The Association Between Extra-Genital Congenital Anomalies & Hypospadias Outcome

Fahad Al-Juraibah[1,2], Angela Lucas-Herald[1], Rachael Nixon[1], Christine Toka[1], Cunyi Wang[1], Martyn Flett[3], Stuart O'Toole[3], S Faisal Ahmed[1]

1. Developmental Endocrinology Research Group, Royal Hospital for Children, University of Glasgow, Glasgow

2. Department of Paediatrics, King Abdulaziz Medical City, Riyadh, Saudi Arabia

3. Paediatric Urology, Royal Hospital for Children, Glasgow

Short title: Extra-genital anomalies and hypospadias outcome

Correspondence to:-

Professor S Faisal Ahmed MD FRCPCH

Developmental Endocrinology Research Group, School of Medicine, Dentistry & Nursing, University of Glasgow, Royal Hospital for Children, 1345 Govan Road, Glasgow G51 4TF, United Kingdom

Tel +44 141 451 5841, Faisal.ahmed@glasgow.ac.uk

Keywords

Anomaly, complication, disorder of sex development, DSD, malformation

Abstract

Extra-genital congenital anomalies are often present in cases of hypospadias but it is unclear whether they have an association with the outcome of hypospadias surgery. The aim of this study was to review all hypospadias cases that had surgery between 2009 and 2015 at a single centre and identify clinical determinants of surgical outcome. An extra-genital congenital anomaly was reported in 139 (22%) boys and 62 (10%) had more than one anomaly. Of the 626 boys, 54 (9%), including 44 with proximal hypospadias had endocrine as well as limited genetic evaluation. Of these, 10 (19%) had biochemical evidence of hypogonadism and 5 (9%) had a molecular genetic abnormality. At least one complication was reported in 167 (27%) of patients with 20% of complications occurring after 2 years of surgery; fistula was the most frequent complication. The severity of hypospadias and existence of other anomalies were clinical factors that were independently associated with an increased risk of complications ($p<0.001$). In conclusion, complications following surgery are more likely in those cases that are proximal or who have additional extra-genital anomalies. To understand the biological basis to these complications, there is a greater need to understand the aetiology of such cases.

Introduction

Hypospadias is a common congenital anomaly affecting approximately 1 in 300 male births (Ahmed et al., 2004) and its underlying aetiology may be multifactorial [Bouty et al., 2015]. Several congenital conditions that are associated with a disorder of sex development (DSD) including a disorder of gonadal development, disorder of androgen synthesis or a disorder of androgen action can be associated with hypospadias [Ahmed et al., 2016]. Over 20% of boys with hypospadias are also known to have other extra-genital congenital conditions [Ahmed et al., 2004; Cox et al., 2014; Lu et al., 2017]. In addition to pinpointing the underlying genetic diagnosis [Bashamboo et al., 2017], a thorough knowledge of these associated conditions in the individual patient may also facilitate better care. Although several advances have been achieved in the surgical management of hypospadias, early and late complications may be encountered in approximately a quarter of cases [Spinoit et al., 2013]. Several studies report an association of these complications with factors such as the length of follow-up following the operation, severity of hypospadias, age at surgical repair, surgical technique, and pre-conditioning with sex steroids [Lee et al., 2013; Snodgrass et al.,2014]. More recently, it has also been reported that the outcome may also be influenced by the underlying genetic condition with a higher likelihood of multiple hypospadias surgery in those with genetically proven partial androgen insensitivity syndrome [Lucas-Herald et al., 2016]. However, the extent of investigations that are performed in boys to understand the underlying cause in hypospadias is very variable [Rodie et al., 2011; Swartz et al., 2017] with some studies identifying the presence of extra-genital anomalies as a factor that influences the likelihood of undertaking investigations [Rodie et al., 2011]. An association between extra-genital congenital anomalies and complications following hypospadias surgery has been rarely studied [Lu et al., 2017].

Thus, the aim of the current study was to perform a review of cases of hypospadias that had undergone surgery at a single centre, and investigate the relationship of surgical complications to clinical factors including extra-genital anomalies.

