HYPERTENSION ASSOCIATED WITH CONGENITAL ADRENAL HYPERPLASIA

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ABSTRACT

Background: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from the deficiency of one of the five enzymes required to synthesize cortisol, and hence, increased production of adrenocorticotropic releasing hormone (ACTH) which leads to adrenal hyperplasia. In 11β-hydroxylase and 17α-hydroxylase deficiencies, the accumulation of the mineralocorticosteroids or 11-deoxy-cortisol can lead to hypertension.

Design and settings: A retrospective, hospital based study, was conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, during the period January 1989 and December 2014.

Methods: Medical records of children who were diagnosed to have congenital adrenal hyperplasia were retrospectively reviewed. Data included age, sex, clinical presentation and results of the relevant laboratory and radiological investigations.

Results: During the period under review, 95 Saudi patients with CAH were diagnosed. Of these 76 (80%) were due to 21α-hydroxylase deficiency, 15 (15.8%) patients with 11β-hydroxylase deficiency, and 4 (4.2%) patients were due to 3β-hydroxysteroid dehydrogenase deficiency. Six (40%) patients with 11β-hydroxylase deficiency developed persistent hypertension during the course of follow-up.

Conclusion: Hypertension is common occurrence in congenital adrenal hyperplasia due to 11β-hydroxylase deficiency and should be considered in the differential diagnosis of hypertension.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from the deficiency of one of the five enzymes required to synthesize cortisol, figure 1. As a result increase production of adrenocorticotropic releasing hormone (ACTH) leads to adrenal hyperplasia. (Al Jurayyan 2015, Speicer & White 2003, Merke & Borstein 2005) More than ninety-percent of patients of CAH are due to a deficiency in the enzyme 21α-hydroxylase which is also associated with the production of excess androgen. Aldosterone deficiency may or may not be involved depending in the severity of the enzyme deficiency. 11β-hydroxylase deficiency is the second most common, accounts for about 10 percent of patients depending on the ethnic group and the geographic locations. Although somatic virilization and hypertension are considered the main feature of the disease, great variability in the clinical expression has been reported, with complete dissociation between the degree of enzyme deficiency and severity of the clinical manifestation. The other three enzyme deficiencies: 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and 20, 22 desmolase are rare. 17α-hydroxylase usually presents with hypertension. (Levine et al., 1980, Al Jurayyan 1995, Rosa et al., 2007, Simard et al., 2002, Metherel, 2009) Hypertension as a clinical problem in children has recently advances in our ability to identify, evaluate, and care for hypertension. These have led to an increase awareness of hypertension in modern management (Guideline, the Fourth Report on high BP, 2004). This report presents our experience over 25 years (January 1989 and December 2014) in a major teaching hospital in Riyadh, Saudi Arabia.

METHODS

During the period January 1989 and December 2014, 103 (95 Saudi and 8 non-Saudi) children with the diagnosis of congenital adrenal hyperplasia were seen in the Pediatric Endocrine Unit of the King Khalid University Hospital (KKUH) of the King Saud University, Riyadh, Saudi Arabia.
The diagnosis was suspected on clinical grounds and confirmed in all patients by demonstrating the appropriate biochemical findings. (Al Jurayyan, 2015). Records of all patients were retrospectively reviewed, and data extracted for analysis included, age, sex, clinical manifestations, relevant family history and results of all laboratory, and ancillary investigations performed. Details of management as well as outcome were also reviewed. For blood pressure, the normal value of task force on blood pressure control in children was used. The severity of the virilization of external female genitalia was rated according to Prader’s classification. (Prader, 1954)

