

MEDICAL AUDIT OF CHILDREN WITH AMBIGUOUS GENITALIA- REVIEW OF CHILDREN TREATED OVER 18 YEARS

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ABSTRACT

Introduction: The survival of a newborn or a child presenting with ambiguous genitalia depends upon the timely diagnosis and institution of appropriate medical care. We undertook this study with the aim to determine if appropriate clinical and confirmatory diagnosis was arrived on time and if the treatment instituted was relevant and satisfactory. **Methods:** All children who were evaluated for ambiguous genitalia under the Department of Pediatric Endocrinology over the preceding 18 years were invited for a review. Data including time taken to make a clinical diagnosis, time taken to confirm the diagnosis, reasons for delay if any, and appropriateness of the sex assigned for rearing and treatment instituted were collected from the charts. Patients were evaluated for adequacy of response to treatment, compliance, problems encountered if any and subjective parental satisfaction. **Results:** A total of 165 children were diagnosed to have conditions with ambiguous genitalia and were called for a review. 33 children attended the review. 15 were being raised as boys and 18 as girls. 12 children had virilising congenital adrenal hyperplasia (CAH), 6 had cryptorchidism, 6 had hypospadias, 3 had complete and 1 had partial testicular feminisation, 2 had mixed gonadal dysgenesis (MGD), 2 had hypogonadism and 1 was a true hermaphrodite. An appropriate clinical diagnosis was made in 30 children on the day one and a final confirmatory diagnosis was made within a month in 23. **Conclusion:** In most conditions presenting with ambiguous genitalia, a clinical and confirmatory diagnosis can be made in a short duration. Initiation of appropriate treatment results in favourable outcomes in terms of growth sexual identity and adaptation.

INTRODUCTION

A neonate with abnormal genitalia presents with a difficult diagnostic and treatment challenge. Relevant clinical findings and investigations are useful in making an accurate diagnosis. Specific guidelines are available for the same^[1, 2, 3]. It becomes essential to make a definitive diagnosis at the earliest to initiate appropriate treatment and minimize complications.

Ambiguous genitalia is defined as a condition in which there is difficulty in assigning sex of an individual based on the appearance of external genitalia^[4]. The term ambiguous genitalia applies to any confusing appearance of the external genitalia^[5]. This includes any infant with

1. A phallus but bilaterally un palpable testes
2. Unilateral cryptorchidism and hypospadias
3. Penoscrotal or perineoscrotal hypospadias, even if the testes are descended

If an infant has a phallus that is intermediate in size between a normal penis and a normal clitoris, an aberrantly located urethral opening, and at least one impalpable gonad, the term ambiguous genitalia may be used^[2].

Aims and objectives

1. To identify the time interval from presentation to diagnosis and the reason for any undue delay if present.
2. To assess the appropriateness of the final diagnosis based on the investigations done.

3. To assess the compliance with drugs, follow up and advice given to patients who came for review.
4. To assess the appropriateness of the current height, growth velocity and pubertal stage for age.
5. Identify and enlist problems faced by the child or parent and suggest remedial measures.

MATERIALS AND METHODS

Study Design: A retrospective, descriptive study using review of charts and a clinical reassessment of patients who were diagnosed to have a condition with ambiguity of genitalia over the prior 18 years by the Department of Pediatric Endocrinology, Christian Medical College, Vellore. After ethical clearance, 165 patients who were diagnosed to have a condition with ambiguity of genitalia were invited by post for a review. Inclusion Criteria: All patients who attended the review and had a condition causing ambiguity of genitalia as final diagnosis were included in to the study.

Exclusion criteria: Patients who did not attend the review were excluded. 33 patients attended the review and had a condition causing ambiguity of genitalia and were included in to the study after an informed consent.

Data Collection: Data including age at presentation, clinical diagnosis, time taken for assigning a clinical diagnosis, investigations done, treatment given and time taken for assigning a final diagnosis were collected from the charts. Patients were assessed for response to

treatment, growth, bone age, compliance with treatment and satisfaction with sex assigned for rearing.

Statistical analysis: Percentage, mean and range were used to describe continuous and categorical variables, respectively.

