The Etiologies of Adrenal Insufficiency in 73 Thai Children: 20 Years Experience

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Background: Adrenal insufficiency (AI) is an event caused by an inadequate secretion or action of adrenal hormones. It can be classified as primary (1°) and secondary (2°). AI may result in severe morbidity and mortality when undiagnosed or ineffectively treated.

Objective: To determine the etiologies of AI in Thai children

Material and Method: Data of children with AI presented to the authors’ pediatric endocrine service between 1982 and 2002 (20 years) were retrospectively collected and analyzed.

Results: AI was diagnosed by clinical and laboratory data in 73 children (31 boys and 42 girls). Sixty-two (84.9%) patients had 1° AI while 11 (15.1%) had 2° AI. The majority of patients with 1° AI (87.1%) were diagnosed with congenital adrenal hyperplasia (CAH). Other causes of 1° AI were uncommon such as ACTH unresponsiveness (4.8%) and no definite diagnosis (8.1%). Most children with 1° AI presented with hyperpigmentation. Causes of 2° AI were as follows: panhypopituitarism (63.6%), isolated ACTH deficiency (9.1%), and low birth weight (27.3%).

Conclusion: In the present study, CAH was the most common cause of 1° AI while panhypopituitarism was the most common cause of 2° AI. Other causes of AI were quite uncommon. Definite causes of AI have not yet been identified in some children. Further clinical observation and special tests including molecular studies in these children are warranted for diagnostic and prognostic importance.

Keywords: Adrenal insufficiency, Children, Etiologies, Congenital adrenal hyperplasia

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Degree of AI by Perry et al at the Sainte-Justine Hospital, Montreal, Canada showed that CAH was the most frequent cause of 1° AI(1). A report of 16 patients by Simm et al. showed that autoimmune adrenal insufficiency and adrenal hypoplasia congenita were the most common causes of 1° AI(2).

The present review will illustrate the etiologies of both 1° and 2° AI in children who presented with signs and symptoms of AI to the Department of Pediatrics, Siriraj Hospital over 20 years. The author will further discuss clinical presentation of these children with AI in detail.

Material and Method

Data of children who presented with signs and symptoms of AI to the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand for a period of 20 years (1982-2002) were retrospectively collected. Clinical presentation and laboratory data were reviewed. Children presented with hyperpigmentation, hypoglycemia were determined to have GC deficiency, while children presented with hyponatremia, hyperkalemia and metabolic acidosis were determined to have MC deficiency. Since nausea, vomiting, abdominal pain, weakness, or hypotension can be associated with either GC or MC deficiency, they were not used to classify types of deficient adrenal hormones.

Results

Seventy-three children diagnosed with AI (31 boys and 42 girls) were included. Among children with AI, 62 (84.9%) had 1° AI while 11 (15.1%) had 2° AI.

1° adrenal insufficiency (n = 62) (Table 1)

Among children with 1° AI, 54 (87.1%) were diagnosed with CAH while three (4.8%) were diagnosed with ACTH unresponsiveness. However, five (8.1%) patients with 1° AI did not have final diagnoses.

All children with CAH presented with mixed GC and MC deficiency. Children with ACTH unresponsiveness presented with GC deficiency alone. Poor weight gain, hyperkalemia, metabolic acidosis and skin hyperpigmentation were the most common signs and symptoms (>90%) in children with 1° AI (Fig. 1).

Congenital adrenal hyperplasia (CAH)

Fifty-four children were diagnosed with CAH (21-OH deficiency in 53 and lipoid CAH in one). All patients with CAH presented with salt-losing. The diagnosis of 21-OH deficiency was confirmed by elevated serum 17-OH progesterone either randomly or after 250 mcg ACTH stimulation tests. All girls with 21-OH deficiency presented with ambiguous genitalia. The patient with lipoid CAH had female genitalia and bilateral palpable gonads at inguinal area. Chromosome study revealed 46, XY. 250 mcg ACTH stimulation test revealed low levels of all adrenal hormones.

