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ORIGINAL ARTICLE

Characterization of a cohort of pediatric patients with Congenital Adrenal Hyperplasia

Caracterización de una cohorte de pacientes pediátricos con Hiperplasia Suprarrenal Congénita

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What do we know about the subject matter of this study?

Congenital adrenal hyperplasia (CAH) is the most common adrenal disorder in pediatrics which includes all those inherited conditions that present an enzymatic deficiency that alters the synthesis of adrenal components, and its main clinical features depend on the variant.

What does this study contribute to what is already known?

This study shows the sociodemographic and clinical characteristics of patients with CAH in Medellín, Colombia, which have not been well documented so far. Salt-wasting crisis is still a very frequent clinical presentation in our population, which could be avoided with neonatal screening.

Abstract

Congenital adrenal hyperplasia (CAH) is the most common adrenal disorder in childhood. **Objective:** To describe the clinical and laboratory characteristics of pediatric patients with CAH and perform an exploratory analysis comparing some clinical and laboratory variables according to the types of CAH. **Patients and Method:** Observational descriptive longitudinal study. Medical records from the pediatric endocrinology outpatients from four institutions in Medellín, Colombia were reviewed. Sociodemographic, clinical (type of CAH, salt-wasting crisis, associated endocrinopathies), laboratory (17-hydroxyprogesterone, testosterone, dehydroepiandrosterone sulfate, androstenedione, cortisol, and adrenocorticotropic hormone) variables were analyzed. A descriptive statistical analysis was carried out. **Results:** 132 patients (65% female) were included. The median age at diagnosis was 2 months, 44.7% neonatal diagnosis. Seventy-nine children with classical salt-wasting CAH, 31 with simple virilizing, and 22 with non-classical form were documented. Median 17-OHP at diagnosis was 4820 ng/dl. Sexual differentiation disorder was presented in 47% of patients and 48% presented with

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adrenal crisis (AC) at diagnosis; the median age of the first AC was 15 days. Ninety-three patients required fludrocortisone and 32 patients presented AC after diagnosis and treatment. Median height/age (last appointment): -0.49 SD, difference between bone and chronological age: 26 months. More than 60% of patients had elevated androstenedione and/or testosterone at the last appointment. **Conclusions:** Sociodemographic and clinical characteristics are similar to those reported in the literature. In 48% of patients, AC was the initial manifestation, making neonatal screening important, as it would allow an early diagnosis. We found virilization in 71% of women in our study. A CAH should be suspected in a newborn with different genitalia.

Introduction

Congenital adrenal hyperplasia (CAH) is the most common adrenal alteration in pediatrics[1] which includes all those inherited conditions that present an enzymatic deficiency that alters the synthesis of adrenal components[2-4], has an autosomal recessive inheritance[5,6], and 95% correspond to 21-hydroxylase deficiency[3,7,8].

21-hydroxylase deficiency is mainly caused by mutations in the *CYP21A2* gene, which encodes the 21-hydroxylase enzyme. The phenotype can have a wide clinical variability and depends on the mutation and the level of residual enzyme activity it determines[9].

The classification is based on clinical manifestations and age of presentation, divided into two main groups: classical and non-classical[10]. Classical CAH has an incidence of 1:10,000-20,000 live births/year[4] and is further subdivided into 2 forms: classical salt-wasting CAH (SW-CAH), which is characterized by salt-wasting crisis (SWC) and disorders of sex development (DSD), and classical simple virilizing CAH (SV-CAH), which is characterized by more subtle virilization signs and the absence of SWC, with a delayed diagnosis[11]. The non-classical variant (NC-CAH) is more frequent, reaching up to 1% in special populations[3], and presents with later signs and symptoms of hyperandrogenism, manifesting even in adulthood.

Complications of CAH include hydroelectrolytic alterations, DSD, and, in the long term, premature adrenarche, precocious puberty, virilization, short final stature, metabolic syndrome, decreased fertility in women, and altered bone mineral density, among others[1,9,12,13].

In Colombia, neonatal screening for this pathology is not routinely performed, therefore, it is suspected in the presence of clinical manifestations or alterations on the physical examination, which may delay diagnosis and treatment, leading to comorbidities or even death in the case of late identification of SWC.

