Non-classic congenital adrenal hyperplasia. Clinical experience versus clinical guidelines

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Abstract

The ability to diagnose non-classic congenital adrenal hyperplasia (NC-CAH) has improved drastically over the past decade due to standardization of laboratory assays and refinement of molecular studies. However, the optimal clinical management for this patient population is still evolving. Thus, we describe the clinical presentation and diagnostic approach of children with non-classic congenital adrenal hyperplasia (NC-CAH). A retrospective chart review was done to identify all subjects diagnosed with late-onset CAH or NC-CAH at a single institution during the last decade. Eighteen subjects were identified. Fourteen were diagnosed as NC-CAH, and four with NC-CAH with 3 beta-hydroxysteroid dehydrogenase (3βHSD) deficiency. The approach to evaluation was different according to the provider. Re-evaluation of steroid hormone concentrations using updated diagnostic criteria revealed one patient had ACTH-stimulated hormone concentrations consistent with classic CAH (non-salting variant) and four patients initially thought to have NC-CAH with 3βHSD had steroid hormone concentrations consistent with premature adrenarche. Age and clinical presentation did not differentiate subjects with NC-CAH from those with premature adrenarche. Skeletal age was 2 standard deviations advanced only in those patients with NC-CAH. Variations in the diagnostic approach to evaluate children for NC-CAH exist. We provide a practical algorithmic recommendation, incorporating the most recent diagnostic guidelines, to aid the clinician in the evaluation of this disorder.

Introduction

The ability to diagnose non-classic congenital adrenal hyperplasia (NC-CAH) has improved drastically over the past decade due to standardization of laboratory assays and refinement of molecular studies. However, optimal clinical management for this patient population is still evolving and only recently have evidence-based guidelines for the diagnosis of NC-CAH been published.1

The diagnosis of NC-CAH encompasses a number of adrenal enzyme deficiencies causing excessive androgen secretion with onset in childhood. This disorder is estimated to be prevalent in 0.1-3% of the general population,2 although studies in more select groups report a prevalence of up to 10%.2 While 21-hydroxylase enzyme deficiency (21-OHD) accounts for up to 90% of cases of NC-CAH, deficiencies in the other adrenal enzymes such as 3 beta-hydroxysteroid dehydrogenase (3βHSD) and 11 beta-hydroxylase deficiency (11β-OHD) can rarely occur.1,3,5

The diagnosis of NC-CAH is not always easily established. The clinical presentation may be asymptomatic or may mirror premature adrenarche (PA) in childhood and polycystic ovarian syndrome or functional ovarian hyperandrogenism in adolescence, as the degree of androgen excess varies widely in these patient groups.3-5 The gold standard for differentiating between the different adrenal enzyme defects is the adrenocorticotropic hormone (ACTH) stimulation test with measurement of basal and stimulated adrenal steroid concentrations.6-8 Using long established criteria, ACTH stimulation testing does not always lead to a clear diagnosis. For example, there exists significant overlap in both basal and ACTH-stimulated steroid concentrations for patients with NC-CAH 3βHSD and PA.4,9,12 Finally, although molecular testing for NC-CAH is now available, it is not always routinely used, at least in part because of its high cost and inad- equate of insurance coverage.

The aim of this study was to review the clinical experience with NC-CAH at Cincinnati Children’s Hospital Medical Center (CCHMC) during the last decade. We suspected that, even with the availability of hormone-genotype correlation testing, there would still be variations in the diagnostic approach of this disorder. Thus, the purposes of this study were to i) Describe the clinical presentation of our patients diagnosed with NC-CAH; ii) Review the diagnostic criteria used in the work-up of NC-CAH; and iii) Provide a practical algorithm to aid in the clinical evaluation of this disorder.