RESULTS

There were 95 patients, 44 males and 51 females, with congenital adrenal hyperplasia (CAH), aged between newborns to 13 year of age. Of these, 76 (80%), 34 males and 42 females, were having CAH due to 21α-hydroxylase deficiency, with salt-wasting in 71 (93.4%) patients, 15 (7 males and 8 females) (15.8%) patients with 11β-hydroxylase deficiency, and only 4 (4.2%), three males and one female, were due to 3β-hydroxysteroid dehydrogenase deficiency, all salt-wasters. None of our patients were noted to have 17α-hydroxylase or 20, 22 desmolase deficiency. (Rosa, 2007, Simard et al., 2002, Metherel, 2009) Hypertension (HT) in children is usually defined as blood pressure consistently above the 95th percentile for age, sex and height of the child. Blood pressure should be measured with an appropriate sized pediatric cuff, with the child supine or sitting down. Renal or vascular causes are the commonest, but hypertension in younger children is almost always secondary unless otherwise proved. Endocrine hypertension per se is often asymptomatic in children, but signs of the underlying diseases may be evident, like features of Cushing’s syndrome, growth failure and pubertal abnormalities. Sustained severe hypertension in children can represent with headache, seizures, epistaxis, visual disturbance, unexplained cardiac and renal failure.

DISCUSSION

Congenital adrenal hyperplasia (CAH) is one of the common endocrine problems, encountered by the practitioner, in this part of the world due to increased prevalence of consanguineous mating. (Saedi-Wong et al., 1989) It is caused by reduced or complete absence of any of the enzymatic activity of the steroid biosynthesis pathway. The commonest enzyme deficiency is 21α-hydroxylase, followed by 11β-hydroxylase. Other rare enzyme deficiency may be due 3β-hydroxysteroid dehydrogenase or 17α-hydroxylase and 20, 22 desmolase. (Rosa, 2007, Simard et al., 2002, Metherel, 2009)

Patients were controlled on hydrochlorothiazide and amlodipine. There was clear dissociation between the clinical picture and severity of hypertension.

**Figure 1. Schematic structure for biosynthesis of adrenal cortex hormones (glucocorticosteroids, mineralocorticosteroids and sex steroid hormones)**

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Table 1. Distribution of 95 patients with CAH and enzyme deficiency

<table>
<thead>
<tr>
<th>Enzyme deficiency</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-α-hydroxylase</td>
<td>76</td>
<td>80</td>
</tr>
<tr>
<td>11-β-hydroxylase</td>
<td>15</td>
<td>5.8</td>
</tr>
<tr>
<td>3-β HSD</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Total of patients</td>
<td>95</td>
<td>100%</td>
</tr>
</tbody>
</table>

CAH – congenital adrenal hyperplasia
3βHSD – 3-β-hydroxysteroid dehydrogenase
* 71 patients were salt-wasters
** All patients were salt-wasters

Table 2. Clinical data of 15 patients with 11-β-hydroxylase deficiency congenital adrenal hyperplasia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Genitalia</th>
<th>Hypertension</th>
<th>Hypokalemia</th>
<th>11-deoxycortisol &lt;30nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.8 y</td>
<td>M</td>
<td>Precocious puberty</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>1 w</td>
<td>F</td>
<td>Ambiguous genitalia</td>
<td>-</td>
<td>-</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>12 w</td>
<td>M</td>
<td>Normal genitalia</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>12 y</td>
<td>F</td>
<td>Ambiguous genitalia P&lt;</td>
<td>+</td>
<td>+</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>4 y</td>
<td>M</td>
<td>Precocious puberty</td>
<td>+</td>
<td>+</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>3 y</td>
<td>M</td>
<td>Precocious puberty</td>
<td>+</td>
<td>+</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>Newborn</td>
<td>F</td>
<td>Ambiguous genitalia P&lt;</td>
<td>+</td>
<td>+</td>
<td>160</td>
</tr>
<tr>
<td>8</td>
<td>7 y</td>
<td>F</td>
<td>Mild virilization P&lt;</td>
<td>-</td>
<td>-</td>
<td>34</td>
</tr>
<tr>
<td>9</td>
<td>5 y</td>
<td>F</td>
<td>Mild virilization P&lt;</td>
<td>-</td>
<td>-</td>
<td>181</td>
</tr>
<tr>
<td>10</td>
<td>Newborn</td>
<td>M</td>
<td>Normal genitalia</td>
<td>-</td>
<td>-</td>
<td>123</td>
</tr>
<tr>
<td>11</td>
<td>1 m</td>
<td>F</td>
<td>Ambiguous genitalia P&lt;</td>
<td>-</td>
<td>-</td>
<td>78</td>
</tr>
<tr>
<td>12</td>
<td>1 m</td>
<td>M</td>
<td>Moderate virilization P&lt;</td>
<td>-</td>
<td>-</td>
<td>58</td>
</tr>
<tr>
<td>13</td>
<td>3 y</td>
<td>F</td>
<td>Mild virilization P&lt;</td>
<td>+</td>
<td>+</td>
<td>164</td>
</tr>
<tr>
<td>14</td>
<td>1 y</td>
<td>F</td>
<td>Mild virilization P&lt;</td>
<td>+</td>
<td>+</td>
<td>81</td>
</tr>
<tr>
<td>15</td>
<td>2 y</td>
<td>M</td>
<td>Precocious puberty</td>
<td>-</td>
<td>-</td>
<td>38</td>
</tr>
</tbody>
</table>

