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The cryptorchidism prevalence among infants in the general population of Rotterdam, the Netherlands

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Summary

Published trends and geographical differences in cryptorchidism rates are almost exclusively derived from hospital-based birth defect registers, which are sensitive to selection bias and incomplete reporting. This study aimed to accurately assess the cryptorchidism prevalence in the general population of Rotterdam. Of 7652 consecutive male live births, 7292 (95%) were examined for cryptorchidism at Child Healthcare Centres around the age of 1 month. In a subgroup of cases, the persistence of cryptorchidism was re-assessed during a follow-up examination by expert specialists. The cryptorchidism rate at the median age of 35 days was 1.2% (89/7292). In the re-examined subgroup (median age 95 days) 69% of the boys (24/35) had persistent cryptorchidism, of which 20 were unilateral and four bilateral. The population rate of 1.2% falls within the range of 0.9–9% reported by others. Differences in case ascertainment and population characteristics probably explain part of the differences between studies. Our cross-sectional design does not allow for analysis of a temporal trend, but provides a baseline for future trend studies. To study cryptorchidism rates, trends, and risk factors, a systematic case ascertainment is warranted.

Keywords: cryptorchidism, epidemiology, paediatrics, prevalence, urology

Introduction

The prevalence of cryptorchidism is around 0.9–9% among normal male births, and ranges up to 30% in premature and low birth weight births (Scorer, 1964; van Gelderen & Vermeer-de Bondt, 1986; John Radcliffe Hospital Cryptorchidism Study Group, 1986; Toppari & Kaleva, 1999; Ghirri *et al.*, 2002; Boisen *et al.*, 2004). Cryptorchidism is associated with an elevated risk for male subfertility and testicular germ cell tumours (Swerdlow *et al.*, 1997; Møller & Skakkeback, 1999; Herrinton *et al.*, 2003).

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Infertility is two to six times more frequent in men with a history of cryptorchidism (Lee & Coughlin, 2001). Although there is still controversy on the optimal treatment strategy for cryptorchidism, recent papers indicate that detection and treatment of persistent cryptorchidism well before puberty provides a better prognosis in terms of testis function and testicular cancer in adulthood than treatment post-puberty (Hadziselimovic, 2001; Lee & Coughlin, 2002; de Gouveia Brazao *et al.*, 2003; Herrinton *et al.*, 2003).

In recent years, scientific and public concern has risen over a possible increase in the occurrence of testicular tumours, hypospadias, cryptorchidism and abnormal semen quality (Skakkebæk *et al.*, 2001). As these disorders are

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interrelated to some extent, it has been suggested that they share a common aetiology during foetal life, described by Skakkebæk as the testicular dysgenesis syndrome (TDS; Skakkebæk *et al.*, 2001). Foetal exposure to natural (e.g. phytoestrogens) or man-made substances (e.g. chemicals and pharmaceuticals) that disrupt normal endocrine physiology is one of the suggested causes of TDS. Analysis of temporal and geographical trends in the cryptorchidism rate is complicated by methodological concerns such as changes in population demographics (e.g. age of the boy), notification procedures and diagnostic trends (Toppari *et al.*, 2001).

In order to establish reliable information on the occurrence of cryptorchidism, all male births in the open population have to be examined systematically, and reports on such an approach are very few (van Gelderen & Vermeerde Bondt, 1986). The aim of the present study was to accurately assess the prevalence of cryptorchidism in the general population.