RESULTS

Data from 33 patients who attended the review was collected and evaluated. 15 children (45%) were being raised as boys and 18 (55%) were being raised as girls. Virilising Congenital Adrenal Hyperplasia (CAH) was the commonest diagnosis and was made in 12 (37%) patients. Cryptorchidism and Hypospadias (penoscrotal and perineoscrotal) were the next common cause with 6 children in each group. This was followed in frequency by Testicular Feminisation (complete - 3, partial - 2), Mixed Gonadal Dysgenesis (2), Hypogonadism (2) and true hermaphroditism (1).

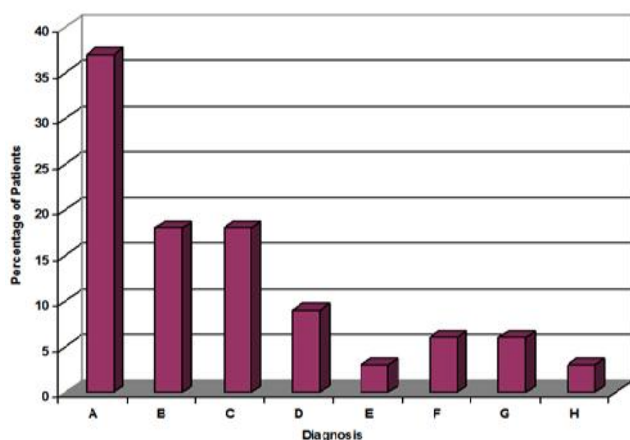


Fig 1: Final Diagnosis of Children Presenting with Ambiguous Genitalia

Virilizing Congenital Adrenal Hyperplasia (A), Cryptorchidism (B), Hypospadias (C), Complete Testicular Feminization (D), Partial Testicular Feminization (E), Mixed Gonadal Dysgenesis (F), Hypogonadism (G), True Hermaphrodite (H). As evident from the figure CAH was the commonest diagnosis in our study.

Five children were on follow up for more than 15 years, 6 between 10 to 15 years, 13 between 5 to 10 years and 9 were on follow up for less than 5 years. This long period of follow up allowed us to study the effect of treatment on long term outcomes like height attained, growth velocity and age of onset of pubertal changes.

Table 1: Duration of follow up

Duration of follow up	Number of Patients	Percentage
Less than 5 years	9	27
5 to 10 years	13	40
10 to 15 years	6	18
More than 15 years	5	15
Total	33	100

Thirty of the 33 patients who attended the review had an appropriate clinical diagnosis assigned on the day of presentation. For 3 children an appropriate clinical diagnosis was given only after a month since

presentation. One of these children presented as a girl with inguinal hernia, no ambiguity was suspected and testes were detected per operatively. The other two patients (both had mixed gonadal dysgenesis) were not given an exact diagnosis till the surgery and biopsy were undertaken. In 23 children an appropriate confirmatory diagnosis was assigned following investigations. Delay in 8 children were due to delay in performing karyotyping (4), hormonal investigations (3) or biopsy (1), and in two it was due to patient's social factors like delay in returning.

Table 2: Reasons for Delay in Diagnosis

Reason for delay	Number	Percentage
Biopsy awaited	1	10
Karyotype awaited	4	40
Hormonal investigations	3	30
Delay in follow up	2	20
Total	10	100

All the patients who came for the review had diagnoses which were appropriate as per the AAP guidelines^[1]. All the patients with mixed gonadal dysgenesis, testicular feminization or true hermaphroditism had undergone a karyotyping. But only 4 patients with congenital adrenal hyperplasia and 2 patients with perineoscrotal hypospadias had had a karyotyping done. None of the patients with cryptorchidism or hypogonadism were subjected to karyotyping.

Medical management of children with CAH: All the 12 children with CAH claimed to be on very regular treatment and apparently don't miss even a single dose except on a very rare occasion. All of them were satisfied with the outcome. They all had an understanding of the risks of discontinuing treatment and the need to modify drug dosages during illnesses. Also they were compliant with the advices given. Height for age in all these was between the 3rd and 97th centile, but the growth velocity was below the 50th centile in 5 (41%).

Table 3: Height for Age at Review

Final height	Number of patients	Percentage
<3 rd centile	0	0
3 rd to 50 th centile	7	58
50 th to 97 th centile	5	42
>97 th centile	0	0
Total	12	100

Pubertal signs were appropriate for age in 10 children and were delayed in 2. No child had advanced pubertal signs, though the ones who had already attained full maturity may have done so earlier than normal.