Patients and methods

A retrospective review was conducted of the clinical records of all boys who had hypospadias surgery according to the theatre records at the Royal Hospital for Children, Glasgow, over a 7 year period from the start of 2009 and end of 2015. Cases where the first hypospadias surgery was performed at another hospital were not included. Clinical information that was collected included the presence of other genital anomalies (unilateral or bilateral undescended testis, bifid scrotum, and micropenis), extra-genital anomalies, results of endocrine and genetic evaluations, age at first hypospadias surgery, type of surgical technique and the timing and nature of complications requiring further surgery. Staged procedures were all regarded as one surgery. The hypospadias was classified according to the meatal opening documented at preoperative assessment. In case of a discrepancy in the description between the preoperative and intraoperative assessment, the latter was used for this study. In this study, hypospadias was categorised as 'distal' if the meatal opening was at the glanular, coronal, or subcoronal and 'proximal' if the opening was penoscrotal, scrotal, or perineal. All other forms of hypospadias with the meatal opening on the shaft of the penis were categorised as 'middle'. External masculinization score (EMS) was calculated as described (Ahmed et al., 2000) to objectively document the degree of masculinization of the genitalia.

The data were analysed using SPSS, version 21.00 (IBM, NY, US). Continuous data were described as medians (2.5^{th} and 97.5^{th} centile). The association between categorical data was assessed using Pearson's chi-square tests. Mann–Whitney U and Kruskal–Wallis tests were used for comparing continuous variables in paired and multiple, unpaired samples, respectively. Logistic regression analysis was used to test the association between post-surgical complications and type of hypospadias, presence of genital and extra-genital anomalies, age at the surgical repair, and the type of procedure. A probability (p) value of less than 0.05 was considered statistically significant. The study was classed as an evaluation of routine health care and did not require ethical approval.

Results

Genital & Extra-Genital Anomalies

Of the 748 boys who were recorded as having first hypospadias surgery over the study period, 122 were excluded as they were duplicated in the list, incomplete or incorrectly categorised as hypospadias. Of the remaining 626 cases hypospadias was reported as distal, middle, proximal and unknown in 422 (67%), 108 (17%), 80 (13%) and 16 (3%) of the boys, respectively (Table 1); 73 (12%) had at least one other genital anomaly and 139 (22%) had at least one extra-genital anomaly. Of the 80 cases with proximal hypospadias, 35 (44%) had an extra-genital anomaly, compared to 100 (19%) in the 530 cases of distal and middle hypospadias ($p<0.001$, odds ratio [OR] =3.60 [95% CI: 2.17 - 5.98] compared to 1.39 [95 % CI: 0.83 - 2.32]) for middle hypospadias. Of the 139 boys, 62 (45%) had more than one extra-genital anomaly. Of the 139 boys with an extra-genital anomaly, 55 (40%) were small for gestational age (SGA). Other commonly affected organ systems included central nervous system (CNS) in 31 (22%), urinary tract in 26 (19%), cardiovascular system (CVS) in 24 (17%), and craniofacial anomalies in 22 (16%) boys (Fig.1).

Endocrine & Genetic Evaluation

Of the 626 boys, comprehensive endocrine and a limited genetic evaluation had been conducted in 54 (9%) of which 10 (19%) had an abnormality pointing toward a disorder of gonadal developmental, androgen synthesis disorders or other in 5, 3 and 2 boys, respectively. In 5 of these 10 boys, a genetic diagnosis of 5 α reductase type 2 (5ARD2) deficiency was confirmed in two, sex chromosome mosaicism in one, steroidogenic factor 1 (SF1) deficiency in one, and 17 β hydroxysteroid dehydrogenase type 3 (17 βHSD 3) in one. There was a significant difference in terms of EMS, where the cases with abnormal evaluations tend to have lower EMS value compared to the other group with normal evaluation; however, type of hypospadias, presence of extra-genital anomaly and the median age of the first surgical repair did not show any significant difference (Table 2).

First Hypospadias Surgery

The median age at the time of the surgery was 19.6 months (2.5th and 97.5th, 10.9, 95.6). Boys with proximal hypospadias had surgery at a median age of 22.6 months (12.3, 95.6) which was at an older age compared to boys with middle hypospadias who had a median age of 17.8 months (10.7, 97.5) (p=0.001) and distal hypospadias with a median age of 19.3 months (10.9, 108.2) (p=0.013). Of the 626 boys, 563 (90%) had a single stage approach; the remaining 63 (10%), had 2 or more staged procedure and which was more frequently performed in the boys with proximal hypospadias (Table 1).