Subjects and Methods

In a cross-sectional design, 7292 consecutive newborn boys were examined for cryptorchidism and hypospadias at their first visit to Child Health Care Centres (CHC) in Rotterdam. In the Netherlands, CHC are notified of live births within 2 days after registration in the municipal birth register. CHC invite all parents to participate in the national preventive child healthcare programme, including early detection of health risk factors, health education and vaccination that are free of charge. Of 7652 boys registered in the birth register, 7292 boys (95%) were examined by the physicians. After training in a standardized examination, CHC physicians ($n = 30$) examined the external genitalia of boys born in Rotterdam during the period October 1998 to October 2000, at their first visit to the CHC. During the course of the study, new CHC physicians were also instructed on the standardized examination, and every 6 months a meeting with the CHC physicians was organized to re-inform the physicians on the study procedures. We stimulated the completeness of reporting by sending reminders to CHC physicians when they had not electronically reported the testes position after the boys' first visit to the CHC. Testicular examination took place in a warm room with the child in supine posture. Testes deviating from the normal distal scrotal position were gently but firmly manipulated with warm hands, along the normal pathway of descent, to their most distal position (de Muinck Keizer-Schrama, 1987). Boys were diagnosed as cryptorchid if one or both testes were non-palpable, or when they could not be manipulated to a stable position in the scrotum. Retractile testis can be manipulated to a stable scrotal position and were not considered cryptorchidism, whereas cases of retentio testis may be manipulated to a scrotal position but will return to their abnormal position after release of the pressure, and were therefore classified as cryptorchid (de Muinck Keizer-Schrama, 1987). The presence of cryptorchidism was recorded electronically (yes or no). Hypospadias was also diagnosed and classified in this population, as described earlier (Pierik *et al.*, 2002).

In a substudy, parents of cases were contacted after registration of cryptorchidism by a CHC physician, and invited for a re-examination of the boy by a paediatric urologist and a paediatric endocrinologist at the Sophia Children's Hospital, Erasmus Medical Center. This re-examination procedure was only performed in a subgroup of cases born after 1 October 1999, the start date of a case–control study nested within the cohort of 7292 boys, which allowed us to determine whether cases diagnosed around the age of 1 month were still cryptorchid around 3 months of age. During this visit, the position of the testes was assessed before and after manipulation. Whereas, because of time restraints, CHC physicians only reported the presence or absence of cryptorchidism for a boy, the paediatric urologist and endocrinologist also reported the laterality (left, right, bilateral) and location (e.g. inguinal, non-palpable) of testes. The testis position before manipulation (in rest) was classified as non-palpable, inguinal, ectopic or scrotal. After manipulation the location was classified non-palpable, ectopic, inguinal at scrotal entrance, non-stable in scrotum (not remaining at the normal scrotal position after release of the pressure) or stable in scrotum (normal). The manipulation was performed as described for the CHC physicians.

The institutional medical ethics review board has approved the study protocol.

Statistics

For comparison of cryptorchidism rates, chi-squared statistics are calculated, based on 2×2 cross-tabulations. The Mann–Whitney *U*-test was used to compare age between index cases and healthy boys. Medians are presented with the 25th and 75th percentile (interquartile range). Statistical analyses were carried out with the SPSS 11.0 for Windows statistical software package (SPSS Inc., Chicago, IL, USA).

Results

The prevalence of cryptorchidism during the first visit of boys to the Child Healthcare Centres was 1.2% (89/7292) with a 95% confidence interval of 1.0–1.5%. The median age at the time of examination was 35 days (25th and 75th percentile; 30–64) for cases and 34 days (30–49) for boys without cryptorchidism ($p = 0.45$).

The parents of 42 cases were contacted for the substudy, to determine the persistence of cryptorchidism. Of the contacted cases, 35 (83%) were willing to come to the Sophia Children's Hospital, Erasmus MC Rotterdam, for re-examination of the testes. The median age at re-examination was 95 days (75–115), the median birth weight was 3430 g (3205–3700), two had a low birth weight

(<2500 g), and nine were born two or more weeks before the estimated date of delivery. On average, 52 days (38–80) had passed after the examination at the CHC. Cryptorchidism (i.e. abnormal location *after* manipulation) was still present in 69% of the boys (24/35) who were initially diagnosed with cryptorchidism in the CHC. In boys with persistent cryptorchidism, the finding was unilateral in 20 (83%) and bilateral in four (17%) cases. During the re-examination, 10 of the 29 individual testes with an abnormal location 'at rest' could be brought into a lower position along the normal pathway of descent by gentle manipulation. One of the 29 testes that were abnormal 'at rest' could be manipulated into a stable normal scrotal position. After manipulation, the 28 non-scrotal testes were non-palpable ($n = 7$) or located inguinal ($n = 15$), non-stable in the scrotum ($n = 1$), or at the scrotal entrance ($n = 5$). Two boys with cryptorchidism also had hypospadias, both cases had unilateral cryptorchidism, and the hypospadias were of the glandular ($n = 1$) and midshaft ($n = 1$) subtype.

