Reconstructive surgery for females with congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a review from the Prince of Wales Hospital

CH Houben *, SY Tsui, JW Mou, KW Chan, YH Tam, KH Lee

ABSTRACT

Objectives: To present the results of feminising genitoplasty done in female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

Design: Case series.

Setting: A tertiary referral centre in Hong Kong.

Patients: Female patients with congenital adrenal hyperplasia undergoing corrective surgery for virilisation between 1993 and 2012.

Main outcome measures: The operative result was judged with a scoring system (1-3) for four areas: appearance of clitoris, labia and vagina, plus requirement for revision surgery.

Results: A total of 23 female patients with congenital adrenal hyperplasia with a median age of 17.5 (range, 1.5-33.8) years were identified. Of these individuals, 17 presented in the neonatal period and early infancy, of which four had an additional salt-losing crisis. Six patients—including four migrants from mainland China—were late presenters at a median age of 2 (range, 0.5-14) years. Twenty-two patients had corrective surgery at a median age of 2 (range, 1-14) years. Clitoral reduction was performed in all, and further surgery in 21 patients. The additional surgery was flap vaginoplasty in 10 patients, a modified Passerini procedure in six, and a labial reconstruction in five; one patient with prominent clitoris was for observation only. Minor revision surgery (eg mucosal trimming) was required in three patients; a revision vaginoplasty was done in one individual. Of the 23 patients, 18 (78%) with a median age of 20 (range, 9.3-33.8) years participated in the outcome evaluation: a 'good' outcome (4 points) was seen in 12 patients and a 'satisfactory' (5-9 points) result in five patients.

Conclusions: Nearly three quarters of our cohort (n=17) presented with classic virilising form of 21-hydroxylase deficiency. Only four (25%) patients experienced a salt-losing crisis. Female gender assignment at birth was maintained for all individuals in this group. 'Good' and 'satisfactory' outcomes of surgery were reported in nearly all participants.

Hong Kong Med J 2014;20:481–5
DOI: 10.12809/hkmj144227

CH Houben *, MD, FRCSEd
SY Tsui, MB, ChB, MRCS
JW Mou, MB, ChB, FHKAM (Surgery)
KW Chan, MB, ChB, FHKAM (Surgery)
YH Tam, MB, ChB, FHKAM (Surgery)
KH Lee, MB, BS, FHKAM (Surgery)

Division of Paediatric Surgery and Paediatric Urology, Department of Surgery, Prince of Wales Hospital, Shatin, Hong Kong

* Corresponding author: chhouben@web.de

Part of this research was presented at the RCSEd / CSHK Conjoint Scientific Congress 2012 (Poster), Hong Kong, 22-23 September 2012.

This article was published on 18 Jul 2014 at www.hkmj.org.

New knowledge added by this study

- This is the most comprehensive analysis of the surgical management of congenital adrenal hyperplasia (CAH) in Asian women.
- CAH presenting as salt-losing crisis was seen in less than 25% of this cohort.
- In our region, a proportion of young women (eg migrants) may present late for corrective surgery.

Implications for clinical practice or policy

- Early gender assignment in conjunction with the primary carers (parents) and the multidisciplinary team is the preferred option in this Asian community.
- The first 2 years of life is the preferred time for reconstructive surgery in this condition. Notwithstanding, some women may present late in our region.

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders representing, by far, the most common disorder of sex development for XX karyotype.[1,2] The condition is characterised by impaired cortisol synthesis; the most frequent defect—present in approximately 95% of the patients—is 21-hydroxylase deficiency. The enzyme

因21羥化酶缺乏症而患上先天性腎上腺皮質增生症的女性進行女性化生殖器成形術：威爾斯親王醫院病例回顧

CH Houben、徐紹恩、繆蔚章、陳健維、譚煜謙、李劍雄

目的：本文報告因21羥化酶缺乏症而患上先天性腎上腺皮質增生症的女性進行女性化生殖器成形術的術後結果。

設計：病例系列。

安排：香港一所提供第三層醫療服務的轉介中心。

患者：1993至2012年期間因患上先天性腎上腺皮質增生症而接受男性化矯正手術的女性患者。

主要結果測量：利用計分制（1-3分）按四方面評估手術結果：陰蒂、陰唇和陰道的外觀，以及是否須進行修正手術。

結果：共有23個先天性腎上腺皮質增生症女性患者，她們年齡中位數為17.5歲（介乎1.5-33.8歲）。17例於新生兒期和嬰兒早期已被診斷，當中4例有失鹽症狀。另6例（包括4名來自中國的移民）均於年齡中位數為2歲（介乎0.5-14歲）時才被診斷。22例在年齡中位數為2歲（介乎1-14歲）時已接受修正手術。她們均接受陰蒂縮小手術，其中21人進一步接受手術治療，包括皮瓣陰道成形術10例、修改Passerini程序6例，以及陰唇重建5例。另1例突出的陰蒂只接受觀察。3例須進行小型修正手術（如粘膜修整）；1例須接受修正的陰道成形術。23名患者中，18人（78%）參與結果評估計劃，她們的年齡中位數為20歲（介乎9.3-33.8歲）：12人把結果評為「良好」（4分），5人把結果評為「滿意」（5-9分）。

