Normotensive, Normokalemic Hyperaldosteronemia of a Grown-up Woman Diagnosed as Salt-Losing 21-Hydroxylase Deficiency in Neonatal Period

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Abstract
A woman in her mid-30’s with salt-losing 21-hydroxylase deficiency diagnosed in neonatal period had been supplemented gluco- and mineralo-corticoids before she quit the regimen because of steroid-induced obesity. After quitting, she was referred to the author. Review of endocrine records in preceding two years revealed hyper-reninemic hyperaldosteronism without hypertension and hypokalemia. Because of stubborn refusal to continue the supplementation of gluco- and mineralo-corticoids, she was allowed to be off the supplementation for two months after possible consequences were explained. When she returned two months later, she was normotensive and normokalemic in the face of hyperaldosteronemia. Since then up to the present, she has been free of gluco- and mineralo-corticoids on days not portend physical or psychosocial stress. She has maintained normotension and normokalemia. Overproduction of progesterone and 17α-hydroxyprogesterone, known to have anti-aldosterone activity, appears responsible for hyper-aldosteronemia and apparent aldosterone refractoriness of this patient.

Keywords: 21-hydroxylase deficiency; Aldosterone; Cortisol; Progesterone; 17-hydroxyprogesterone

Background
Almost three decades have elapsed since congenital adrenal hyperplasia was included in neonatal screening program in Japan. Many patients with this disorder supposedly have reached adulthood. Problems related to care transfer from pediatric endocrinologists were recently reviewed by Auchus RJ, et al. [1], who wrote the goal of mineralocorticoid replacement [for grownup patients with salt-losing 21-hydroxylase deficiency (21-OHD)] is to maintain plasma renin activity as low as possible without causing hypertension, hypokalemia, orthostatic hypotension, or salt craving [sic]. As for mineralocorticoid supplementation in adult patients with 21-OHD, the panel of the recent diagnostic and management guideline of The Endocrine Society write as follows: the optimal dose of Fludrocortisones (FC) supplementation in adult patients with 21-OHD has not been critically studied; most non-hypertensive adults with 21-OHD benefit from continued mineralocorticoid treatment; maintenance treatment of FC of 0.05 to 0.2 mg per day is suggested [2].

Case Presentation
The patient with 21-hydroxylase deficiency (vide infra) was 34 years old when her endocrine care was asked by a pediatric endocrinologist of her childhood. He had treated the patient with varying doses of Hydrocortisone (HC) and FC until her care was transferred to an endocrinologist at the age of 32 years. Then, she had been supplemented with varying doses of Dexamethasone and FC in subsequent two-year period (vide infra) before she quit his care because of being intolerant of steroid-associated obesity. She returned to the pediatric endocrinologist, who asked the author to take over her care. At the time of the transfer to the author, the patient brought to the second document, data of blood tests related to corticosteroids and mineralocorticoids included in two sets of documents, i.e., narrative summary of an endocrine history of 32 years from her neonatal period by the pediatric endocrinologist and data sheets of subsequent two years under the second endocrinologist's care.

In the first document, following items were depicted: she was born with a weight of 2,420 grams with ambiguous genitalia; her serum sodium concentration was 121, 125 mEq/L and potassium 5.4 ~ 8.0 meq/L two weeks after birth; a gas chromatographic study of urinary steroids was reportedly consistent with 21-hydroxylase deficiency. In the second document, data of blood tests related to corticosteroids and mineralocorticoids had been recorded in a chronological order. The author re-arranged these data in reference to corticosteroid regimens in five periods 1 through 5 (Table 1). From Table 1 it was learned that ACTH level was brought in the recommended range of the guideline of 21-OHD management [1] in Period 5 where in regimen of dexamethasone 0.875 mg/day without FC was employed. Normokalemia had been maintained in the presence of high plasma renin activities and normal or high aldosterone levels by supplementation with either 0.025 or 0.05 μg of FC per day in Periods.
Table 1: Selected Electrolyte and Endocrine Data in Five Periods Treated with Varying Combination of Hydrocortisone, Dexamethasone, and Fludrocortisone.

<table>
<thead>
<tr>
<th></th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>Period 5</th>
<th>Reference ranges**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period (dates)</td>
<td>(~09/7*)</td>
<td>(09/8 ~ 10/5)</td>
<td>(10/6 ~ 10/10)</td>
<td>(10/10 ~ 11/1)</td>
<td>(11/2 ~ 11/7)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>0.835</td>
<td>0.9</td>
<td>0.9</td>
<td>0.875</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td></td>
<td>475</td>
<td>114</td>
<td>33.9</td>
<td>16.3</td>
<td>7.9</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.025</td>
<td>0.025</td>
<td>7.2 - 63.3</td>
</tr>
<tr>
<td>Cortisol (μg/dl)</td>
<td>2</td>
<td>1.6</td>
<td>1</td>
<td>1</td>
<td>1.2</td>
<td>4.5 - 21.1</td>
</tr>
<tr>
<td>17-OH progesterone (ng/ml)</td>
<td>310</td>
<td>320</td>
<td>17</td>
<td>n.m.</td>
<td>n.m.</td>
<td>0.2 - 4.5</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>1.2</td>
<td>6.4</td>
<td>2.4</td>
<td>2.7</td>
<td>5</td>
<td>0.3 - 4.0</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>19.2</td>
<td>41.8</td>
<td>10.8</td>
<td>13.8</td>
<td>23.9</td>
<td>3.0 - 15.9</td>
</tr>
<tr>
<td>Aldosterone/renin ratio†</td>
<td>16.0</td>
<td>6.5</td>
<td>4.5</td>
<td>5.1</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>3.9</td>
<td>4.2</td>
<td>4.0</td>
<td>4.6</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

Blood samples were drawn after the subject being kept in supine position for 30 minutes.