Despite being the most frequent adrenal alteration in pediatrics, studies in low- or middle-income countries are scarce, with no epidemiological data that show the reality of this pathology in our region. The objective of this study was to describe the clinical characteristics and laboratory parameters in pediatric patients with CAH in four reference centers in Medellin, Colombia.

Patients and Methods

Longitudinal descriptive observational study conducted in 4 pediatric endocrinology referral centers in Medellín, Colombia.

Population

We included children under 18 years of age with a clinical diagnosis of CAH with 17-hydroxyprogesterone (17-OHP) levels > 1000ng/dl or with a confirmatory adrenocorticotropic hormone (ACTH) stimulation test in those with 17-OHP values > 200 ng/dl, or despite not having the initial report of diagnostic 17-OHP levels, the treating pediatric endocrinologist had a high clinical suspicion and it had been so recorded in the clinical history. Patients with incomplete medical record were excluded.

Medical records were reviewed, and information was recorded in Excel from Google Forms, creating a database.

Data collection

All records of care at each health center that had one or more ICD-10 codes related to CAH (E250, E258, E259) in the diagnosis were reviewed. Inclusion criteria were verified and the following were retrospectively analyzed: sociodemographic variables (age, sex, origin), clinical variables (type of CAH, SWC, associated endocrinopathies, hyperandrogenism, and DSD), laboratory variables (17-OHP, testosterone, dehydroepiandrosterone sulfate DHEA-S, androstenedione, cortisol, ACTH, renin, sodium, potassium, glycemia, and karyotype), and treatment (hydrocortisone, fludrocortisone, and genitoplasty). For the evaluation of height-for-age, the Z-score was calculated according to WHO growth charts and expressed in standard deviation (SD)[1].

17-OHP levels were measured by MICROELISA. The reference values of Speiser et al were considered for 17-OHP levels[4]. Reference values for testosterone, DHEA-S, androstenedione, cortisol, ACTH, direct renin, sodium, potassium, and glycemia were obtained from Endocrinology Expected Values[14], considering as high values those above the range referred to as normal, normal values as those within the range referred to, and low values as those below the lower limit referred to.

Statistical analysis

The quantitative variables were analyzed with measures of central tendency (mean or median) and dispersion (standard deviation -SD- and interquartile range -IQR-) according to normality evaluated with the Shapiro-Wilk test. Qualitative variables were analyzed by absolute frequencies and proportions.

Laboratory (androgens) and treatment variables at diagnosis were compared with the last visit. An exploratory analysis was performed comparing the type of CAH with some clinically relevant variables using the Kruskal-Wallis test. Statistical significance was defined with a p-value < 0.05. The information was analyzed with SPSS software version 20.

This study was approved by the ethics committee of 3 study institutions (*IPS University*, *Hospital Pablo Tobón Uribe* (HPTU), and *Hospital Universitario San Vicente Fundación* (HUSVF). The Noel Clinic Foundation accepted these endorsements.

Results

437 medical records were reviewed and 162 met the inclusion criteria; of these, 30 were excluded due to incomplete information, resulting in a final sample of 132 patients. All patients had 21-hydroxylase deficiency.

There were no reports of prenatal diagnosis. The median age at diagnosis was 2 months, ranging from 1 day to 13 years of age (table 1).

Ten patients (8%) had a history of consanguinity and 12/132 (9%) had CAH in first-degree relatives. The median follow-up time was 65 months (IQR 21.5 and 140 months). Patients with variant SW-CAH had a median follow-up of 70 months, patients with SV-CAH 84 months, and patients with NC-CAH 29.5 months.

Table 2 shows the clinical characteristics of the population. 62 (71%) female patients presented DSD. The median height Z-score for age at diagnosis was 0.27 SD (IQR -1.49-1.34); with respect to this variable, 11/64 patients (17%) had a Z-score ≤-2 SD (short stature) and 11/64 patients (17%) had a Z-score ≥ + 2 SD (tall stature).