w – week; m – month; y – year; m – male; f – female
Prader classification for virilization of the external female genitalia; P = potassium level > 3.5, < 3 mmol/L +, < 3 mmol/L ++

(Bhavani, 2011) Biglieri and associate have described a syndrome were defective 17-α-hydroxylase is present in the adrenal and gonads. The resultant low levels of cortisol, acting via the negative feedback mechanism, stimulate ACTH i.e. ease with subsequent bilateral hyperplasia and excessive secretion of corticosterone and deoxycorticosterone. These in turn CAH due to 17-hydroxylase deficiency is associated with hypertension and excess of deoxycorticosterone (DOC) which is the second most common naturally occurring mineralocorticoid after aldosterone. DOC excess typically is associated with hypertension, hypokalemia and renin and aldosterone suppression. Cause sodium retention, potassium loss and as a result hypertension and hypokalaemicalkosis. Renin levels are also suppressed. (Cerame & New, 2000, Wranock 2000) In the presence of 11-β-hydroxylase deficiency, defective cortisol secretion lead to a secondary elevation of ACTH and to bilateral adrenal hyperplasia. In addition, there are high circulating levels of 11-deoxycorticisol and deoxycorticosterone. (White, 2001)

The variability in the clinical and biochemical findings, however, could be due to different genetic mutations. Also, it is tempting to say that increased tissue sensitivity to DOC, or the presence of the metabolites such as 18-OH DOC with none marked mineralocorticoid activity is responsible for hypertension. (AJ Jurayyan, 1995) Although, we do not have any patient with 17-α-hydroxylase deficiency, it is rare and accounts to less than one percent of all cases of CAH. The gene for this enzyme has been mapped to chromosome 10 and mutations, are common in Duch Mennonites.

17-α-hydroxylase is the enzyme which converts pregnenolone and progesterone to 17-hydroxy pregnenolone and 17-hydroxy progesterone, respectively. When this enzyme is deficient, 17 deoxy steroids are produced in excess leading to increased serum concentrations of DOC and corticosterone which have mineralocorticoid activity. So renin is suppressed and aldosterone levels are decreased and patients have hypotension and hypokalaemia. But since the precursors cannot enter the androgenic pathway as well, the males with 46 XY chromosomes have under virilization in uterus, leading to genital ambiguity, at puberty they develop gynaecomastia due to unknown reasons. Females with 46XX constitution have no ambiguity, but have sexual infantilism at puberty. Elevated levels of 17-deoxysteroids such as progesterone, pregnenolone, DOC and corticosterone in the plasma establish the diagnosis. (Bhavani, 2011, Cerame and New 2009, Scaroni et al, 1994)

Conclusions

Although, endocrine causes of hypertension are still rare in children, excess levels and/or action of mineralocorticosteroids associated with low renin levels inCAH can lead to the right diagnosis.

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REFERENCES


