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SPECTRUM OF CONGENITAL ADRENAL HYPERPLASIA; PATIENTS PRESENTING TO ADULT ENDOCRINE CLINIC

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Abstract

OBJECTIVE

To determine the different modes of presentation of CAH and response to various treatment strategies in an adult population.

METHODOLOGY

A descriptive cross-sectional study was performed at the Endocrine and Diabetes Unit, Jinnah Postgraduate Medical Centre, Karachi, Pakistan from 2007 till date. It encompassed 48 adult patients aged 18 to 40 years, either gender, diagnosed with congenital adrenal hyperplasia with regards to their varied presentation modes early (pre-adolescence), i.e., patients coming from pediatric setups and late (post-adolescence), usually coming for the first time to adult endocrine clinic and hormonal response patterns to treatment were evaluated. The primary medical treatment was steroid therapy and surgical interventions (clitoroplasty and orchidectomy). Data were analyzed by SPSS version 26.

RESULTS

The mean ± standard deviation of the age was 18.48 ± 3.47 years. Of 48 patients, 91.7% were females and 8.3% were male. 26 (54.2%) patients presented early, and 22 (45.8%) presented late. Clitoroplasty underwent 62.5%, while 37.5% of late presentation patients had the procedure (OR 1.508, 95% CI: 0.31–7.17, p=0.452). Orchidectomy was performed on 33.3% early and 66.7% late presentation patients, showing insignificant association (OR 0.400, 95% CI: 0.03–4.73, p = 0.436).

CONCLUSION

This research elucidates that adult patients with congenital adrenal hyperplasia (CAH) exhibit a diverse array of clinical manifestations, contingent upon the

timing of diagnosis. Early presenters—typically referred from pediatric settings—predominantly displayed ambiguous genitalia, whereas late presenters more frequently manifested primary amenorrhea, menstrual irregularities, or genital ambiguity. Although steroid therapy and surgical procedures such as clitoroplasty and orchidectomy were routinely utilized, no statistically significant correlation was identified between the timing of presentation and treatment modalities. These results underscore the necessity for prompt identification, personalized treatment strategies, and comprehensive psychosocial support to enhance long-term outcomes, particularly in resource-constrained settings.

INTRODUCTION

Adult patients with congenital adrenal hyperplasia (CAH) present unique challenges, especially with a lack of awareness of the general population in countries like Pakistan. Then, the limited resources also hinder the management. The differing clinical manifestations of CAH depend on genetic, environmental, and healthcare variables, which dictate the diagnostic and therapeutic trajectories [1]. Evidence suggests a wide range of symptoms among adults, from uncertain genital grounds to better management. Still, many adults continue to suffer the complications of the condition because of delays in diagnosis or inappropriate treatment methods [2].

Hormonal imbalance in the body is a characteristic aspect of CAH, which presents many rare psychosocial challenges and, consequently, negatively impacts the quality of life of people with this disease. Parents of children, especially girls with CAH, cite stigma and social perceptions, causing intense feelings of pain, leading to difficulty adhering to treatment and psychological outcomes [2]. Long-term implications of CAH also conclusively include metabolic syndromes, highlighting the need for holistic and tailored treatment paradigms [3].

The primary treatment modalities for CAH are glucocorticoid replacement therapy and supplementation with mineralocorticoids with variable efficacy. The success of these therapies relies on the timely diagnosis and management of the patient [4]. The difficulty in managing these patients and preventing the development of complications emphasizes the urgent requirement for an integrative, tailored management strategy by considering patient characteristics and comorbidities [5].

Access to a defined list of treatment options, hydrocortisone and fludrocortisone, should be a priority for healthcare systems [6]. As for patients, improving management, providing adequate support to affected families, and providing appropriate education about the disease and treatment options are essential [7]. Also, this may assist health professionals in the battle against diseases by allowing the targeting of educational strategies considering the different perceptions of health concerning treatment for females and males [8].

This research emphasizes early diagnosis as we saw that many of the patients with ambiguous genitals were presenting in adolescence. Further, the focus must be on assessing the long-term outcomes of patients with CAH treated on various protocols. The combined management of the psychosocial elements of the disease in conjunction with medical management is needed to improve the quality of life of these individuals who continue to navigate the convoluted social landscapes [9]. Further research on mental health and social attitudes is needed, advocating for a comprehensive approach to the treatment of CAH in adults from different cultural backgrounds [10]. Today, the broad designation of management can change patients' experiences with CAH, enhance their well-being, and decrease the degree of stigmatization.