*Arabic figures of periods 1 through 5, e.g., 09/7 designates July, 2009.

**provided by B.M.L., Saitama, Japan, †, ng/dl divied by ng/ml/h.

Abbreviation: not measured for cancellation of the release of 17-OH progesteron assay kit (September, 2010).

Studies of chemistry and hormone of blood and urine were repeated twice (Table 2, Periods 8 and 9). The results of electrolytes and creatinine of this period were similar to those of other periods. An arterial gas analysis revealed pH 7.40, pO₂ 93 mmHg, pCO₂ 35.6 mmHg, and bicarbonate 21.7 mmol/l. (obtained between period 6 and period 7). In this period, urine was acidic and urine showed positive anion gap (Table 2), an indirect measure of ammonium ion in urine [3].

The measurements of ACTH, plasma rennin activity, plasma aldosterone concentration, urinary concentrations of cortisol and aldosterone were performed by Biomedical Laboratory (BML, Saitama, Japan).

Discussion

Although the account of her neonatal period is suggestive of salt wasting 21-OHD, her current phenotype appears consistent with simple virilizing 21-OHD. The gene analysis of CYP21A2 has not been done.

In this patient, cortisol levels and urinary excretion of cortisol of this patient were in low-normal range in periods 6 and 7 (Table 2). Her cortisol production has apparently ameliorated modestly by overproduction of ACTH over many years. As the secretory rate of aldosterone is three-order magnitude less than that of cortisol, i.e. 1.5-12.5 μg/day (excretion rate, without salt restriction) [4] vis. 9.9 ± 2.7 mg/day (production rate) [5], the recovery of aldosterone production could be understood. Another explanation of aldosterone production in patients with 21-OHD is provided by Gomes and coworkers [6], i.e. aldosterone is synthesized from 21-hydroxylation of progesterone (not from 17-OHO) by hepatic enzymes, CYP2C19 and CYP3A4, though less efficiently than CYP21A1, in five children with 21-OHD.

Despite hyperaldosteronemia and hyperaldosteronuria, she had neither hypertension nor hypokalemia. Serum aldosterone levels and urinary excretion of aldosterone were more than the reference values in recent years (Table 2). An arterial gas analysis revealed...
compensated mild metabolic acidosis. Acidic urine and positive urine anion gap were against distal renal tubular acidosis. Hence, hyperaldosteronism reportedly associated with distal renal tubular acidosis [7] is unlikely responsible in this patient. During pregnancy, elevated plasma renin activity [8,9] and increase in plasma levels of progesterone and aldosterone [10,11] have been known. The patient's plasma renin activity and levels of aldosterone and progesterone were elevated to the similar magnitude as those described in the literature [11]. Antagonistic activity of progesterone and 17-OHP against aldosterone receptor is shown in COS-7 cells, a cell line derived from African green monkey kidney, transfected with human mineralocorticoid receptor DNA [12]. Development of hypertension and hypokalemia appears to be prevented by overproduction of 17-OHP and progesterone.

Development of adrenal adenoma manifested by Cushing syndrome was reported in a young woman with late onset of 21-OHD, who had been treated as polycystic ovary syndrome without supplementation of glucocorticoid and mineralocorticoid [13]. If serum cortisol and aldosterone levels of this patient further increase, the image study of the adrenals would be necessary. The long-term outcome of persistent amenorrhea conceivably attributable to unsuppressed progesterone production needs to be clarified.

Though she has been not supplemented with glucocorticoid and mineralocorticoid unless she foresees physical or psychosocial stress, she is provided with several days' supply of hydrocortisone in case of need and instructed to carry medical alert card depicting the diagnosis as well as treatment at acute care facilities.

**Conclusion**

An adult woman with salt-losing 21-OHD diagnosed in neonatal period remained normotension and normokalemia without glucocorticoid and mineralocorticoid supplementation in the face of hyper-reninenia and hyperaldosteronemia suggestive of aldosterone resistance presumably resulting from unsuppressed progesterone secretion. Long-acting glucocorticoid of a dose sufficient to suppress secretion of ACTH, progesterone and 17-OHP could partially ameliorate renal and aldosterone secretion in a tradeoff of intact menstruation and steroid-induced obesity. Optimal treatment of 21-OHD of grown-up remains to be a difficult issue.

**Declaration of Interest and Funding**

The author declares that there is no conflict of interest. The author is the patient's current attending endocrinologist. Dr. Takuma Kondo referred the patient and provided endocrine data since neonatal period. Endocrine data in two-year period prior to the patient's first clinic visit were collected by Dr. Hiroyuki Koshiyama. Both of them granted use of their data in this paper. This research did not receive any specific grant from any funding agency of commercial or non-profit sector.
Patient’s Consent

The patient has submitted written informed consent to publish this observation after reading translated version of the manuscript.

References


