by Eijsbouts et al, Sijstermans et al, and Hack et al. Eijsbouts et al (Eijsbouts SW et al 2007) evaluated prospectively 107 patients (132 acquired UDT) with a mean age 8.9±2.9 years. The mean follow-up was 4.5 years (range 0.3-12.1 years). The results showed that 75/132 (56.8%) testes descended spontaneously at puberty. Orchidopexy was
performed in 57/132 (43.2%) testes. They noted that acquired UDT showed an increasing chance of descending spontaneously with increasing age, and an appropriate for the age testicle volume. Sijsterman et al (Sijsterman K et al 2006) reported that among 129 acquired UDTs, (mean follow-up 2.5 years, range: 0.2-8.5 years), 98 (76%) descended spontaneously at puberty with appropriate testicular growth; in the remaining 31 (24%) orchidopexy was performed at puberty, due to non-descent. Hack et al (Hack WW et al 2010) assessed prospectively the natural history and long-term testicular growth of acquired UDT after spontaneous descent or pubertal orchidopexy in case of non-descent, in 391 boys with 464 acquired UDT. At the time of referral the median age was 7.1 years. The mean follow-up was 4.7 years (range 0.1-12.0 years). They found that a 77.7% has a tendency of spontaneous descent at puberty, and in nearly all cases, after spontaneous descent or after pubertal orchidopexy, with long-term testicular volumes appropriate for age. Pubertal surges in luteinizing hormone and testosterone, as also is seen in the first 3 months after birth (Hamza AF et al 2001) when spontaneous descent of congenital UDT can still occur, are hypothesized to be responsible for pubertal spontaneous descent (Sijsterman K et al 2006).

### 3.3 Acquired UDT and fertility

There is limited evidence from the available data of the literature about the impact of acquired UDT in the fertility. As mentioned above, biopsies taken from ascending testes showed comparable histological findings to biopsies taken from the contralateral descended testes and primary undescended testes (Rusnack SL et al 2002). Gracia et al (Gracia J et al. 1997) reported an impaired spermatogenic potential in 25/ 35 (71.4%) biopsied ascending testes. Meijer et al (Meijer RW et al 2004) reported that 24 / 30 acquired UDTs (80%) were small for the children’s age and 1 (3%) was atrophic. These findings imply that acquired UDTs might influence fertility.

### 3.4 Acquired UDT and cancer

It is generally accepted that UDT is a risk factor for testicular cancer (Pettersson A et al 2007). Among men who have had UDTs the risk of cancer is increased two to eight times, and among all men with testicular cancer have a history of cryptorchidism (Topari J & Kalieva M 1999, Dieckemanman KP et al 2004). However, orchidopexy does not reduce the risk of cancer but renders the retained testis amenable to self-estimation later in adulthood (Hack WW et al 2010). It remains unknown whether the risk of malignancy in acquired UDT and congenital UDT is the same. Nevertheless, the risk of cancer in acquired UDT might be lower than in congenital UDT, since neonatal gonocytes have transformed normally before the abnormality develops (Hutson JM & Clarke MC 2007).

### 4. Diagnosis

Past history and clinical examination are essential for the correct diagnosis of an acquired UDT. Commonly, acquired UDT is seen after the age of 4-5 years ((Myers NA & Officer CB 1975), and peaks around age 8 (Wohlfahrt-Veje C et al 2009). Clinically, acquired UDTs may be distinguished from retractile testis because they have a smaller size, immediate retraction out of the scrotum and pain after manipulation (Agarwal PK et al 2006).
However, early forms, even in boys less than 1 year, have also been recognized (Hack WW 2007b). Wright (Wright JE 1989) proposed the following criteria that have to be satisfied for the diagnosis of acquired UDT: a) it must be recorded by an experienced observer that the testis once had reached the bottom of the scrotum, b) the same or an equally experienced observer must later be unable to manipulate it into the scrotum, and the testis must remain above the scrotum when the child squats or sits bolt upright with the thighs abducted. c) there must have been no surgery or inflammatory episode to have caused the ascent, and d) the testis must remain above the scrotum when the child is anesthetized.

Potential impediments that may interfere in the correct diagnosis an ascending testis include: a) obesity, b) a small contracted scrotum, and c) an uncooperative or fretful patient (Redman JF 2005). The contractions of the cranasteric muscles, hydroceles, thick walled hernia sacs, and long looping vasa are further possible factors to a correct diagnosis (Redman JF 2005).

5. Management

The proper management of acquired UDT remains controversial mainly due to a lack of longitudinal follow up data ((Hack WW et al 2010). Currently two main polices have been proposed: a) the policy of prompt surgical correction (Taghizadeh AK & Thomas DF 2008, Bonney T et al 2008) and b) conservative policy either of "wait and see" (Meij-de Vries A et al 2010) or hormonal treatment (Meijer RW et al 2001). The target of the first policy is to achieve normal or at least improved fertility, and to prevent malignancy (Hack WW et al 2010). However, it is still unknown whether the risks of infertility and cancer might benefit at all from surgery as in congenital UDT (Hack WW et al 2010). In addition, it must be noted that there is no evidence that the ascended testis has a higher malignancy rate compared with the normal descended testis (Ong C et al 2005). The second policy is based on studies which showed a spontaneous descent of acquired UDTs at the beginning of puberty in 57% to 77.5% of the cases, with normal testicular growth (Hack WW et al 2010, Acerini CL et al 2009). This policy is supported by the following: 1) surgery itself can lead to complications such as direct injury to the vas deferens or testicular vessels (Mouriquand PDE 2008), 2) Meijer et al (Meijer RW et al 2001) treated successfully with human chorionic gonadotropin (HCG) 14/15 acquired UDTs (93.3%) (54). In addition, Hutson et al (Hutson JM & Basley SW 1991) predicted acquired UDTs to respond well to HCG therapy. These findings suggest that surgery should be reserved for those testes which fail to respond to hormonal therapy and those with anatomical abnormalities; 3) there is no strong evidence that early operation in boys 4-14 years has any effect on subsequent fertility (Chilvers C et al 1986). Although these results seem promising of a conservative approach to acquired UDTs, more long term follow-up studies are necessary to determine the consequences in fertility potential of boys with a history of acquired UDTs.

6. Conclusions

This study showed, that there is an ongoing interest for the exact pathogenesis and the optimal mode of treatment of acquired UDTs. However, the data are inconclusive, as there
are no available studies reaching a worldwide consensus. Large series, randomized-controlled studies and close follow-up beyond the puberty are recommended to further elucidate acquired UDT.

7. References


Hutson JM, Clarke MC. Current management of the undescended testicle. (2007). *Semin Pediatr Surg*, 16, pp. 64-70


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