METHODOLOGY

A descriptive cross-sectional study of adults with congenital adrenal hyperplasia regarding their varied modes of presentation and hormonal response patterns to treatment at the Endocrine and Diabetes Unit, Jinnah Postgraduate Medical Centre, Karachi, Pakistan, from the year 2007 till date.. A total of 48 adult patients aged 18 to 40 years, of either gender, diagnosed with congenital adrenal hyperplasia (CAH) were recruited. The inclusion criteria were females presenting with the absence of secondary sexual

characteristics or hyperandrogenism and males presenting with precocious puberty. Early and late presentations were based on the age of the patient. Patients diagnosed with polycystic ovarian syndrome (PCOS), adrenal tumors, pituitary or brain tumors causing precocious puberty, and chronic systemic illnesses leading to delayed puberty were excluded. Extensive clinical evaluations included histories, physical examinations, laboratory studies (17-hydroxyprogesterone, DHEAs), chromosomal analyses, and imaging studies of patients with genital ambiguity. The primary medical treatment was steroid therapy and surgical interventions (clitoroplasty and orchidectomy to treat genital ambiguity) for those with ambiguity, and gender reassignment was performed based on patients' preferences. Data were analyzed by SPSS version 26 and presented as mean
± standard deviation for continuous variables and frequency and percentage for categorical variables. Chi-square tests were conducted for early vs. late presentation with a 95% confidence interval and odd ratio.

RESULTS

The study was conducted in 48 patients with mean age (18.48 ± 3.47 years). Most patients (n = 29, 60.4%) were older than 18, while 19 patients (39.6%) were 12- to 18-years-old. Of 48 patients, 44 (91.7%) females and only 4 (8.3%) males comprised most of the study population. Genital ambiguity was identified on clinical exams in 12 patients (25.0%). In addition, one patient (2.1%) had complete feminization of external genitalia with gonadal tissue in the inguinal region. (TABLE 1)

Patients were classified as early and late presentation CAH. Those patients who had presented in childhood at the pediatric setups were labeled as early presenters, and those who came to the adult clinic first time at or after adolescence were; labeled late presenters. Of 48 patients, 26 (54.2%) presented early, and 22 (45.8%) presented late. Ambiguous genitalia were the most frequent reason for early presentation (19 cases, 73.1%), followed by hirsutism (5 cases, 19.2%) and precocious puberty (2 cases, 7.7%). In the case of late presentations, of the 22 cases, the reasons were evenly split between genital ambiguity (6 cases, 27.3%) and primary amenorrhea (6 cases, 27.3%). Other symptoms included hirsutism and irregular menses in 4 patients (18.2%) each and incontinent cyclic hematuria in 2 patients (9.1%) as shown in TABLE 2.

The comparison of surgical treatment modalities for Congenital Adrenal Hyperplasia (CAH) patients with different modes of presentation yielded varied results. Out of 8 patients (62.5%) of early presentation, 5 patients underwent clitoroplasty, and out of 8 patients (37.5%) of late presentation, 3 patients underwent clitoroplasty with an odds ratio (OR) of 1.508 (95% CI: 0.31- 7.17) and p = 0.452. Orchidectomy was performed on 1 (33.3%) early presentation and 2(66.7%) late presentation with OR 0.400 (95% CI: 0.03–4.73) and significance p value 0.436, likewise even after performing orchidectomy, there was no significant association between timing of presentation and approach TABLE 3.

DISCUSSION

Congenital adrenal hyperplasia (CAH) constitutes a collection of autosomal recessive disorders, primarily attributable to a deficiency in 21-hydroxylase, which culminates in disrupted cortisol production and an overabundance of androgen secretion. The manifestations of CAH in adults exhibit considerable variability and are significantly influenced by the timing of diagnosis and subsequent intervention. This investigation sought to evaluate the clinical spectrum and therapeutic responses among adult patients, classified as early (pre-adolescence), namely those transitioning from pediatric medical environments, and late (post-adolescence), typically presenting for the inaugural time at adult endocrine clinics.

Early presenters comprised 54.2% of the cases, predominantly referred from pediatric facilities owing to ambiguous genitalia (73.1%). Conversely, late presenters (45.8%) were more inclined to exhibit primary amenorrhea (27.3%) or genital ambiguity (27.3%), in addition to symptoms such as hirsutism and irregular menstrual cycles. These observed patterns underscore the ramifications of delayed diagnoses, frequently attributable to a lack of awareness, socioeconomic factors, or sociocultural stigmas surrounding genital anomalies, which is consistent with the findings in global literature.

Our results are congruent with prior investigations. Khalid et al. documented early presentations in 59% of CAH patients [22], while Milyani et al. observed

ambiguous genitalia in over 50% of early-presenting individuals [24]. Another study reported the prevalence of early presentation at 59.7% and late presentation at 40.3% [23].

Claahsen-van der Grinten et al. underscored the heterogeneous manifestations of CAH and the consequential challenges it presents for timely diagnosis, particularly in non-classical forms [12]. Likewise, Livadas and Bothou advocated for a patient-centered methodology in females with non-classical CAH due to the overlap with conditions such as polycystic ovary syndrome (PCOS) [11]. The management of CAH necessitates lifelong glucocorticoid therapy to mitigate ACTH-driven androgen excess, with mineralocorticoid supplementation implemented as necessary.