Discussion

We report a cryptorchidism prevalence of 1.2% (95% confidence interval 1.0–1.5%) among newborn boys in Rotterdam, the Netherlands. As it was impossible to have all boys examined at the same age in this study, this 1.2% represents the prevalence for a range of ages, with a median of 35 days (25th and 75th percentile for cases are 30 and 64 days). As spontaneous descent of non-scrotal testes is common in early life, the prevalence will vary within this age range (e.g. higher and lower than 1.2% at 1 and 2 months, respectively). A recent study demonstrated that more than 50% of the non-scrotal testes at birth had descended spontaneously at the age of 3 months (Boisen *et al.*, 2004). Previous studies have reported prevalences of 0.9–9% in the first few months of life (Scorer, 1964; van Gelderen & Vermeer-de Bondt, 1986; John Radcliffe Hospital Cryptorchidism Study Group, 1986; Berkowitz *et al.*, 1993; Toppari & Kaleva, 1999; Ghirri *et al.*, 2002; Boisen *et al.*, 2004). There are several reasons for these differences between studies, such as random or natural variation, methodological issues and temporal changes. Random fluctuations in prevalence rates are frequently observed in birth defect registries (Paulozzi, 1999), which is in part the result of the low occurrence (typically <1%) of the majority of birth defects. Paulozzi performed an extensive review of cryptorchidism trends over nearly three decades from 29 registries in 21 countries, where no data was available for cryptorchidism in the Netherlands (Paulozzi, 1999). Although time trends were observed in several systems in certain periods, these were typically followed by an opposite trend in subsequent years.

Methodological limitations can be divided into numerator and denominator problems. In most registry systems, the numerator is prone to be incomplete because not all newborns are structurally examined for their abnormality. Furthermore, reporting is usually based on notifications by physicians or review of medical archives and depends on the completeness of this system. Differences in case definition (e.g. inclusion of retractile testis) and treatment strategy may affect the numerator. For example, a tendency to treat more cases with surgery may increase the chance of detection by a registry, as the condition will appear more widespread in medical records, and it has been suggested that the increasing awareness that cryptorchidism is associated with testicular tumours may have emphasized the importance of diagnostic recognition (Paulozzi, 1999). When not all children are examined for congenital abnormalities in a designated population of newborns, the denominator has to be estimated. For example, hospital-based prevalence rates may use as denominator the number of births in the area they service. However, not every pregnant woman living in this catchment area will deliver in the hospital.

A major bias affecting the denominator and numerator is selection bias. The characteristics of a hospital (e.g. waiting lists, specialization) may result in selective referral for cryptorchidism treatment, or over-representation of a population at risk, such as subfertile couples or complicated pregnancies.

Previous studies were almost exclusively based on hospital populations that may not be representative for the general population. The strength of the present study is that the prevalence rate is based on structural examination of a large cohort of 7292 boys in the general population (95% participation), so that some of the problems affecting the numerator and denominator (i.e. underreporting, selection of a hospital population, estimation of denominator) were prevented. It is unlikely that the prevalence rate is significantly biased by differential response. Even under the assumption that the 360 non-participants were all at increased risk for cryptorchidism (i.e. birthweight of <2500 g with a cryptorchidism prevalence of 19% (Berkowitz *et al.*, 1993) the overall prevalence would be 1.9% and not significantly higher than the rate observed in previous studies. The assumption that the 5% non-respondents all had a birthweight <2500 g is extreme, because, in general, <3% of the population is below this reference value (Freeman *et al.*, 1995). Although the CHC physicians were instructed by an expert paediatric urologist or endocrinologist on a standardized testis position examination protocol, we have not assessed interobserver agreement. However, the prevalence of cryptorchidism was comparable for different CHC locations.