結論：本研究有接近四分之三（17例）的患者因有21羥化酶缺乏症出現男性化特徵。只有4例（25%）有失鹽症狀。所有患者出生時維持女性的性別。幾乎所有參與結果評估計劃的患者把手術結果評為「良好」或「滿意」。

deficiency leads to a block in cortisol synthesis followed by a build-up of cortisol precursors which, in turn, are diverted to androgen synthesis.[1] The increased androgen concentration triggers a variable degree of virilisation in female newborns. Approximately 75% of patients with this classic form of CAH have an additional mineralocorticoid deficiency leading to salt-wasting, failure to thrive or even hypovolaemic shock.[1] Mild forms of CAH present, typically, later in life with a variable degree of increased androgen excess.

We present the outcome of a cohort of Asian individuals with genital ambiguity secondary to 21-hydroxylase deficiency. The emphasis is on presentation, surgery performed, and the anatomical and cosmetic outcomes.

Methods

This was a retrospective review of demographics and presentation of patients with CAH secondary to 21-hydroxylase deficiency who were managed by a multidisciplinary team at our tertiary referral centre between 1993 and 2012.

Generally, surgery is considered at the age of 12 to 24 months as a one-stage feminising genitoplasty; clitoral reduction plus further corrective surgery is performed depending on the intra-operative findings. This could range from a labiaplasty to flap vaginoplasty or modified Passerini procedure.[3-5]

Following the initial healing phase, dilatation of the vagina is recommended according to our protocol until the tissue is supple, usually after a few months. At the time of puberty, the vagina is again assessed and dilatations are recommended, as necessary, by the gynaecologist. Highly motivated patients achieve an appropriate-sized vagina with daily dilatations within a couple of months or even weeks.

The operative treatment was planned as a one-stage procedure at our institution. The results of this cohort were assessed as part of the ongoing review in the out-patient setting in 2012/13. A scoring system (1-3) established previously was used for four areas: appearance of the clitoris, labia and vagina, plus requirement for revision surgery.[6,7]

The criteria for scoring each were as follows: 1—designated for a near-normal appearance, 2—only a medically trained person would be able to see the result of an intervention, and 3—other appearances.[6,7] The necessity for revision surgery constituted the fourth factor in the evaluation: score of 1 for no revision, 2 for minor revision, and 3 for a major revision. Overall marks of 4 points were classified as 'good', marks of 5 to 9 points 'satisfactory', and marks from 10 to 12 points 'unsatisfactory' (Table 1).

Results

Twenty-three females with 21-hydroxylase deficiency and a median age of 17.5 (range, 1.5-33.8) years timed on 31 December 2012 were identified.

Seventeen patients presented in the neonatal period and early infancy, of which four had an additional salt-losing crisis. Six patients were late presenters at a median age of 2 (range, 0.5-14) years. Four of these were migrants from mainland China diagnosed at the age of 1, 3, 8, and 14 years, respectively. The diagnosis was established by identifying increased levels of 17-hydroxyprogesterone.

The sex of rearing in the group of neonates was decided in consultation between the parents, paediatric endocrinologists, and paediatric urologists. All patients, including the late presenters, persisted with the female gender assigned at birth. Twenty-two patients had corrective surgery at a median age of 2 (range, 1-14) years. Clitoral reduction was performed in all 22, and further surgery in 21 patients. The additional surgery consisted of flap

vaginoplasty in 10 patients, modified Passerini procedure in six, and labial reconstruction in five. One patient with prominent clitoris and otherwise normal appearance of the vaginal and urethral opening is currently for observation only (Fig).

Eighteen individuals with a median age of 20 (range, 9.3-33.8) years were part of the outcome evaluation in 2012/13. The other five patients below the age of 5 years were considered too young for a meaningful assessment. At the time of diagnosing CAH, all 18 patients had an enlarged clitoris; separate openings for vagina and urethra were seen in six individuals, low (intrasphincteric) confluence in six, and high (suprasphincteric) confluence in other six individuals. Table 2 summarises the results in accordance with the initial anatomical findings—high confluence, low confluence, and separate openings for vagina and urethra. Minor revision surgery (eg mucosal trimming) was required in three patients. A 'good' outcome was seen in 12 patients and 'satisfactory' result in five; one required a revision vaginoplasty (Table 2).