Medical management of conditions other than CAH: Of the 2 children with hypogonadism, one was treated with human chorionic gonadotropin (hCG) and the other was treated with testosterone. The child who was on hCG showed adequate response. The child on testosterone also had cerebral palsy and significant mental retardation. Hence his parents were unenthusiastic about further treatment. Two children with perineoscrotal hypospadias were treated with hCG. Both showed response though one child's response was inadequate and his penile length remained smaller for his age. Testosterone injections had been planned. The other child showed good response and his secondary sexual characters were appropriate for his age.

Surgical management: One child with cryptorchidism had undergone treatment with hCG with no response. Orchidopexy was done and the outcome was satisfactory. The child with true hermaphroditism was on testosterone propionate after he had undergone left salpingo oophorectomy, hypospadias correction and bilateral mastectomy. His height, external genitalia, penile length and other secondary sexual characters were appropriate for his age. All the patients with mixed gonadal dysgenesis, testicular feminization or true hermaphroditism had undergone surgery and the parents were fully satisfied with the outcome (subjective grading of 5 on a scale of 1 to 5). Two patients with perineoscrotal hypospadias had undergone surgery and four were planned. All the parents were fully satisfied with the outcome (subjective grading of 5 on a scale of 1 to 5). 11 patients with CAH had undergone a feminizing genitoplasty and 1 more was planned. Of these 11 only one mother seemed unsatisfied (subjective grading of 2 on a scale of 1 to 5). The genitalia however seemed near normal and was as expected. Four patients with cryptorchidism had undergone orchidopexy and all of them were satisfied with the outcome. Surgery has been advised for the others, of which one had been lost to follow up since his earlier visit.

Parental knowledge and psychological aspects: Most children were well adjusted to their family and the society and the sexual identity and orientation were consistent with the assigned sex. One child with mixed gonadal dysgenesis raised as a girl had behavioral features of a boy as observed by her mother. But her gender identity was to be that of a girl. All parents of children with mixed gonadal dysgenesis, testicular feminization and true hermaphroditism had the knowledge that their child would be infertile and had come to terms with that. Parents of children with CAH were unsure of the fertility of their children. Besides, all the parents of children with CAH (except one) found it hard to bear the expenses incurred in the management of their children and expected financial problems in the future. One universal feature noticed was that all parents were unsure of the long term outcome of their children and were apprehensive of the medical, psychological, marital, sexual and social problems that their child would face in the future.

DISCUSSION

This study was undertaken as an audit of all the patients with ambiguous genitalia treated in the Christian Medical College and Hospital (CMCH), Vellore. Various aspects including time interval between arrival of a patient and an appropriate diagnosis, treatment compliance, outcome and psychological aspects were studied. Of the total 165 patients with ambiguous genitalia treated in CMCH, 33 (20%) came for the review. This could be due to the fact that most of the patients were from other states and were probably unable to come for the review. But this could also be that patients with good compliance or those who were satisfied with their treatment alone came for the review and thus give falsely good or confounding results. There were a higher number of female patients, as many conditions in patients with ambiguous genitalia favour female sex of rearing as compared to a male sex of rearing. Kulkarni et al, Erdogan S et al and Joshi et al in their studies found 46XY to be the commonest karyotype [6, 7, 8]. As most of our patients did not have a karyotype this could not be compared. The commonest condition in our study was a virilizing congenital adrenal hyperplasia in a female child (37% of all the patients). This is consistent with other studies which have found CAH to be the commonest cause of disorders of sexual differentiation [9, 10, 11]. CAH was followed in frequency by cryptorchidism and hypospadias. Other conditions included partial and complete testicular feminization, mixed gonadal dysgenesis, hypogonadism and true hermaphroditism.