Materials and Methods

Subjects

The study was approved by the Institutional Review Board at CCHMC. Retrospective chart review was done on all patients with a diagnosis of NC-CAH late-onset CAH followed in the endocrine clinic at CCHMC during the last decade. Patients were identified from medical records bearing the diagnostic code of adrenogenital disorder/CAH (ICD-9 code 255.2). Subjects with with evidence of central precocious puberty at diagnosis (females with breast development before the age of 8 years and males with testicular enlargement before the age of 9 years) were excluded from this analysis. Recorded parameters included: age, pubertal staging, laboratory data, skeletal age radiographs and treatment as documented by the treating endocrinologist.

Similarly, retrospective chart review was conducted on children with the diagnosis of PA during the same time frame. This population served as a control group. An equal number of patients were reviewed for age at presentation, clinical signs and symptoms, laboratory data and skeletal age radiographs.

Hormone assays

All patients had basal steroid measurements done. A standard ACTH corticotropin stimulation test was done in the morning (before 10.00 a.m.) at the discretion of the evaluating endocrinologist. Blood samples were obtained before and 60 min after corticotropin 0.25 mg/m2 was given as a slow intravenous bolus. With the exception of cortisol (C), which was assayed directly on aliquots of diluted serum, all other steroid hormones, including serum 17-hydroxyprogesterone (17-OHP), 17-hydroxyprogrenolone (Δ5-17P), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA sulfate) and androstenedione (Δ4-A) were analyzed by a combination of extraction and chromatographic purification (13, 14). All samples were sent to Esoterix, Inc for evaluation.
Diagnosis of adrenal enzyme deficiency

Prior to characterizing this population, the authors wanted to ensure each subject truly had the disorder. Based on the most recent literature, the following steroid hormone concentrations were used to classify the subjects: i) Heterozygote Carrier 21-OHD; baseline 17-OHP < 200 ng/dL (6 nmol/L), and ACTH-stimulated 17-OHP < 1666 ng/dL (50 nmol/L); ii) NC-CAH 21-OHD, Baseline 17-OHP > 200 ng/dL (6 nmol/L), and ACTH-stimulated 17-OHP between 1000-10,000 ng/dL (31-300 nmol/L); iii) Classic Simple Virilizing (CSV) 21-OHD, baseline 17-OHP > 200 ng/dL (6 nmol/L), and ACTH-stimulated 17-OHP > 10,000 ng/dL (300 nmol/L); iv) NC-CAH 3βHSD, ACTH-stimulated Δ5-17P ≥6678 ng/dL (201 nmol/L) and Δ5-17P to C ratio ≥363.

Results

Eighteen subjects (10 males, 8 females) were identified on retrospective review labeled as having NC-CAH or late-onset CAH. Demographics, skeletal age, clinical information and laboratory data are presented in Table 1. Fourteen subjects had been diagnosed with NC-CAH 21-OHD and four subjects with NC-CAH 3βHSD. After the authors’ review of basal and ACTH-stimulated steroid concentrations from initial diagnosis, one patient was subsequently re-classified as C-SV 21-OHD. Seven subjects had not undergone ACTH-stimulation testing and therefore re-classification was not possible. The four subjects originally diagnosed with NC-CAH 3βHSD were no longer believed to have this disorder when newer criteria for diagnosing NC-CAH 3βHSD, which is based on genotype-hormone correlations, were applied. These four subjects were re-classified as PA.

The mean age at presentation for all subjects was 8 years ± 3 years 2 months (range 3-15 years). When assessed by our re-classification method, the average age of presentation for the NC-CAH 21-OHD group was 8 years 7 months ± 3 years 2 months. This group had an average skeletal age advancement of 4 years ± 2 year 1 month. Eleven of those with NC-CAH 21-OHD presented with premature pubarche, pubic hair Tanner stage II-IV, while two patients presented with a single complaint of either excessive acne or clitoromegaly. No patients had clinical or biochemical evidence of salt wasting.

Eleven patients had undergone ACTH stimulation testing (Table 1). For those in the NC-CAH 21-OHD group, all had basal 17-OHP concentrations >200 ng/dL (6 nmol/L) with ACTH-stimulated values, when obtained, >1,000 ng/dL (31-300 nmol/L). A 0' and 60 minute ACTH stimulation values. To convert to Standard International units multiply Δ5-17P, 17-OHP, DHEA, and A by 0.03.