Arterial hypertension was present at diagnosis in 2/132 patients (2%). Table 3 shows some clinically relevant features and the laboratory findings at diagnosis and the last visit according to the clinical variant of CAH. The median ACTH level at diagnosis was 58 pg/ml (IQR 11-304) and, at the first consultation, direct renin was 77 ng/L (IQR 1.4-975) and glycemia 77 mg/dl (IQR 69-93).

Molecular testing of the *CYP21A2* gene was performed in 14/132 patients (11%), observing that the most common mutation was in exon 7, Val281Leu (c.844G > T (p.Val282Leu).

7/132 patients (5%) had ultrasonography confirming adrenal hyperplasia.

At diagnosis, 129/132 patients (97%) received glucocorticoids. The median hydrocortisone equivalent glucocorticoid dose at baseline was 15.7 mg/m^2/day (IQR 12 - 20), similar to the dose at the last visit, with a median of 15 (IQR 8.8-28.3).

93 patients (70%) received fludrocortisone at some point during follow-up. The starting dose was 0.1 mg/day in 62 patients (70%), 14 (16%) received lower doses, and 12 (14%) required more than 0.1 mg/day. The dose of fludrocortisone reported at the last visit was 0.1 mg/day in 52 patients (56%), < 0.1 mg/day in 34 patients (37%), and 0.2 mg/day or higher in 7 patients (7%). In 81 patients (61%), there was no change in the fludrocortisone dose, in 33 (25%) it was decreased, and in 19 (14%) it was increased at the last visit compared with the initial dose. Two patients had arterial hypertension secondary to the use of fludrocortisone at some time during their treatment.

Surgical management for modification of poorly differentiated genitalia was reported in 36 of 87 female patients (41%).

After diagnosis and initiation of treatment, 32/79 patients (40%) presented SWC.

Table 1. Sociodemographic characteristics of the study population

	n (%)
Sex	
Female	87 (66)
Male	45 (34)
Age at diagnosis	
Less than 30 days	46 (35)
1 - 12 months	42 (32)
Older than 12 months	44 (33)
Origin	
Urban	92 (70)
Rural	40 (30)

Table 2. Clinical characteristics of the population

Characteristic	n = 132
Clinical variant, n (%)	
Classical salt-wasting	79 (60)
Classical simple virilizing	31 (23)
Non-Classical	22 (17)
Age at first salt-wasting crisis (Median, IQR)	15 days (10.25-24.25)
Clinical hyperandrogenism, n (%)	82 (62)
Different sexual development in women, n (%)	62 (71)
Prader scale, n (%)	
Completely feminine	22 (17)
1	7 (5)
2	4 (3)
3	25 (19)
4	18 (13)
5	2 (2)
Completely masculine	32 (24)
Not reported	22 (17)
17-OHP (ng/dL) level at diagnosis (Median, IQR)	4820 (2300-13900)
CAH diagnosis according to the 17-OHP value, n (%)	
CAH (17-OHP >1000 ng/dL)	74/79 (94)
Suspected CAH (17-OHP 200 -1000 ng/dL)	5/79 (6)
Associated endocrinopathies, n (%)	
Short stature	33/117 (28)
Precocious puberty	28/132 (21)
Obesity	6/132 (4)
Hypothyroidism	3/132 (2)
Exogenous Cushing's	1/132 (1)

IQR: Interquartile range, ng: nanogram, 17-OHP: 17-hydroxyprogesterone, CAH: Congenital adrenal hyperplasia.

Height-for-age at the last visit had a median Z-score of -0.49 SD (IQR -2.2-1.04); 33/116 (28%) patients had short stature, 11/116 (10%) tall stature (Z ≥+ 2 SD), and 72/116 (62%) normal stature. Regarding growth velocity at the last consultation, a median of 6.4 cm/year (IQR 1.59 - 10 cm/year) was observed. An analysis of prepubertal age patients (girls aged between 5 and 8 years and boys between 5 and 9 years) was performed, finding that 6/53 females (11%) and 5/29 males (17%) had accelerated growth velocity. At some point during follow-up, 49/132 patients (37%) had advanced bone age.

Exploratory Analysis

When comparing the age at diagnosis according to the clinical variant, we found that in patients with SW-CAH, the median was significantly lower (p = 0.001) (table 3).

