Long-term urinary symptoms in adolescent and adult women with congenital adrenal hyperplasia

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Summary

Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition resulting in excess androgen production. Females are typically born with ambiguous genitalia and often undergo feminising genitoplasty in infancy or childhood. Recently, there has been considerable international debate as to whether distressing urinary symptoms in CAH patients are truly present and, if so, whether these urinary problems are a consequence of the feminising genitoplasty.

Objective

To identify and assess any urinary symptoms in an Australian cohort of adolescent and adult women with CAH who have undergone feminising genitoplasty in infancy, childhood or adolescence as a part of their management.

Study design

Females with CAH aged 12–40 years, who had undergone feminising genitoplasty, and were identified from a hospital database (n = 72). Those aged 12–15 years were assessed using the Paediatric Incontinence Symptom Index questionnaire in conjunction with sections of the Bristol Female Lower Urinary Tract Symptoms Scored Form questionnaire. Those aged 16–40 years were assessed using the Bristol Female Lower Urinary Tract Symptoms Scored Form questionnaire. Uroflowmetry studies and post-void residual volume ultrasounds were also conducted. Previously published normative data were used for the control population.

Results

Responses to the questionnaire indicated that CAH patients had a higher incidence of urgency, frequency, urge incontinence, unexplained incontinence and nocturnal incontinence, when compared to previously published control data. Average and maximum urine flow rates measured by uroflowmetry were within normal range; however, the 16–40-year-old age group had significantly increased mean post-void residual volumes (P < 0.001) (Summary table).

Discussion

The presence of lower urinary tract symptoms in these patients has previously been interpreted as a direct outcome of feminising genitoplasty; however, these results could also be accounted for by the virilisation of pelvic floor musculature. Androgens have been shown to increase skeletal muscle mass, but their exact impact on the pelvic floor musculature requires further research. Three previous studies have measured post-void residual volumes in patients with CAH, all of which found it them be raised.

Conclusions

Patients with CAH appeared to have overall normal urinary flow but increased post-void residual volumes. The data suggested that this population of patients has an increased probability of incontinence, urgency, and frequency when compared to a control population. These results confirmed findings of other small studies; however, it remains unclear if these changes reflected the underlying diagnosis or were a consequence of management.

<table>
<thead>
<tr>
<th>Symptom type</th>
<th>Congenital adrenal hyperplasia patients</th>
<th>Control population</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinence symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of incontinence episodes</td>
<td>59% (10/17)</td>
<td>15% (3/20)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>41% (7/17)</td>
<td>25% (5/20)</td>
<td>0.48</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>59% (10/17)</td>
<td>5% (1/20)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Unexplained incontinence</td>
<td>47% (8/17)</td>
<td>5% (1/20)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Nocturnal incontinence</td>
<td>29% (5/17)</td>
<td>0% (0/20)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Voiding symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent stream</td>
<td>38% (8/21)</td>
<td>30% (6/20)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>48% (10/21)</td>
<td>25% (5/20)</td>
<td>0.133</td>
</tr>
<tr>
<td>Frequency (9+)</td>
<td>24% (5/21)</td>
<td>0% (0/20)</td>
<td>0.020*</td>
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<tr>
<td>Filling symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturia (2+)</td>
<td>14% (3/21)</td>
<td>5% (1/20)</td>
<td>0.317</td>
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<tr>
<td>Bladder pain</td>
<td>24% (5/21)</td>
<td>10% (2/20)</td>
<td>0.240</td>
</tr>
<tr>
<td>Straining</td>
<td>14% (3/21)</td>
<td>0% (0/20)</td>
<td>0.079</td>
</tr>
<tr>
<td>Urgency</td>
<td>57% (12/21)</td>
<td>20% (4/20)</td>
<td>0.015*</td>
</tr>
</tbody>
</table>

*P < 0.05 regarded as significant.
Introduction

Congenital adrenal hyperplasia (CAH) is the commonest cause of ambiguous genitalia of the newborn [1,2]. Females born with the classical form CAH usually have some degree of genital ambiguity; thus, feminising genitoplasty is undertaken in order to not only correct the appearance of their genitalia, but also to facilitate normal menstrual and urinary function, and enable the potential for sexual function [3]. This surgery may involve the clitoris, and/or the urogenital sinus.

Recently, there has been considerable international debate as to whether distressing urinary symptoms in CAH patients are truly present, and, if so, whether they are an outcome of feminising genitoplasty. Currently, there is a lack of systematic long-term surgical evaluation [4], with different centres and different surgeons using various surgical procedures and techniques when operating on these patients [5–8]. The current hospital is the primary referral centre in Victoria, Australia, and almost all patients with CAH in this state are referred here for care during their childhood, along with others from international locations.