Table 1. Clinical and laboratory data for children after re-classification.

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<tr>
<th>n</th>
<th>Sex</th>
<th>CA (years)</th>
<th>Skeletal age (years)</th>
<th>Clinical presentation</th>
<th>Δ5-17P (ng/dL) 0’</th>
<th>17-OHP (ng/dL) 0’</th>
<th>DHEA (ng/dL) 0’</th>
<th>A (ng/dL) 0’</th>
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<td>60’</td>
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<td>1</td>
<td>F</td>
<td>5 years 2 months</td>
<td>7 years 10 months</td>
<td>T3 PH</td>
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<td>3340</td>
<td>777</td>
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<td>6950</td>
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<td>2</td>
<td>F</td>
<td>7 years 9 months</td>
<td>10 years</td>
<td>T2 PH</td>
<td>227</td>
<td>1110</td>
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<td>88</td>
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<td>3</td>
<td>M</td>
<td>8 years 2 months</td>
<td>10 years</td>
<td>T3 PH</td>
<td>177</td>
<td>1160</td>
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<td>122</td>
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<td>5</td>
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<td>8 years 2 months</td>
<td>13 years</td>
<td>T3 PH</td>
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<td>4260</td>
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<td>6</td>
<td>M</td>
<td>9 years</td>
<td>13 years</td>
<td>T4 PH 1746</td>
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<td>7249</td>
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<td>14 years 6 months</td>
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<td>7</td>
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<td>15 years 10 months</td>
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<td>Clitoromegaly</td>
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<td>8</td>
<td>M</td>
<td>7 years 4 months</td>
<td>12 years 6 months</td>
<td>T2 PH</td>
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<td>1631</td>
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<td>9</td>
<td>M</td>
<td>10 years</td>
<td>13 years</td>
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<td>1036</td>
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<tr>
<td>11</td>
<td>M</td>
<td>3 years 10 months</td>
<td>11 years</td>
<td>T3 PH</td>
<td>-</td>
<td>7900</td>
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<tr>
<td>12</td>
<td>M</td>
<td>7 years 7 months</td>
<td>13 years 6 months</td>
<td>T3 PH</td>
<td>-</td>
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<tr>
<td>13</td>
<td>F</td>
<td>7 years 2 months</td>
<td>9 years</td>
<td>T3 PH</td>
<td>-</td>
<td>4170</td>
<td>-</td>
<td>104</td>
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</table>

NC-CAH 21-OHD now SV 21-OHD

14  F   5 years 2 months | 8 years 10 months | T3 PH              | 1269             | 5608            | 1456           | 219         |
|    |     |             |                     |                     | 1615             | 10441           | 951           | 208         |

M, male; F, female; CA, chronological age; T, tanner staging; PH, pubic hair; NC-CAH, non-classic congenital adrenal hyperplasia; 21-OHD, 21-hydroxylase enzyme deficiency; 17-OHP, 17-hydroxypregnenolone; Δ5-17P, 17-hydroxypregnenolone; DHEA, dehydroepiandrosterone. 0’ and 60 minute ACTH stimulation values. To convert to Standard International units multiply Δ5-17P, 17-OHP, DHEA, and A by 0.03.
ng/dL (31 nmol/L). The one patient reclassified in the SV-CAH 21-OHD group, basal 17-OHP values was > 200 ng/dL (6 nmol/L) with an ACTH- stimulated value ≥ 10,000 ng/dL (300 nmol/L). The four patients originally diagnosed as NC-CAH 3βHSD had elevated ACTH- stimulated Δ5-17P and DHEA concentrations, and ratios of Δ5-17P to 17-OHP or DHEA to Δ4- A >2 standard deviations (SDS) above the mean for age or pubertal stage of normal subjects, and met previously established diagnostic criteria.9,12,21

However, when these four patients were reassessed with newer diagnostic criteria for NC-CAH 3βHSD (evaluation by ACTH- stimulated Δ5-17P and Δ5-17P to C ratio), using the lowest absolute hormone concentrations for genotype-confirmed 3βHSD, their steroid concentrations did not meet the criteria, thus these patients were re-classified as premature adrenarche9,10,12 (Table 2).