Complications

Of the 626 boys, 167 (27%) had at least one complication which required further surgical intervention. These 167 boys had a total of 220 complications and these included urethral fistula in 78 cases (47%), tight or excess foreskin in 42 (25%), wound dehiscence in 37 (22%), urethral or meatal stricture in 34 (20%), urinary tract infection in 23 (14%), and urethral diverticulum in 6 (4%). The median time taken for the presentation of the first complication was 9 months (0.2, 66.3) after the first hypospadias surgery. There was no significant difference in the timing of the presentation of the complication between each type of hypospadias (p=0.407). Although 64 (38 %) of the complications presented within the first 6 months after the first operation, and 132 (80%) within 2 years from the first repair, a substantial number were first manifested after 2 years.

Association of Complications to Clinical Variables

Of the 167 boys with complications, proximal, middle and distal meatal opening was reported in 43 (54%), 45 (42%) and 71(17%) cases, respectively. The likelihood of complications was significantly greater for the middle and proximal categories compared to distal (p<0.001, OR=3.6 [95% CI: 1.41 - 3.77], 5.4 [95% CI: 3.57 - 8.88], respectively). In the proximal hypospadias cases, presence of extra-genital anomalies was another independent factor that was significantly associated with the occurrence of complications (p=0.002) (Table 3). There were five cases of proximal hypospadias in

whom SGA was the sole extra-genital anomaly and despite excluding these cases, the association between extra-genital anomalies and complications persisted (p=0.012) . Presence of other genital anomalies, endocrine abnormalities, age at surgical repair and surgical procedure used did not show any significant association (Table 3). A trend towards a reduction in complication rates in different calendar year was also evident (p=0.015), which coincided with a relatively similar pattern in the percentage of cases with extra-genital anomalies (Fig. 2). The percentage of cases of proximal hypospadias stayed similar in each year's cohort (Fig.2).

Discussion

Whilst the prevalence of extra-genital anomalies in hypospadias has been previously reported to range from 12% to 46% [Schneuer et al., 2015; Fernandez et al., 2016; Lu et al., 2017], the prevalence rate of 22% reported in this study is similar to that in other large cohort studies where information on associated congenital anomalies was systematically collected [Ahmed et al., 2004; Cox et al., 2014; Nixon et al., 2017]. The pattern of extra-genital anomalies that were encountered in this cohort was also similar to that reported before with a disorder of intrauterine growth manifested as being small for gestational age [Ahmed et al. 2004; Nordenvall et al., 2014; Poyrazoglu et al., 2017]. It is well known that extra-genital anomalies are more likely to be present in those boys who have proximal hypospadias (Nissen et al, 2015) but the current study shows that the additional presence of extra-genital anomalies in cases of proximal hypospadias is associated with a higher risk of complication. it is useful to note that the cohort of cases of hypospadias that were studied had a similar proportion of cases of proximal hypospadias to that reported previously [Spinoit et al., 2013].

It is clear from the current study as well as previous reports [Spinoit et al., 2013; Snodgrass et al., 2014; Schneuer et al., 2015] that the occurrence of overall complications depends on the length of follow-up of the patient. In the current cohort, approximately, a fifth of the complications presented two years after the surgery thus emphasizing the need for prolonged follow-up. The complications were also more likely in those who had proximal hypospadias and/or extra-genital anomalies. Proximal hypospadias is more likely to be associated with a reduced anogenital distance, a marker of prenatal androgen exposure [Cox et al., 2017] and given that conditions associated with a defect in the androgen receptor (AR) are more likely to be associated with multiple hypospadias surgery [Lucas-Herald et al., 2016], it is plausible that the increased rate of complications in cases of proximal hypospadias may be partly related to the effect that reduced androgen exposure may exert during critical periods of prenatal development. In cases of hypospadias, extra-genital anomalies may also be part of a constellation that points towards a specific genetic aetiology [Van der Zanden et al., 2012; Bouty et al., 2015]. For instance, cases of XY DSD with normal gonadal function that are small for

gestational age are less likely to have a mutation in the AR gene (Poyrazoglu et al, 2017). In the current study, 19% of the boys evaluated had abnormal endocrine results, which is comparable to the results of another systematic evaluation of XY DSD, in which the prevalence of endocrine abnormality was 23% [Nixon et al., 2017]. In the current cohort, an underlying genetic condition was rarely explored but with the increasing trend towards investigating the genetic diagnosis [Alhomaidan et al., 2017] as well as any associated endocrinopathy, the link between genetic conditions and complications will become clearer over the next decade. However, this form of analysis will require systematic studies of even larger cohorts through platforms such as the I-DSD Registry [Kourime et al., 2017].