A single-stage feminising genitoplasty technique has been developed; it combines, when necessary, girth-reduction clitoroplasty with flap vaginoplasty, and the use of dorsal clitoral skin to create labia minora [8]. This technique has been consistently used at the current institution for over 40 years. The goal of the current study was to evaluate the prevalence of lower urinary tract symptoms, using standardized questionnaires and uroflowmetry, in an Australian cohort of female CAH patients who have undergone feminising genitoplasty.

Materials and methods

Ethics approval was granted by the hospital ethics committee, and female patients with CAH were identified through records from the Gynaecology Department, Health Information Services, and the operating suite database from 1974 to 2014. The contact details of the females identified through the database were then confirmed through records and the state electoral roll. Letters inviting participation were sent to those where current contact details could be confirmed. All participants were asked to complete a survey and uroflowmetry examination that included a bladder scan for assessment of their post-void residual volume. All data were collected between March and October 2014.

In females aged 12–15 years (Group 1) lower urinary tract symptoms were assessed using the Paediatric Incontinence Symptom Index questionnaire (ISI) [9] in conjunction with the voiding and frequency sections of the Bristol Female Lower Urinary Tract Symptoms Scored Form questionnaire (BFLUTS-SF) [10]. In females aged 16–40 years (Group 2) lower urinary tract symptoms were assessed using the BFLUTS-SF.

Control data for the voiding, filling and incontinence parts of the BFLUTS-SF were taken from the Bristol Female Lower Urinary Tract Symptom questionnaire (BFLUTS) validation study [11]. Control data were unavailable for the sexual function and quality of life sections of the BFLUTS-SF. Control data for responses to ISI was taken from the ISI validation study [9].

Uroflowmetry studies and post-void residual volumes (PVR) by ultrasound were conducted on CAH patient participants. Uroflowmetry was conducted using the ‘UROCAP III by Laborie’ equipment (ON, Canada) and UDS120 software (Laborie Medical technologies, ON, Canada). The PVR volumes were measured using the portable ultrasound scanner ‘BARD Bladderscan BVI 2500’ (Bard Medical, Crawley, UK). Control data for uroflowmetry results were taken from previously published normative data [12–14].

Analysis of data was performed using STATA version 13 (StataCorp LLC Texas USA). Fisher’s exact test and Chi-squared were applied to survey data, and Student’s t-test was applied to uroflowmetry data. Missing values were excluded from the analysis. A P-value of <0.05 was considered significant.

Results

Survey results

A total of 72 females were identified in the database, but 34 were able to have their contact details confirmed. Five patients declined participation and eight did not respond after initial contact was established.

In Group 1 (12–15 years old), there were four girls (mean age 12.8, SD ± 1.5): three completed the survey and uroflowmetry examination, and one completed the survey only. In Group 2 (16–40 years old), there were 17 participants (mean age 27.9, SD ± 9.0): ten (59%) completed the survey and uroflowmetry, and seven (41%) completed the survey only.

Of the patients surveyed, 52% (11/21) had undergone their first feminising genitoplasty at ≤5 months of age, 10% (2/21) between 6 and 12 months, 24% (5/21) between 13 and 24 months, and for the remaining two at 4 years and 15 years. There was no difference in age at time of surgery between those recruited and non-participants. Prader staging at time of first surgery was available in 20/21 patients: Prader I-II in four, Prader III in nine, Prader IV in six and Prader V in one. No difference in Prader score was found at time of surgery between the current participants and non-participants.

Of all patients surveyed, 73% (16/21) had undergone their first genital surgery in the hospital, with 50% of those (8/16) having had the same surgeon perform their operation. Of those who had undergone genital surgery prior to attending the Royal Children’s Hospital, this consisted of clitoral surgery, where a variety of techniques had been used. Age at the time of surgery was before 22 months of age in 81% (13/16), at 4 years in 6% (1/16) and at 15 years in 13% (2/16). Prader staging at the time of first surgery was Prader III in 50% (8/16) of these patients and Prader IV in 31% (5/16).

Responses to the BFLUTS-SF questionnaire indicated a higher probability of CAH patients than the control population experiencing urgency (P = 0.015), as well as urge incontinence (P = 0.001), unexplained incontinence (P = 0.005), and nocturnal incontinence (P = 0.014). Three patients reported needing to change their outer clothing during the day due to urinary incontinence, and 35% of...
patients (6/17) reported that their urinary symptoms had negatively affected their quality of life.