On follow-up, it was noted that all patients older than 12 years (n=15) experienced menarche without any obstruction of menstrual blood flow; 13 individuals had regular cycles; one had her cycle supported by medication, and one patient started menstruating in the last 6 months, but her cycles remained irregular.

Two women have given birth by caesarean section. Both women have two healthy children each, following successive pregnancies. They delivered successfully by caesarean section as recommended by the multidisciplinary team.[8] A third woman is currently pregnant.

A systematic interview including a psychological evaluation was not part of this review, but a tendency to more masculine behaviour traits within this cohort of women was a persistent observation by clinical staff.

TABLE 1. Scoring system for anatomical outcome (based on Creighton et al's study[7])

Score	1	2	3
Clitoris	Normal	Acceptable	Prominent/atropic
Vagina	Normal	Localised narrowing	Persistent confluence
Labia	Normal	Partial fusion	Total fusion
Revision	None	Minor	Major

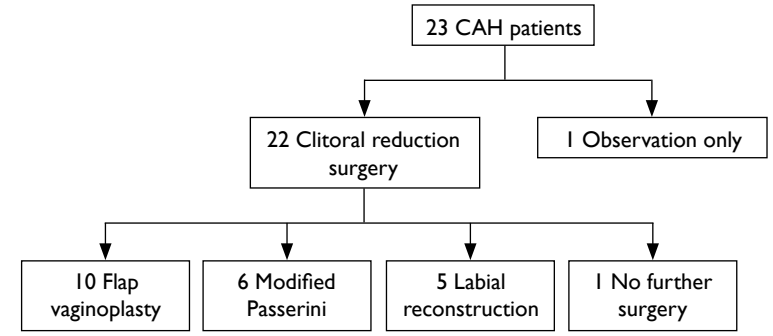

FIG. Surgical management of all patients with congenital adrenal hyperplasia (CAH)

TABLE 2. Results of scoring the operative outcomes in patients with congenital adrenal hyperplasia who underwent reconstructive surgery (n=18; median age, 20 years; age range, 9.3-33.8 years)

Anatomical findings	No.	Results (scoring points)		
		Good (4)	Satisfactory (4-9)	Unsatisfactory (10-12)
High confluence	6	4	1	1
Low confluence	6	4	2	0
Separate openings	6	4	2	0
Overall	18	12	5	1

Discussion

The majority of this cohort of individuals—nearly three quarters—presented as classic virilising CAH, of which four experienced an additional salt-wasting crisis.[1] The proportion of individuals affected by aldosterone deficiency causing salt-losing CAH was less than 25%. It is generally expected for 50% to 75% of the patients with the classical form to have a sufficiently high mineralocorticoid deficit to provoke a salt-losing crisis.[1,9] We have no explanation for why this group of Asian individuals had such a low rate of salt-losing crisis.

Just over a quarter of this cohort were late presenters, which is higher than the expected 10% to 20% late presenters described in a large case series.[2] It appears that four of these patients arrived as migrants from mainland China, explaining the slightly large number of late presentations.

The female gender assigned at birth was maintained by all individuals. This finding confirms our current knowledge on 21-hydroxylase deficiency insofar as only a small minority of CAH patients experience gender dysphoria.[2,10] It may well be possible that some individuals in this cohort suffered from gender issues, but a detailed interview or questionnaire on this topic was not part of our evaluation. A review of 250 patients identified only 5.2% suffering from gender identity problems.[10]

In the recent past, the concept of surgery

at an early age for this group of patients has been criticised.[7,9] However, there has been an inclination to summarise data of patients with a highly variable background, who were operated on by a number of different groups.[11] It is now recognised that CAH patients should be managed by a multidisciplinary team in designated centres and the corrective surgery may be undertaken at an early age.[1,12,13]

Once a decision has been reached regarding the sex of rearing by the medical team and the parents/legal guardian, corrective surgery can be planned. Clearly, if the clinical findings are favourable to divert surgical intervention—as illustrated in one of our patients—only regular review may be required (Fig). Nevertheless, it is our impression that there is a cultural need to decide on the sex of rearing at an early age, as it helps to reduce the anxiety and anguish for the family.

There is now even a tendency among practitioners in this field to perform corrective surgery in the first few months of life.[14] It appears that the tissue planes are easier to develop whilst the baby is still under the influence of maternal oestrogen effects.[14]

In our institution, the surgery is usually performed in the first or second year of life. However, four patients came to our attention late as a result of their migration to Hong Kong. This explains the small number of individuals in our cohort who had their respective surgery later in life or even as teenagers.

'Good' or 'satisfactory' results were identified in nearly all patients in this cohort (Table 2). Other investigators have demonstrated similar results.[3,4] As identified by van der Zwan et al,[15] there is a trend for a less satisfactory outcome in patients with high confluence. This confirms our impression that finding high confluence poses a more difficult challenge for the operative correction.