It was interesting to note that the rate of complications in the latter years was lower than those in the former years. Whilst it is possible that some of this difference may be due to a shorter period of follow-up for the cases in the latter cohort, it is unlikely that this is the sole reason, given that 80% of complications usually present in the first two years after hypospadias surgery. The number and proportion of cases that had proximal hypospadias did not change over this period either. It is possible that the lower rate of associated anomalies may also be due to a lower rate of detection or manifestation of such anomalies in these relatively new cases. The finding that the trend of complications coincided with the rate of extra-genital anomalies emphasises the need to collect these data when evaluating trends in complications.

Whilst the strength of this study was that it was performed at a single centre, a limitation was that, in the absence of a standard proforma, it is possible that some complications and some genital and extra-genital congenital anomalies were not recorded systematically. Given that cases of proximal hypospadias may undergo more thorough clinical evaluation, it is possible that congenital anomalies may be recorded more often in these cases. As a description of chordee, penile torque, and glans size were not recorded routinely, these were not included in the analysis. However, some of these features, such as chordee, are more likely to occur in those with proximal hypospadias (Stojanovic et

al, 2011). Although the relatively large sample size was helpful to address the original hypothesis and investigate the link between associated anomalies and complication rate, investigating a link with endocrine and genetic characteristics was not possible given the relatively low prevalence in the cohort studied. Nevertheless, there was a trend that needs further investigation in larger cohorts. Whilst it could be speculated that complications may occur in those with greater neurocognitive disability, the number of cases with CNS problems was low even though neurocognitive ability was not investigated systematically. This study has also not examined other factors such as the level of experience of the surgeon. Given that the main finding of this work is the association of complications with extra-genital anomalies, it is unclear whether there would be any association of the experience of the surgeon with the likelihood of them operating on a case with or without extra-genital anomalies.

In summary, **h**ypospadias, and especially proximal hypospadias, is a challenging surgical condition which may be associated with a complication in about a quarter of cases. The greater likelihood of complications in those boys with extra-genital congenital anomalies suggests that the complications that are encountered may partly have a biological basis and this requires further study.

Ethical statement

The study was classed as an evaluation of routine health care and did not require informed consent.

Disclosure statement

The authors do not have any conflicts of interest.

Abbreviations

DSD, disorder of sex development; EMS, external masculinization score; 5ARD2, 5α reductase type 2; 17 βHSD 3, 17 β hydroxysteroid dehydrogenase type 3; SF1, steroidogenic factor 1; AR, androgen receptor; SGA, small for gestational age; CNS, central nervous system; CVS, cardiovascular system; CFA, craniofacial anomaly; GI, gastrointestinal; RESP, respiratory; UH, umbilical hernia.

Author Contributions

FA, ALH, MF, SOT and SFA provided insight into the design of the study. FA, ALH, RN and CT collected the data and FA and CW analysed the data. FA, MF and SFA interpreted the data. FA and SFA prepared the first draft and all authors were involved in the revision and approval of the final version. SFA acts as the guarantor of the work.

Reference

Ahmed SF, Khwaja O, Hughes IA. The role of a clinical score in the assessment of ambiguous genitalia. BJU Int. 85(1):120-4 (2000).

Ahmed S, Dobbie R, Finlayson A, Gilbert J, Youngson G, Chalmers J, et al. Prevalence of hypospadias and other genital anomalies among singleton births, 1988–1997, in Scotland. Arch Dis Child Fetal Neonatal Ed. 89(2):F149-F51 (2004).

Ahmed SF, Achermann JC, Arlt W, Balen A, Conway G, Edwards Z, et al. Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015). Clin endocrinol(Oxf). 84(5):771-88 (2016).

Alhomaidah D, McGowan R, Ahmed S. The current state of diagnostic genetics for conditions affecting sex development. Clin Genet. 91(2): 157-62 (2017).

Bashamboo A, Eozenou C, Rojo S, McElreavey K. Anomalies in human sex determination provide unique insights into the complex genetic interactions of early gonad development. Clin Genet. 91(2):143-56 (2017).