ACTH unresponsiveness (n = 3)

Familial glucocorticoid deficiency (FGD) (n = 2)

Two children were clinically diagnosed FGD. They were siblings (1 girl and 1 boy). Both presented with recurrent hypoglycemic seizures and darkening of skin at 1.5 years of age in the boy and 2 5/12 years of age in the girl. Both had inadequate cortisol response after 250 mcg ACTH stimulation tests and during hypoglycemic crisis. The girl and the boy were followed-up until 21 8/12 and 19 8/12 year old. They entered puberty normally and had normal pubertal progression.

Triple A syndrome (n = 1)

A 9 10/12 year old boy had classic triads of Allgrove syndrome, which were alacrima, achalasia, and presumably ACTH unresponsiveness. He presented at 3 months old with hyperpigmentation, frequent vomiting, drowsiness, fever and diarrhea. Serum ACTH was high (430 pg/ml) and there was no rising of serum cortisol during hypoglycemic episodes. Alacrima was found at 2 years after initial presentation. Achalasia was diagnosed by Barium swallow- ing after 8 years of initial presentation.

No definite causes (n = 5) (Table 3)

The definite diagnoses were not made in five children (4 boys, 1 girl) with 1° AI. Hyperpigmentation was observed in each individual. The mean age of onset was 9.0 ± 3.6 years. Possible diagnoses are shown in Table 3.

Fig. 1 Clinical signs and symptoms of children with 1° AI at initial presentation
Three boys presented with only GC deficiency at 5, 7, and 10 years of age whereas another 5 year-old boy presented with combined GC and MC deficiency. A one-month-old girl who presented with both GC and MC deficiency had a history of multiple consanguinity and infant death in her family.

2° adrenal insufficiency (n = 11) (Table 2)

Causes of 2° AI in the presented patients were panhypopituitarism (63.6%), isolated ACTH deficiency (9.1%) and low birth weight infants (27.3%). All children with 2° AI presented only with GC deficiency. Hypoglycemia and drowsiness were the most common presenting signs and symptoms (100%) in children with 2° AI (Fig. 2).

Panhypopituitarism (n = 7)

Panhypopituitarism was the major cause of 2° AI (66.7%). Magnetic resonance imaging of pituitary glands and brain showed septo-optic dysplasia in three, pituitary aplasia or hypoplasia in three, and frontonasal meningoencephalocele in one.

Isolated ACTH deficiency (n = 1)

A boy (age 6 5/12 years) first presented at 2 3/13 years old with hypoglycemic seizure. No rising of serum cortisol was observed during hypoglycemic episodes. No hyperpigmentation was noted. Growth hormone response to hypoglycemia was normal. The patient had normal growth and thyroid function. MRI of the pituitary gland was normal.

Immaturity of hypothalamic-pituitary-adrenal axis (HPA axis) in preterm infants (n = 3)

Two preterm boys (born at 28 and 36 weeks) presented with neonatal hypoglycemia at the second day of life, which lasted for 3 and 4 weeks. They had no micropenis or prolonged jaundice. Their serum

Table 1. Etiologies, types of adrenal hormone deficiency, age of onset and age at diagnosis of 62 children with 1° AI

<table>
<thead>
<tr>
<th>Causes of 1° AI</th>
<th>n</th>
<th>%</th>
<th>(Age of onset mean ± SD)</th>
<th>Age at diagnosis (mean ± SD)</th>
<th>GC def alone</th>
<th>MC def alone</th>
<th>GC + MC def</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAH</td>
<td>54</td>
<td>87.1</td>
<td>32.3 ± 66.4 days</td>
<td>61.1 ± 46.9 days</td>
<td>-</td>
<td>-</td>
<td>54</td>
</tr>
<tr>
<td>21-OH deficiency</td>
<td>53</td>
<td>85.5</td>
<td>52.3 ± 51.2 days</td>
<td>120.9 ± 111.8 days</td>
<td>-</td>
<td>-</td>
<td>53</td>
</tr>
<tr>
<td>Lipoid hyperplasia</td>
<td>1</td>
<td>1.6</td>
<td>14 days</td>
<td>30 days</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>ACTH unresponsiveness</td>
<td>3</td>
<td>4.8</td>
<td>1.9 ± 0.5 years</td>
<td>2.3 ± 1.1 years</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Familial GC deficiency</td>
<td>2</td>
<td>3.2</td>
<td>2.0 ± 0.7 years</td>
<td>2.5 ± 1.5 years</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Allgrove syndrome</td>
<td>1</td>
<td>1.6</td>
<td>1.7 years</td>
<td>1.9 years</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>8.1</td>
<td>9.0 ± 3.6 years</td>
<td>11.1 ± 3.5 years</td>
<td>2</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