A bivariate analysis was performed comparing the clinical variant with some variables of interest, finding higher androstenedione values in SW-CAH at the last consultation (p = 0.02) (table 3). When comparing the height at the last consultation, we found a lower Z-score in patients with SW-CAH (-1.3 SD) and better scores in NC-CAH (0.2 SD) (p = 0.04). No statistically significant differences were found when comparing the clinical variant with 17-OHP at diagnosis (p = 0.5), androstenedione at diagnosis (p = 0.5), frequency of precocious puberty (p = 0.1), height at diagnosis (p = 0.1), and accelerated bone maturation (p = 0.9).

Regarding glucocorticoids, the median hydrocortisone equivalent dose at diagnosis was higher in SW-CAH (18.65 mg/m^2/day) and lower in NC-CAH (10.54 mg/m^2/day) (p = 0.001) (chart 1.A). In NC-CAH, 19 patients (86%) received steroids initially. The hydrocortisone dose at the end of follow-up was lower in patients with NC-CAH (10.16 mg/m^2/day) and higher in SV-CAH (17.09 mg/m^2/day) (p = 0.003) (chart 1.B).

Discussion

In this study, all the patients had 21-hydroxylase deficiency according to the clinical characteristics and the literature reported that 95% of CAH corresponds to this cause[15].

The sociodemographic variables, age at the onset, and clinical characteristics of the variant were similar to those reported in previous studies.

SW-CAH constitutes 75% of the classic forms[11]; in our study, a ratio close to these percentages was maintained (71.8%). However, according to the literature, NC-CAH can be up to 10 times more frequent than the classical ones[5], with an incidence of 1:500 - 1:1,000 live births[15]. In our study, this variant was the least frequent, possibly because only pediatric patients were included, and many of these cases are diagnosed in adulthood[10]. Regarding local references, in 2007 Montoya et al. reported similar results in a referral hospital in Medellín, where the most frequent presentation was SW-CAH (45.1%) followed by SV-CAH (28%), and finally NC-CAH (17%)[16].

Females were the most frequently affected, independently of the clinical variant, probably because virilization is more evident in women[5,7,13]. This finding is similar to that published by Montoya et al.[16] for CAH in general, however, in the SW group, they found 64.9% of males.

There was a statistically significant difference in the age at diagnosis of each clinical variant, as expected by clinical presentation and severity of these. The age

Table 3. Comparison between clinical variants

Characteristic	Classical Salt-wasting (n = 79)	Classical Simple virilizing (n = 31)	Non-Classical (n = 22)
At diagnosis			
Age in months (Median, IQR)	0.5 (0.1-0.2)	22 (2-60)	89.5 (83.75-105)
Associated endocrinopathy, n (%)	39/79 (49)	25/31 (81)	7/22 (32)
Different sexual development, n (%)	44/79 (56)	18/31 (58)	0
Clinical hyperandrogenism, n (%)	46/79 (58)	23/31 (74)	13/22 (59)
Salt-wasting crisis, n (%)	64/79 (81)	0	0
17-OHP (ng/dL), (Median, IQR)	6860 (4260-27710)	3010 (1291-5236)	2350 (1170-4708)
Total testosterone*, n (%)	n = 23	n = 6	n = 11
High	10 (43)	4 (67)	10 (90)
Normal	6 (26)	3 (33)	1 (10)
Low	7 (31)	0	0
Cortisol (µ/dL), (Median, IQR)	4.2 (2.5-6.6)	4.5 (3.8-6.6)	14.6 (9.2-110)
DHEA-S*, (µg/dL), n (%)	n = 22	n = 12	n = 14
High	13 (59)	8 (67)	7 (50)
Normal	8 (36)	4 (33)	7 (50)
Low	1 (5)	0	0
Androstenedione*, (ng/dL), n (%)	n = 10	n = 7	n = 10
High	5 (50)	6 (86)	8 (80)
Normal	5 (50)	1 (14)	2 (20)
Sodium (mEq/L), (Median, IQR)	125 (119-139)	140 (139-146)	138 (121 a 140)
Hyponatremia	21/79	0	0
Potassium (mEq/L), (Mean, SD)	6.57 (1.48)	4.56 (0.66)	4.14 (0.81)
Hyperkalemia	65/79	3/31	0
Karyotype, n (%)			
46XX	32 (41)	8 (26)	
46XY	1 (1)	3 (10)	
(27) 46XX/ (23) 46X del q24 q27	1 (1)		
No data	45 (57)	20 (64)	22 (100)
Hydrocortisone equivalent dose (mg/m2/day), (Median, IQR)	18 (15-21)	14.7 (10-19.5)	10 (8-12.3)
At the last follow-up appointment			
Testosterone*, (ng/dL), n (%)	n = 44	n = 11	n = 11
High	28 (64)	11 (100)	9 (81.8)
Normal	16 (36)	0	2 (18)
Androstenedione* (ng/dL), n (%)	n = 44	n = 18	n = 15
High	27 (61)	7 (39)	13 (87)
Normal	15 (34)	7 (39)	2 (13)
Low	2 (5)	4 (22)	0
Direct Renin level (ng/L), (Median, IQR)	54 (22-292)	36 (16-72)	22 (9.3-83)
Fludrocortisone use, n (%)	64/75 (85)	14/15 (93)	1/3 (33)
Hydrocortisone equivalent dose (mg/m2/day), (Median, IQR)	15.5 (11.65-20)	15 (10.6-20.5)	10 (8.3-11.5)
Genitoplasty, n (%)	23 (29)	13 (42)	0