Treatment regimens for all subjects are listed in Table 3. Thirteen patients were treated with glucocorticoid (GC) therapy to suppress adrenal androgen overproduction and protect adult height potential. The average GC dose as hydrocortisone (HC) equivalent was 12 mg/m²/day. Two patients were treated with stress dosing GC only. Three patients received no GC treatment. By sub-group, all children in the NC-CAH 21-OHD group were treated with either maintenance or stress dosing GC. Only one patient in the presumed NC-CAH 3β HSD group was being treated with GC. None of the subjects identified on retrospective review had undergone molecular testing.

Data from a similar size control group (n=14) consisting of children with PA were also reviewed (details not shown). Included in this group were the 4 children initially classified as NC-CAH 3βHSD. Twelve presented with premature pubarche pubic hair Tanner stage II-III, while two presented with a single complaint of excessive acne or early axillary hair growth. The average age of presentation was 6 years 9 months ± 1 year 5 months. Skeletal age advancement was 1 year 5 months ± 1 year. In all subjects DHEA sulfate and 17-OHP steroid concentrations were normal for pubertal/tanner stage consistent with the diagnosis of premature adrenarche and did not overlap with those in the NC-CAH groups.

### Table 2. Laboratory data of the four patients suspected of non-classic congenital adrenal hyperplasia 3-beta hydroxysteroid dehydrogenase (NC-CAH 3βHSD).

<table>
<thead>
<tr>
<th>n</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Steroid concentrations using older evaluation criteriaa,b,c</th>
<th>Steroid concentrations based using newer evaluation criteriaa,b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Δ5-17P / 17-OHP (ng/mL) 0' 60'</td>
<td>Δ5-17P/C (nmol/L) 0' 60'</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>T3 PH, acne</td>
<td>2.5 2.9</td>
<td>4.6 8.8</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>Acne</td>
<td>1.9 1.0</td>
<td>5.4 7.7</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>T3 PH</td>
<td>15.7 15.1</td>
<td>8.5 9.7</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>T2 PH, acne</td>
<td>20.3 20.7</td>
<td>10.0 11.5</td>
</tr>
</tbody>
</table>

T. Tanner staging, PH, pubic hair, 17-OHP; 5-17P, 17-hydroxyprogesterone; DHEA, dehydroepiandrosterone. To convert to Standard International units, multiply Δ5-17P, 17-OHP, DHEA and A by 0.03. To convert to metric units (ng/dL), multiply Δ5-17P and F by 33.1.

### Discussion

We reviewed the clinical presentation and diagnostic evaluation of 18 patients initially diagnosed with NC-CAH at our institution during the last decade. Within our large endocrine diagnostic group (n=10) we demonstrate heterogeneity in the diagnostic process. All patients, based on their late clinical presentation, were initially diagnosed as late-onset CAH or NC-CAH. Only eleven underwent ACTH stimulation testing. On our repeat assessment of their basal and ACTH- stimulated steroid concentrations we found one subject with steroid concentrations consistent with SV-CAH 21-OHD.13 Four patients initially diagnosed as NC-CAH 3βHSD had to be re-classified as having PA using newer diagnostic criteria. Finally, when treatment approaches were reviewed we found 13 subjects were treated with maintenance steroids, two with stress dose GC alone and three who were not treated at all. We suspect these variations in care are due to overlap in the clinical presentation of NC-CAH with PA and ovarian hyperandrogenism, non-adherence to the newer diagnostic criteria, and lack of confirmatory genetic testing.