In our evaluation, we did not systematically analyse behaviour traits or perform a psychological assessment, albeit a more boyish or masculine behaviour pattern was apparent in our cohort. Detailed studies on this aspect of individuals with CAH confirm this observation.[16,17]

All individuals sufficiently old enough to have menses (n=15) developed a regular cycle; only two had cycle irregularities or required medication to support the cycle. Two patients have given birth; elective caesarean section is recommended after feminising genitoplasty to avoid damage to the reconstruction; in addition, a more android pelvic structure may result in cephalo-pelvic disproportion.[8] More detailed studies on fertility and pregnancy conclude a reduced pregnancy and delivery rate in women with CAH.[18]

Our evaluation had some limitations. Our cohort encompassed an age-group spanning three decades. In particular, our cohort of patients did not undergo a detailed interview process; these offers were often declined or individuals voiced considerable reservation to participate. Nevertheless, this review represents the largest experience, to date, with surgical management and the outcomes of CAH in Asian women.

Conclusions

Nearly three quarters of our cohort presented as classic virilising form of 21-hydroxylase deficiency. Less than a quarter of the classic presentation experienced an additional salt-losing crisis in this cohort. Female gender assignment at birth was maintained for all individuals in this group. A 'good' and 'satisfactory' outcome of surgery was reported in nearly all patients.

Acknowledgement

We acknowledge the contributions by the Consultant Gynaecologist, Dr Ka-wah Yiu, in the care of these individuals.

References

1. Speiser PW, Azziz R, Baskin LS, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:4133-60.
2. Romao RL, Salle JL, Wherrett DK. Update on the management of disorders of sex development. Pediatr Clin North Am 2012;59:853-69.
3. Farkas A, Chertin B. Feminizing genitoplasty in patients with 46XX congenital adrenal hyperplasia. J Pediatr Endocrinol Metab 2001;14:713-22.
4. Rink RC, Adams MC. Feminizing genitoplasty: state of the art. World J Urol 1998;16:212-8.
5. Passerini-Glazel G. A new 1-stage procedure for clitorovaginoplasty in severely masculinized female pseudohermaphrodites. J Urol 1989;142:565-8; discussion 572.
6. Lean WL, Deshpande A, Hutson J, Grover SR. Cosmetic and anatomic outcomes after feminizing surgery for ambiguous genitalia. J Pediatr Surg 2005;40:1856-60.
7. Creighton SM, Minto CL, Steele SJ. Objective cosmetic and anatomical outcomes at adolescence of feminising surgery for ambiguous genitalia done in childhood. Lancet 2001;358:124-5.
8. Witchel SF. Management of CAH during pregnancy: optimizing outcomes. Curr Opin Endocrinol Diabetes Obes 2012;19:489-96.
9. Ogilvie CM, Crouch NS, Rumsby G, Creighton SM, Liao LM, Conway GS. Congenital adrenal hyperplasia in adults: a review of medical, surgical and psychological issues. Clin Endocrinol (Oxf) 2006;64:2-11.
10. Dessens AB, Slijper FM, Drop SL. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Arch Sex Behav 2005;34:389-97.
11. Alizai NK, Thomas DF, Lilford RJ, Batchelor AG, Johnson N. Feminizing genitoplasty for congenital adrenal hyperplasia: what happens at puberty? J Urol 1999;161:1588-91.

12. Clayton PE, Miller WL, Oberfield SE, Ritzén EM, Sippell WG, Speiser PW; ESPE/LWPES CAH Working Group. Consensus statement on 21-hydroxylase deficiency from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. Horm Res 2002;58:188-95.
13. Vidal I, Gorduza DB, Haraux E, et al. Surgical options in disorders of sex development (dsd) with ambiguous genitalia. Best Pract Res Clin Endocrinol Metab 2010;24:311-24.
14. de Jong TP, Boemers TM. Neonatal management of female intersex by clitorovaginoplasty. J Urol 1995;154:830-2.
15. van der Zwan YG, Janssen EH, Callens N, et al. Severity of virilization is associated with cosmetic appearance and sexual function in women with congenital adrenal hyperplasia: a cross-sectional study. J Sex Med 2013;10:866-75.
16. Mathews GA, Fane BA, Conway GS, Brook CG, Hines M. Personality and congenital adrenal hyperplasia: possible effects of prenatal androgen exposure. Horm Behav 2009;55:285-91.
17. Berenbaum SA, Beltz AM. Sexual differentiation of human behavior: effects of prenatal and pubertal organizational hormones. Front Neuroendocrinol 2011;32:183-200.
18. Hagenfeldt K, Janson PO, Holmdahl G, et al. Fertility and pregnancy outcome in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum Reprod 2008;23:1607-13.