Bouty A, Ayers KL, Pask A, Heloury Y, Sinclair AH. The genetic and environmental factors underlying hypospadias. Sex Dev. 9(5):239-59 (2015).

Cox K, Bryce J, Jiang J, Rodie M, Sinnott R, Alkhawari M, et al. Novel associations in disorders of sex development: findings from the I-DSD Registry. J Clin Endocrinol Metab. 99(2):E348-E55 (2014).

Cox K, Kyriakou A, Amjad B, O'Toole S, Flett ME, Welsh M, et al. Shorter anogenital and anoscrotal distances correlate with the severity of hypospadias: A prospective study. J Pediatr Urol. 13(1):57.e1-. e5(2017).

Fernandez N, Escobar R, Zarante I. Craniofacial anomalies associated with hypospadias. Description of a hospital based population in South America. Int Braz J Urol. 42(4):793-7 (2016).

Kourime M, Bryce J, Jiang J, Nixon R, Rodie M, Ahmed S. An assessment of the quality of the I-DSD and the I-CAH registries-international registries for rare conditions affecting sex development. Orphanet J Rare Dis. 12(1):56 (2017).

Lee OT, Durbin-Johnson B, Kurzrock EA. Predictors of secondary surgery after hypospadias repair: a population based analysis of 5,000 patients. J Urol. 190(1):251-6 (2013).

Lucas-Herald A, Bertelloni S, Juul A, Bryce J, Jiang J, Rodie M, et al. The long-term outcome of boys with partial androgen insensitivity syndrome and a mutation in the androgen receptor gene. J Clin Endocrinol Metab. 101(11):3959-67 (2016).

Lu YC, Huang WY, Chen YF, Chang HC, Pong YH, Shih TH, et al. Factors associated with reoperation in hypospadias surgery—A nationwide, population-based study. Asian J Surg. 40(2):116-22 (2017).

Nissen KB, Udesen A , Garne E. Hypospadias: Prevalence, birthweight and associated major congenital anomalies. Cong Anomalies. 55, 37–41 (2015).

Nixon R, Cerqueira V, Kyriakou A, Lucas-Herald A, McNeilly J, McMillan M, et al. Prevalence of endocrine and genetic abnormalities in boys evaluated systematically for a disorder of sex development. Hum Reprod. 32(10):2130-7 (2017).

Nordenvall AS, Frisén L, Nordenström A, Lichtenstein P, Nordenskjöld A. Population based nationwide study of hypospadias in Sweden, 1973 to 2009: incidence and risk factors. J Urol. 191(3):783-9 (2014).

Poyrazoglu S, Darendeliler F, Ahmed SF, Hughes I, Bryce J, Jiang J, et al. Birth weight in different etiologies of disorders of sex development. J Clin Endocrinol Metab. 102(3):1044-50 (2017).

Rodie M, McGowan R, Mayo A, Midgley P, Driver CP, Kinney M,et al. Factors that influence the decision to perform a karyotype in suspected disorders of sex development: lessons from the Scottish Genital Anomaly Network Register. Sex Dev. 5(3):103-8 (2011).

Schneuer FJ, Holland AJ, Pereira G, Bower C, Nassar N. Prevalence, repairs and complications of hypospadias: an Australian population-based study. Arch Dis Child. 100(11):1038-43 (2015).

Snodgrass W, Villanueva C, Bush NC. Duration of follow-up to diagnose hypospadias urethroplasty complications. J Pediatr Urol. 10(2): 208-11 (2014).

Spinoit AF, Poelaert F, Groen LA, Van Laecke E, Hoebeke P. Hypospadias repair at a tertiary care center: long-term followup is mandatory to determine the real complication rate. J Urol. 189(6):2276-81 (2013).

Stojanovic B, Bizic M, Majstorovic M, Kojovic V, Djordjevic M. Penile Curvature Incidence in hypospadias: can it be determined? Adv Urol. Article ID 813205 (2011).

Swartz JM, Ciarlo R, Denhoff E, Abrha A, Diamond DA, Hirschhorn JN, et al. Variation in the clinical and genetic evaluation of undervirilized boys with bifid scrotum and hypospadias. J Pediatr Urol. 13(3):293-e1 (2017).

van der Zanden LF, van Rooij IA, Feitz WF, Franke B, Knoers NV, Roeleveld N. Aetiology of hypospadias: a systematic review of genes and environment. Hum Reprod Update. 18(3):260-83(2012).