17-OHP: 17-hydroxyprogesterone, DHEA-S: dehydroepiandrosterone sulfate, IQR: Interquartile range, SD: standard deviation. *Value according to sex, age and Tanner, taken from: Labcorp. 2021. Endocrinology. Expected Values & S.I. Unit Conversion Tables; https://specialtytesting.labcorp.com/sites/default/files/2021-07/L5167-0421-

at diagnosis is earlier in SW, usually with SWC onset between the second and third week of life[15], similar to our data (15 days). Overall, when there has been an implemented system of neonatal screening, the age at diagnosis decreases. Thil'en et al. found a median age at diagnosis of 9 days in screened areas and 21 days in unscreened areas[17].

In SV-CAH, the median age at diagnosis was 33 months, with a marked difference between sexes, being 12 months in women and 48 months in men, explained by the more evident virilization in women[7].

The diagnosis of the NC-CAH was delayed, with a median of 7.4 years, similar to previous reports[18]. Berrade et al reported a mean age at diagnosis of 8 ± 2.2 years[6]. In our series, the diagnosis in women was at 7.2 years and in men at 10 years, differing from the literature, which describes that it is usually earlier in men[7].

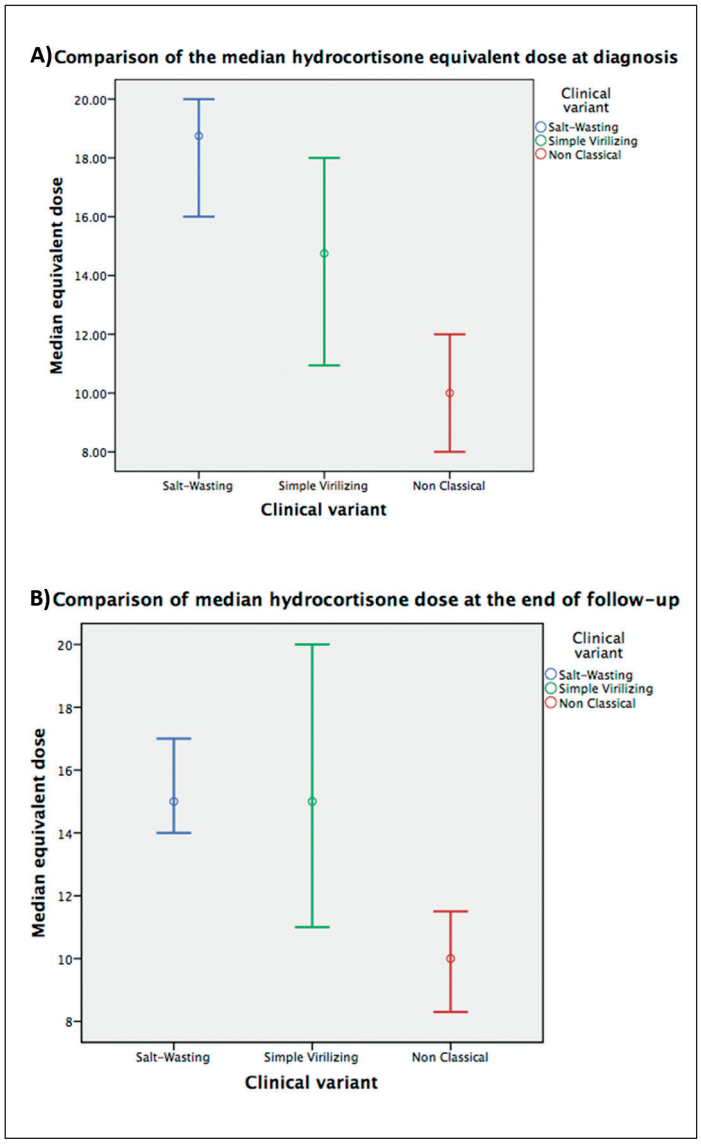

Figure 1. Relationship between Clinical Variant with median glucocorticoid dose at diagnosis (**A**) and at the end of follow-up (**B**).

According to the clinical practice guideline of the Endocrine Society, the diagnosis of CAH due to 21-hydroxylase deficiency is confirmed when the basal or post ACTH stimulation 17-OHP value at baseline or post ACTH stimulation is above 1000 ng/dL[4]. Usually, a higher value predicts a more severe presentation, as observed in the nomogram of Wilson et al.[19] and Sanz[20]. This relationship was also observed in our study and, although there was no statistically significant difference, possibly because of the size of the population studied, baseline 17-OHP values were higher in SW-CAH and lower in NC-CAH, with a median of 2350 ng/dL, exactly the same value found by Berrade et al. (table 3)[6] and the same pattern described by Sanz[20].