A recent study reported a much higher prevalence of cryptorchidism in Denmark compared with Finland, using a nearly identical design in both countries, overcoming most of the methodological problems mentioned above (Boisen *et al.*, 2004). They reported a high prevalence in Denmark vs. Finland (9% vs. 2.4% and 1.9% vs. 1.0% at birth and

3 months, respectively). Our rate around the age of 1 months is comparable with the rate in Finland (in between 2.4 and 1.0% at birth and 3 months, respectively), and clearly lower than the prevalence in Denmark, assuming that the methodology is comparable.

Several studies have reported an increase in cryptorchidism over the past few decades, although others observed no trend, or an opposite trend (Paulozzi, 1999). The birth defect registry in the Netherlands does not include cryptorchidism. Only one previous study on the prevalence of cryptorchidism in the Netherlands was conducted, which does not allow for a trend analysis. That population-based study used CHC in an area just north of the Rotterdam area (van Gelderen & Vermeer-de Bondt, 1986), and reported a prevalence of 3.1% at the age of 3 months (64/2048 boys), which is significantly higher than our estimate of 1.2% at 1 month after birth ($p < 0.001$). We cannot provide an estimate for the prevalence at 3 months, because >90% of the subjects had been examined at the CHC before the age of 3 months. However, a lower than 1.2% prevalence is expected for the age of 3 months because spontaneous testicular descent is a frequent phenomenon in the first months of life (Barthold & Gonzalez, 2003; Boisen *et al.*, 2004). From both cohorts, background data is lacking for a proper interpretation of the difference in cryptorchidism prevalence. Unfortunately, information on known risk factors for cryptorchidism (e.g. race, birthweight) is not routinely collected by the CHC.

At the follow-up examination of a subgroup of boys at the Sophia Children's Hospital around the age of 3 months (median 95 days), cryptorchidism was still present in 69% of the cases (24/35) diagnosed at the first CHC visit. We cannot report on the cryptorchidism prevalence around the age of 95 days or testicular ascent as not all boys were examined again. Gentle manipulation is part of the diagnostic assessment of testicular localization in order to prevent false-positive scoring of retractile testis. During the re-examination, only one of the 29 testes that were not in a normal scrotal position at rest could be manipulated to a stable scrotal position. This implies that retractile testes are uncommon in this age group. Previous studies have shown that the presence of cremasteric reflex and retractility of the testis increases with age (Farrington, 1968; Bingol-Kologlu *et al.*, 2001).

Hypospadias and cryptorchidism have both been described as manifestations of the TDS (Skakkebæk *et al.*, 2001). We observed co-occurrence of hypospadias and cryptorchidism in two of 7292 boys (0.03%), which was not significantly more than expected on the basis of the independent occurrence of both disorders (1.2% cryptorchidism × 0.7% hypospadias (Pierik *et al.*, 2002) = 0.008%). The observed ($n = 2$) and expected ($n = 0.6$) numbers for this sample size are, however, too small for robust statistics.

Men with a history of cryptorchidism are at increased risk of testicular cancer and subfertility. In a subfertile male population, we previously observed a history of cryptorchidism in 9.4% of the men (Pierik *et al.*, 2000), of which 36% had been bilateral. The overrepresentation of a (bilateral) cryptorchidism history compared with the present rate of 1.2% in the general population supports the hypothesis that cryptorchidism and subfertility are interrelated, and that they may partially share a common cause (Skakkebæk *et al.*, 2001).

In summary, we observed a rate of cryptorchidism, which falls within the range reported by previous studies. This cross-sectional study does not allow for analysis of a temporal trend, but provides a baseline for future trend studies. Differences in case ascertainment and population characteristics are probably an explanation for a large portion of temporal and geographical trends in cryptorchidism. A standardized ascertainment of cryptorchidism cases and relevant background data is crucial for a proper evaluation of cryptorchidism trends, and may discern the causes for this abnormality.

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