**Uroflowmetry results**

In terms of uroflowmetry, 11 out of 14 patients returned an abnormal result. Of these 11, four underwent a repeat measurement on a separate occasion, and the abnormal result was confirmed in all. One patient from the 16–40-year-old population was excluded from analysis due to insufficient volume voided (<=50 ml) in initial uroflowmetry testing. Data for both patient groups were compared to age-matched normative data and the Student’s t-test was applied in data analysis (Table 1 and Table 2). In the 16–40-year-old age group, CAH patients had greater residual volumes ($P < 0.001$), and smaller voided volumes ($P = 0.005$) than reported in the normative data [12–14] (Table 2). Overall, patients’ maximum urine flow rates and average urine flow rates were within normal parameters.

**Discussion**

Recently, a study from the UK raised concerns over the urinary outcomes of CAH patients who have undergone genital surgery. The study, which utilised the standardised and validated BFLUTS for data collection and assessment, reported increased rates of hesitancy, urge incontinence, and unexplained incontinence in CAH patients, with a detrimental effect on the patients’ quality of life [15]. The only other published study to have utilised a standardised and validated questionnaire for data collection found no increased rates of lower urinary tract symptoms in patients with CAH when compared to the general population [16].

Although the current study had a relatively small sample size and low participant response rate, previous studies have suffered from the same limitations [15,16]. This may raise concerns over the prevalence of urinary symptoms in non-participants and thus the quality of data collected in the current study. However, the current results are likely to be representative of a total CAH population, as they were from a primary referral centre for patients with CAH in infancy, childhood and adolescence. Additionally, it is felt that the results are likely to be representative of the entire population as there was no difference in participants and non-participants in terms of age at surgery, Prader stage prior to surgery, nor surgical technique used. Although some of the patients had undergone their first genital surgery at other institutions, the previous surgery prior to attending the Royal Children’s Hospital consisted of clitoral surgery and not introitoplasty; hence, was unlikely to have an impact on urinary function.

An age-matched control population could not be recruited due to the time constraints of the project; therefore, existing

| Table 1 | Summary of uroflowmetry data analysis of CAH patients aged 12–15 years and corresponding control population data. |
|---|---|---|
| 12–15-year-olds | | |
| Residual volume (ml) | Control $n = 545$ | Congenital adrenal hyperplasia $n = 2$ | $P$-value |
| | 6.80 (5.87–7.73) | 11.50 (0.00–157.59) | 0.55 |
| | 27.16 (25.58–28.74) | 21.43 (0.00–59.44) | 0.30 |
| | 13.48 (12.60–14.36) | 11.46 (0.00–26.36) | 0.51 |
| | 15.19 (13.98–16.40) | 30.33 (0.00–109.40) | $< 0.001^*$ |
| | 218.24 (198.50–238.40) | 249.67 (0.00–711.32) | 0.65 |

The number of patients analysed in each group is specified by $n$. Data expressed as the mean with confidence interval. $^*P < 0.05$ regarded as statistically significant.

| Table 2 | Summary of uroflowmetry data analysis of CAH patients aged 16–40 years and corresponding control population data. |
|---|---|---|
| 16–40-year-olds | | |
| Residual volume (ml) | Control $n = 308$ | Congenital adrenal hyperplasia $n = 10$ | $P$-value |
| | 2.92 (2.51–3.33) | 23.6 (0.00–50.64) | $< 0.001^*$ |
| | 23.06 (22.01–24.11) | 20.51 (13.12–27.90) | 0.40 |
| | 13.08 (12.41–13.75) | 10.76 (5.35–16.17) | 0.23 |
| | 23.50 (22.10–24.90) | 17.64 (11.33–23.95) | 0.14 |
| | 289.79 (271.12–308.46) | 140 (79.42–200.58) | $< 0.001^*$ |

The number of patients analysed in each group is specified by $n$. Data expressed as the mean with confidence interval. $^*P < 0.05$ regarded as statistically significant.
Long-term urinary symptoms

normative data was utilised where possible. As a result, the control population used for the BFLUTS-SF survey responses could have been a source of bias, as it was a British population with an older mean age [11]. However, given that the current CAH population was comparatively younger, it was expected that the CAH patients would have been less, and more unlikely to have developed lower urinary tract symptoms than the control population. Moreover, the genetic and cultural differences between the Australian and British populations are not particularly diverse, and thus the differences between the two populations should not have affected the outcomes of this study.

In previously published papers, normative data were only available for the voiding, filling and incontinence sections. Consequently, even though some of the patient responses to the sexual function and quality of life sections of the BFLUTS-SF were concerning, such as some patients reporting the need to change outer clothing due to urinary incontinence, it could not be determined whether they actually differed from the general population. Furthermore, the lack of control data to all parts of the questionnaire meant that the symptom scoring system within the BFLUTS-SF questionnaire could not be utilised for data interpretation. Having an Australian age-matched control population would not only have provided a better background on which to interpret the CAH cohort results, but would also have allowed for accurate scoring and analysis of the whole questionnaire.