Liquid chromatography-mass spectrometry is the recommended method for the measurement of 17-OHP since it increases the positive predictive value for the screening of CAH, however, in our country, this technique is not available, and the results could vary depending on the method. Radioimmunoassay and ELISA are the most frequently used but are also prone to false positives[4]. An increase in androgens levels (total testosterone, androstenedione, DHEA-S) was found, corroborating the hyperandrogenemia of these patients[11].

In 81% of patients with SW-CAH, the first manifestation was SWC, a higher frequency compared with other series occurring in 33%[20] and 36%[17], possibly due to the lack of availability of neonatal screening. In the absence of screening, the probability of neonatal death due to adrenal crisis has been established between 0-4%, even in high complexity centers[21]. Of the patients with SW-CAH, 40% presented SWC after diagnosis probably due to the lack of adherence to treatment, which represents a worrying fact. The median sodium (125 mEq/L) and potassium (6.4 mEq/L) levels were similar to those reported by Sanz[20] and Thil'en et al. in Swiss patients, with an average sodium level of 124 mEq/L before initiating screening and 134 mEq/L after its implementation[17].

Hypoglycemia is caused by impaired gluconeogenesis due to glucocorticoid deficiency[11,15]. The median glycemia was slightly lower than that reported in the literature, for SW-CAH it was 77 mg/dL (84 mg/dL) and in SV-CAH it was 76 mg/dL (83 mg/dL)[20]. In the context of SWC, hypoglycemia (< 50 mg/dl) occurred in 5.4% of cases, slightly lower than the reported 8-9%[22,23].

The most common mutation found was c.844G > T (p.Val282Leu), which has 20-50% of the normal enzymatic activity. This is one of the most frequent mutations in NC-CAH[4], previously reported in Colombian patients[24]. The second mutation i2 splice (c.293-

13C > G), describes a residual enzymatic activity of 1% and has been reported with high frequency in classical forms[25].