The clinical presentation was similar in all subjects regardless of diagnosis, indicating that premature pubarche alone does not distinguish patients with NC-CAH from those with PA. Skeletal age determination was helpful. All subjects in the NC-CAH group had skeletal advancement of ±2 SDS for age whereas those subjects with PA on average had skeletal ages within 2 SDS of the mean, a finding consistent with previous reports.24,27 ACTH stimulation testing would have been helpful. Studies have shown basal 17-OHP to be a reliable screening tool for the diagnosis of late-onset 21-OHD5,8,15 but in instances where C-SV may be suspected, ACTH stimulation testing helps to differentiate between C-SV and NC-CAH. This distinction is important as long term treatment differs between these two groups. In our study, 4/7 subjects in the NC-CAH 21-OHD group had...
basal 17-OHP concentrations ≥ 3500 ng/dL (105 nmol/L) suggestive of C-SV.28 In these patients, ACTH stimulation testing may have been helpful to exclude this diagnosis. However, it was not done.

ACTH stimulation testing has also been shown to be helpful in the diagnosis of NC-CAH 3βHSD. In the last decade the diagnosis of NC-CAH due to 3βHSD has been optimized. Prior diagnostic criteria were based on elevated ACTH-stimulated Δ5-17P to 17-OHP or DHEA to Δ4-A ratios.9-12 However, when considered overlap in the hormone concentrations of subjects with and without mutations in the 3βHSD gene were found4,13,14 newer criteria were proposed.18 It was first suggested that ACTH stimulated Δ5-17P and Δ5-17P to C ratio more accurately predict 3βHSD deficiency.24 These data were refined by Mermejo et al providing hormone concentration cutoffs when the diagnosis of NC-CAH 3βHSD should be considered.19 These data should now be used as standard for the diagnosis for NC-CAH 3βHSD.

When the treatment choices were reviewed in our study, 13 children were treated with an average of 12 mg/m²/day of HC equivalent. Five were also treated with fludrocortisone. This variable approach is likely due paucity of long-term outcome data in this population. Although the recommendations are not clear as to when to treat with glucocorticoids, advancement of skeletal age and adult height protection are accepted indications. Use of stress dosing is advocated in NC-CAH when adrenal function is suboptimal or iatrogenically suppressed.1

There is significant overlap in the clinical presentation of patients with NC-CAH (21-OHD or 3βHSD) and PA. For that reason, we recommend using the laboratory cutoffs as outlined by Speiser et al in the Endocrine Society’s 2010 Clinical Practice Guidelines for the diagnosis of CAH.1 In addition, we advocate the use of a skeletal age film and a morning DHEA sulfate (Figure 1). DHEA sulfate is a useful screening test to exclude primary adrenal disorders.

To accurately differentiate between the types of NC-CAH, ACTH stimulation testing is needed. Basal and ACTH-stimulated concentrations of 17-OHP should be obtained during ACTH stimulation testing along with Δ5-17P and C. This will not only diagnose NC-CAH 21-OHD, but allow one to differentiate it from C-SV, and to also differentiate NC-CAH 3βHSD from PA. Special attention must be applied to NC-CAH 3βHSD to avoid false positives. ACTH-stimulated Δ5-17P concentrations ≥6678 ng/dL (201 nmol/L) and a Δ5-17P to C ratio ≥363 should be used for the diagnosis NC-CAH 3βHSD. On the other hand, ACTH-stimulated values of Δ5-17P ≤ 3,223 ng/dL (97 nmol/L) and a Δ5-17P to C ratio ≤122 should exclude this diagnosis. These laboratory cutoffs are generated from the lowest ACTH stimulated Δ5-17P concentrations and Δ5-17P to C ratios assessed in genotype-confirmed subjects, as well as the highest ACTH stimulated values from genotype-negative subjects.18,19 In our four patients with suspected NC-CAH 3βHSD, these diagnostic criteria would have effectively ruled out this disorder. A narrow range still exists between these cutoff values wherein the diagnosis remains unclear. For those subjects, we would recommend molecular testing to confirm or exclude the diagnosis of NC-CAH 3βHSD.