As aforementioned, individual maximum and average urine flow rates were mostly within the normal range for both patient groups. However, due to the small population sample size, each individual point of data, for each uroflowmetric variable, would have had a larger than expected effect on the variable's calculated mean, and thus could have resulted in biased data analysis.

The presence of increased post-void residual volumes and prolonged voiding times could be a reflection of the virilisation of the pelvic floor musculature in females with CAH. Generally, females have a wider and shorter urethra, and less urinary outlet obstruction than males, which is reflected by an overall longer voiding time and lower maximum urine flow rate in the latter [12,17]. Androgens have been shown to increase skeletal muscle mass, and the musculature of the pelvic floor, such as levator ani, has been shown to increase in size, and thus have been a source of bias, as it was a British population with an older mean age [11]. However, given that the current CAH population was comparatively younger, it was expected that the CAH patients would have been less, and more unlikely to have developed lower urinary tract symptoms than the control population. Moreover, the genetic and cultural differences between the Australian and British populations are not particularly diverse, and thus the differences between the two populations should not have affected the outcomes of this study.

Androgens have been shown to increase skeletal muscle mass, and the musculature of the pelvic floor, such as levator ani, has been shown to be sensitive to testosterone [18]. However, the exact impact of androgens on the pelvic floor and lower urinary tract is still unknown and further investigation is warranted [18]. Increased outlet obstruction due to increased muscle mass could result in increased PVR volumes and longer voiding times in female CAH patients compared to normal age-matched controls. This would mean that the presence of urinary voiding and filling symptoms in CAH patients, such as urgency as seen in the current study, or hesitancy as seen in Davies et al., could be accounted for by their exposure to high levels of androgens rather than the result of surgery. Furthermore, perhaps each patient’s adherence to endocrinological management throughout life may also impact their degree of lower urinary tract symptoms. The only two other studies identified in the literature to have measured PVR volumes also both found them to be, on average, increased in their CAH patient populations [6,19].

Overall, there is a surprisingly small amount of research that has investigated whether unobstructed urinary emptying without urinary incontinence or UTI has actually been achieved, despite it being a formally stated goal of surgery for CAH patients undergoing feminising genitoplasty [3]. The majority of published studies has tended to evaluate lower urinary tract symptoms in the context of a surgical technique [6,19–22] or as part of a study investigating multiple outcomes in patients with CAH [7,23–25]. There are limitations in the available literature, with most either not utilising standardised and validated questionnaires for data collection [6,7,19–28], lacking a valid control population [16,24], having low participant response rates [16,25], and/or low participant numbers [15,23,26]. Very few studies have utilised uroflowmetry or urodynamic testing in order to quantify urinary voiding function in their patients [19,23,26], and very few have investigated for lower urinary tract symptoms other than incontinence or UTI [15,16,20].

A suggested explanation for the overall lack of published data regarding lower urinary tract symptoms may be that patients are reluctant to seek medical advice out of embarrassment or, since they do not regularly see a urologist or gynaecologist, a lack of opportunity to discuss their symptoms [15]. Alternatively, patients may not associate their urinary symptoms to be a complication of their genital surgery, but rather a normal part of life, as it has been suggested that patients consistently underestimate the severity of their urinary symptoms when compared to doctors [29]. This could also explain why, in the two published studies that utilised standardised and validated questionnaires, patients rarely reported seeking treatment for their urinary symptoms [15,16].

Overall, this is the fourth known study to investigate for the presence of lower urinary tract symptoms in patients with CAH who have undergone feminising genitoplasty, using standardised and validated tools for data collection and assessment, and the first to do so in an Australian population.

Conclusion

Results of this study suggest that CAH patients who have undergone feminising genitoplasty have an increased probability than the control population of experiencing symptoms of urgency and frequency, as well as urge incontinence, unexplained incontinence, and nocturnal incontinence. Overall, CAH patients also have normal maximum and average urine flow rates relative to their voided volumes, but a higher PVR volume than expected for their age group, which could be accounted for by the virilisation of their pelvic floor musculature or feminising genitoplasty. Currently, further research is needed to investigate the effect of androgens on the female pelvic floor, and to provide insight as to whether lower urinary tract symptoms are a product of feminising genitoplasty or an inherent part of CAH pathophysiology.

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Ethics statement

Ethics approval was granted by the hospital ethics committee, and informed consent was provided by all subjects participating in the study.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpurol.2018.01.006.

References