71% of the female patients presented some degree of DSD, most were SW-CAH, classified with a Prader score 3-4[12], similar to the literature which reported that most women with SW-CAH have some degree of virilization in their external genitalia[15]. In our report, 93% of patients with this variant had some degree of virilization, slightly higher than that of similar series (77%)[1]; in 3 cases, male sex was erroneously assigned, an event reported in other series[20]. Therefore, it is crucial to be aware of findings that may suggest hypervirilization in male newborns or virilization in female patients because this could point to classic CAH and this may alert us before electrolyte alterations or even SWC occur.

Mixed precocious puberty[26] occurs especially in cases of delayed treatment, with advanced bone age[27]; in our study, all patients with precocious puberty had advanced bone age, with a median of +3 years, higher than the +2.16 years found in the total of our population. This may also indicate poor adherence to treatment after diagnosis. The group with NC-CAH was the one with the greatest advanced bone age, with +2.25 years, similar to the findings of Berrade et al, who reported an advancement of +2.09 years[6].

All patients with classic forms received initial management with glucocorticoids, while in non-classic forms, the rate was 73% and this, in some cases, did not require treatment[26]. The glucocorticoid dose was higher in SW-CAH, being above the current recommendations[4], as in reports for SV-CAH[7]. There was a decrease in the final dose in SW-CAH, with no remarkable changes in the other variants. The administration of exact doses of glucocorticoids in neonates, infants, and young children is complex given that hydrocortisone, which is the glucocorticoid of choice, is only available in tablets, therefore, it is often necessary to approximate doses, fractionate tablets, or compounding. This may cause a non-uniform distribution and could interfere with adequate treatment.

17-OHP, androstenedione, and total testosterone are the best indicators of adequate glucocorticoid treatment[11]. Given that the objective is not to normalize 17-OHP since it would indicate overtreatment, glucocorticoid management was evaluated with androstenedione levels. Most patients had increased values for their sex and Tanner stage, suggesting poor management. The androstenedione values were higher in SW-CAH, similar to the series published by Finkielstain et al.[7] where about 40% of patients with classic CAH had elevated androstenedione levels and 15% had elevated total testosterone. However, in the study of Sanz[20], no difference was observed between the clinical variant and androgen levels.

In addition to biochemical analysis, height, growth velocity, and bone maturation are important in the follow-up of glucocorticoid treatment[12]. The median height was within the normal range, but in SW-CAH it was -1.3 SD, indicating a risk of short stature. The literature reports that generally, with adequate treatment, short stature does not occur, however, the classic form accounts for most affected patients, especially SW. Most studies report final height, but in our case, it was not possible because most of the patients were still of pediatric age. The 18-center meta-analysis by Eugster et al. reported a mean final height score of -1.37 SD, a significantly better result in patients diagnosed early[28]. More recent publications show that a final height within the genetic potential can be obtained with proper management[29].

A total of 93 patients required fludrocortisone and most had to start doses of 0.1 mg/day, higher than those reported by Sanz in the SW form (0.075 mg/day)[20]. As in other series, most patients maintained or decreased the dose. Mineralocorticoid monitoring is defined according to blood pressure and plasma renin activity (PRA)[7]. Measurement of PRA was difficult to access in our country, so direct renin concentration (DRC) measurement was used. However, the Endocrinology Society has reported a poor correlation between DRC and PRA, especially at low renin levels[30].

Among the limitations of the study is worth mentioning an information bias due to the retrospective collection of data, with incomplete data from certain variables, in addition to a measurement bias since the laboratory method was unknown for some measurements and there were probably different techniques. Finally, due to the nature of the study, confounding variables cannot be controlled, generating a confounding bias.

Conclusion

This study evidences an important frequency of CAH in pediatric patients. The sociodemographic variables, age at the onset, and the clinical characteristics of the CAH variants were similar to those reported in the literature. 88% of patients had a normal height at the last consultation, although advancing bone age could compromise their adult height since these patients are still growing and developing.

It is essential to suspect the diagnosis of CAH in a newborn with different genitalia, since we found virilization in 71% of females in our series, favoring earlier detection, even before the hydroelectrolytic alterations.

48% of the patients initially presented SW and a significant percentage presented a second event, which are serious events that could be reduced with early

diagnosis through the implementation of neonatal screening in our country. We found elevated total testosterone and androstenedione during follow-up, suggesting poor adherence to glucocorticoid treatment.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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