Most patients (91%) were assigned an appropriate clinical diagnosis within the first day. There seemed to be no undue delay in assigning a clinical diagnosis in any patient. All patients with CAH were correctly diagnosed clinically almost immediately on arrival. This is important as appropriate diagnosis and prompt treatment is essential for survival, given significant mortality even in developed countries [12]. A final diagnosis was assigned to 23 (70%) within 1 month. Delays in diagnosis in the earlier days were mainly due to non-availability of karyotyping facilities (40%). Diagnoses like mixed gonadal dysgenesis and true hermaphroditism required a biopsy be done before a final diagnosis was made. In such conditions there was a delay in the final diagnosis due to a delay in the surgeries, which were undertaken only on a semi urgent basis. Hormonal investigations were not always readily available in the earlier days which resulted in a delay in 3 (30%) patients. Two patients were lost to follow up and had to be called by post for evaluation, which resulted in a delay.

Medical management was the cornerstone of patient with CAH. Compliance with drugs was excellent among the patients with CAH who came for the review. Hundred percent of them (12 patients) had taken the drugs without missing a single dose in the preceding 3 months. They also claimed to have strictly adhered to the advice given regarding the change in dosage during any illness. All the patients with CAH who came for the review had heights between the third and the ninety seventh centiles grossly indicating adequate growth. Similar results were obtained

by Scott A. Rivkees et al who demonstrated that normal growth was achievable by their study on 26 children with CAH using once a day Dexamethasone therapy^[13]. A metaanalysis done by Erica A. Eugster et al also showed that in CAH with 21-hydroxylase deficiency, adult heights within 1 standard deviation of target height was achievable^[14]. But many of our patients (41%) had growth velocities less than the 50th centile for that age indicating the importance of monitoring the height velocity rather than the absolute height. A metaanalysis done by KalpanaMuthusamy et al showed that adult heights attained in patients with CAH were not only lower than normal adult heights but also was lower than their own target heights given their parental heights^[15]. This highlights the importance of monitoring not just the height for age, but also the height velocity over time to pick up growth retardation early for timely intervention. Testosterone and hCG had been used in patients with hypogonadism. The results were satisfactory.

It was noted that all patients managed surgically had a good outcome in terms of anatomical appearance. Almost all patients and parents were satisfied with the treatment. Functionality could not be commented upon as most patients were children or adolescents below the age of 18 years. This is consistent with Newman et al who reported satisfactory anatomic and functional results when clitoral surgery alone was required^[16]. He also reported poor functional results for patients with extensive vaginal reconstruction. This could not be verified in our study. Also Randolph et al in their follow up of 37 patients who had undergone clitoroplasty found that 27 had excellent outcome^[17].

The main area where there was discordance between American Academy of Pediatrics (AAP) guidelines^[1] and the approach used in our patients was in the use of karyotyping in patients with 46 XX patients with CAH. It was not routinely carried out on our patients as it may not contribute much to an otherwise straight forward diagnosis. But caution needs to be exercised before assigning a diagnosis without doing a karyotype and is not recommended by the AAP. The clinical diagnoses at presentation and the final diagnoses based on appropriate investigations were correlating well in all the patients.

One feature that came out as expected was that the financial burden on the parents is enormous and is a probably a major hindering factor in the appropriate management of such children. Detailed counseling is needed to allay the fears and doubts that would be expected in a parent of a child with such conditions. A humane approach is as important as appropriate medical and surgical management followed by adequate follow up.

Limitations: Most patients were too young to understand the condition and its implications and hence could not contribute voluntarily to the assessment on long term psychological outcome. It was also a limiting factor to the assessment of their long-term sexual identity, orientation, satisfaction with the sex of rearing and satisfaction with their marital and sexual life. Long term studies involving a significant number of adolescent and adult patients are needed to address such issues.

CONCLUSION

Most patients were appropriately diagnosed without undue delay. Instances where there was a delay could have been rectified by easier access to investigations like karyotyping and hormonal studies. With the facilities currently available these studies can be carried out without any delay. Both medical and surgical management were associated with favorable outcomes. Compliance with drugs and health promoting advices was excellent among the patients who came for the review. It is important to follow up patients with CAH by their height velocity rather than the absolute height as interventions can be carried out at an earlier stage. Detailed counseling is needed to allay the fears and doubts that would be expected in a parent of a child with such conditions. Long term Indian studies involving a significant number of adolescent and adult patients are needed to address issues of long-term sexual identity, orientation, satisfaction with the sex of rearing and satisfaction with their marital and sexual life.

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Conflict of Interest: Nil.

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