Although molecular testing is available for the diagnosis of the different adrenal enzyme deficiencies causing NC-CAH, these tests can not always be obtained. There is a high cost associated with genetic testing. Insurance coverage for genotyping is often lacking or

![Figure 1. Algorithm for the diagnosis of non-classic congenital adrenal hyperplasia (NC-CAH).](image-url)

**Screening Labs**

- Basal 17-OHP <200ng/dL (6nmol/L)
- DHEA-S normal

**Skeletal Age**

- Morning 17-OHP, DHEA-S
- Basal 17-OHP ≤ 200ng/dL (6nmol/L)
- DHEA-S elevated for pubertal stage

**DX: Premature adrenarche**

**BA ≤ 2 SDS for age**

- Basal 17-OHP <200ng/dL (6nmol/L)
- DHEA-S normal for pubertal stage

**BA ≥ 2SDS for age or**

- Basal 17-OHP >200ng/dL (6nmol/L)
- DHEAS normal or elevated for pubertal stage

**DX: Premature adrenarche**

**Standard dose**

- ACTH stimulation Testing
- Obtain 17-OHP

**DX: NC-CAH 21 OHD**

**DX: C-SV 21-OHD**

**Stimulated 17-OHP**

- < 1000ng/dL (31nmol/L)

**DX: Premature adrenarche**

**Stimulated 17-OHP**

- 1000-10,000ng/dL (31-300nmol/L)
- DX: NC-CAH 21 OHD

**Stimulated 17-OHP**

- >10,000ng/dL (300nmol/L)
- DX: NC-CAH 3βHSD

**DX: NC-CAH 3βHSD**

**Stimulated Δ5-17P ≥ 6678ng/dL (201nmol/L)**

**Δ5-17P/cortisol ≥363**

**DX: NC-CAH 3βHSD**

**Stimulated Δ5-17P ≤ 3233ng/dL (97nmol/L)**

**Δ5-17P/cortisol ≤122**

**DX: Premature adrenarche**

**BA= bone age, SDS= standard deviations, 17-OHP= 17-hydroxyprogesterone, DHEAS= dehydroepiandrosterone sulfate, Δ5-17P= 17-hydroxypregn-4-en-3-one, DX= Diagnosis**

**NC-CAH= Non-Classic Congenital Adrenal hyperplasia, C-SV= Classic simple virilizing, 21-OHD= 21-hydroxylase deficiency, 3βHSD= 3 beta hydroxysteroid dehydrogenase deficiency. **

**Criteria adapted from Luftlah, Mermejo, and Speiser et al.**
patients have very high co-payments preventing this testing to be used on a routine basis. Furthermore, patients may be apprehensive to participate in DNA studies. For these reasons, laboratory evaluation is still the primary means for diagnosis of these disorders in many situations.

The retrospective nature of this study resulted in some missing data. Because not all children underwent ACTH stimulation testing reclassification could not be done in all instances. Additionally, we can not confirm with certainty the diagnosis, as molecular analysis was not done. However, our reclassification methods were based on established diagnostic criteria and therefore likely represent an accurate diagnosis.

In conclusion, significant variations in care regarding the evaluation of NC-CAH exist. We have proposed a practical evaluation algorithm for the diagnosis of NC-CAH to help in the diagnosis of NC-CAH 21-OHD and eliminate erroneous classification of NC-CAH 3βHSD. In situations when the diagnosis is unclear, ACTH stimulation testing should be part of the workup. Genotyping should be attempted when the results of ACTH stimulation testing are equivocal or for the purposes of genetic counseling. Practitioners managing patients with NC-CAH should, in light of the more recent hormonal and genetic information and practice guidelines as well, review their previously made diagnoses, especially for patients with NC-CAH 3βHSD. Future studies are still needed to evaluate the long term outcomes for these disorders and to determine the best therapeutic strategies for this heterogeneous group of patients.

References