In our study, clitoroplasty was performed more frequently among early presenters (62.5%) in comparison to late presenters (37.5%). Orchidectomy was observed more prevalently in late presenters (66.7%) relative to early presenters (33.3%), although both associations lacked statistical significance. These trends indicate an evolution in clinical practices, where surgical interventions are frequently postponed until adolescence or adulthood to correspond with the maturation of gender identity and informed consent processes [13,14].

The long-term management of CAH must take into account the potential hazards associated with chronic steroid therapy, including growth suppression, obesity, hypertension, and diminished bone density. Mallappa and Merke delineated these challenges and emphasized the necessity for individualized steroid regimens [15]. Innovative treatment modalities, including modified-release hydrocortisone and adjunctive therapies, are currently under investigation to mitigate complications and enhance patient outcomes [16].

The molecular comprehension of CAH has progressed significantly. Concolino et al. furnished a thorough overview of CYP21A2 mutations, thereby facilitating more precise diagnoses and tailored therapeutic approaches [17]. Recent reviews also accentuate the prospective role of biomarkers in enhancing monitoring and early detection efforts [16,18].

Beyond clinical considerations, psychosocial challenges are notably pronounced in cases of CAH diagnosed at a later stage. Lawrence et al. identified disparities in access to care and counseling services, while Hubska et al. illuminated issues of emotional distress, stigma, and identity confusion among adults diagnosed with CAH later in life [19,20]. Furthermore, Guo et al. documented reproductive challenges and complications faced by adult CAH patients, thereby emphasizing the necessity for multidisciplinary reproductive support [21].

A significant advantage of our investigation lies in its emphasis on an adult cohort—frequently marginalized in regional datasets. Stratifying patients according to the age of presentation permitted an examination of the interplay between diagnostic timing and management outcomes. The incorporation of both hormonal and surgical data facilitated a more comprehensive understanding of clinical care within a real-world context.

Limitations encompass the restricted sample size, which diminished the statistical power necessary to identify associations. As a single-center, cross-sectional study, the findings may lack generalizability to wider populations. Furthermore, we did not evaluate psychological or quality-of-life outcomes, which are paramount in the management of CAH due to its implications regarding gender and identity. These aspects signify avenues for future investigation, particularly within low-resource environments.

Notwithstanding these limitations, this study provides significant insights into adult presentations of CAH and emphasizes the criticality of early detection, customized treatment, and integrated psychosocial support.

CONCLUSION

This research elucidates that adult patients with congenital adrenal hyperplasia (CAH) exhibit a diverse array of clinical manifestations, contingent upon the timing of diagnosis. Early presenters—typically referred from pediatric settings—predominantly displayed ambiguous genitalia, whereas late presenters more frequently manifested primary amenorrhea, menstrual irregularities, or genital ambiguity. Although steroid therapy and surgical procedures such as clitoroplasty and orchidectomy were routinely utilized, no statistically significant correlation was identified between the

timing of presentation and treatment modalities. These results underscore the necessity for prompt identification, personalized treatment strategies, and comprehensive psychosocial support to enhance long-term outcomes, particularly in resource-constrained settings.

Table 1: Demographic Characteristics of the Patients	
Variable	**Frequency (%)**
Age, Mean ± SD= 18.48 ± 3.47 Years	
12 - 18 Years	19 (39.6)
>18 Years	29 (60.4)
Gender	
Male	04 (8.3)
Female	44 (91.7)
Clinical Examination	
Genital Ambiguity	12 (25.0)
Complete feminization with inguinal gonads	01 (2.1)

Table 2: Different Mode of Presentations of CAH in Patients	
Variable	**Frequency (%)**
Mode of Presentations	
Early Presentation	26 (54.2)
Late Presentation	22 (45.8)
Reason of Early Presentation	
Ambiguous Genitalia	19 (73.1)
Hirsutism	5 (19.2)
Precocious Puberty	2 (7.7)
Reason of Late Presentation	
Genital Ambiguity	6 (27.3)
Hirsutism	4 (18.2)
Incontinent Cyclic Hematuria	2 (9.1)
Irregular Periods	4 (18.2)
Primary Amenorrhea	6 (27.3)

Table 3. Comparison of Different Mode of Presentation with Different Treatment Strategies

Surgical Treatments	Mode of Presentations		OR (C.I.)	P-Value
	Early Presentation	Late Presentation		
Clitoroplasty	5 (62.5)	3 (37.5)	1.508 (0.31 – 7.17)	0.452
Orchidectomy	1 (33.3)	2 (66.7)	0.400 (0.03 – 4.73)	0.436

Applied Chi-Square test; OR (Odd Ratio), C.I. (Confidence Interval)

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