GC = glucocorticoid, MC = mineralocorticoid, def = deficiency

Table 2. Etiologies, age of onset and age at diagnosis of 11 children with 2° AI

<table>
<thead>
<tr>
<th>Causes of 2° AI</th>
<th>n</th>
<th>%</th>
<th>Age at onset (mean ± SD)</th>
<th>Age at diagnosis (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panhypopituitarism</td>
<td>7</td>
<td>63.6</td>
<td>1.9 ± 1.4 years</td>
<td>3.4 ± 2.0 years</td>
</tr>
<tr>
<td>Septo-optic dysplasia</td>
<td>3</td>
<td>27.3</td>
<td>1.3 ± 1.9 years</td>
<td>1.5 ± 1.9 years</td>
</tr>
<tr>
<td>Pituitary hypoplasia</td>
<td>3</td>
<td>27.3</td>
<td>1.3 ± 1.1 years</td>
<td>3.0 ± 3.5 years</td>
</tr>
<tr>
<td>Frontomeningocoele</td>
<td>1</td>
<td>9.1</td>
<td>0.5 months</td>
<td>0.7 months</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>3</td>
<td>27.3</td>
<td>2 ± 1 days</td>
<td>18 ± 6 days</td>
</tr>
<tr>
<td>Isolated ACTH deficiency</td>
<td>1</td>
<td>9.1</td>
<td>2.3 years</td>
<td>2.3 years</td>
</tr>
<tr>
<td>No.</td>
<td>Sex</td>
<td>Age of onset (years)</td>
<td>Age now (years)</td>
<td>Signs and symptoms at presentation</td>
</tr>
<tr>
<td>-----</td>
<td>-------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Female</td>
<td>1 month</td>
<td>4 4/12</td>
<td>Hyperpigmentation, poor weight gain, alteration of consciousness, seizure</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>5 years</td>
<td>15 3/12</td>
<td>Hyperpigmentation, poor weight gain, alteration of consciousness</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>7 years</td>
<td>19 4/12</td>
<td>Hyperpigmentation, poor weight gain, alteration of consciousness, seizure</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>5 years</td>
<td>13 9/12</td>
<td>Hyperpigmentation, poor weight gain, alteration of consciousness, seizure</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>10 years</td>
<td>20 9/12</td>
<td>Hyperpigmentation, poor weight gain</td>
</tr>
</tbody>
</table>
cortisol levels were low during hypoglycemic episodes. Glucocorticoid replacement were started and then discontinued at 3.8 months and at 2.6 years of age. One boy had 1 mcg ACTH stimulation test done after discontinuation of glucocorticoid. Serum cortisol response was normal. Both children grew normally (until 7 months and 4 2/12 years old) with no signs and symptoms of hypoglycemia. Both had normal thyroid function tests.

A girl (2 5/12 yr old) presented with neonatal hypoglycemia at the third day of life. She was a near term SGA infant. Hypoglycemia persisted for 4 weeks. Her serum cortisol was low during one hypoglycemic episode. Glucocorticoid replacement was started with complete resolution of hypoglycemia. She had normal growth and development with normal thyroid function. MRI of the pituitary gland was normal. She was still on a maintenance dose of glucocorticoid at the age of 2 5/12 years.

Discussion

In the authors’ 20-years-experience retrospective study, the authors have demonstrated that 21-OH deficiency CAH was the most common cause of $1°$ AI (87.1%) while panhypopituitarism was the most common cause of $2°$ AI (63.3%).

In the present study, all patients with CAH presented with adrenal crisis and high serum 17-OH progesterone either during crisis or after 250 mcg ACTH stimulation test. They were all identified as classical salt wasting form of 21-OH deficiency except one patient who was diagnosed with lipoid CAH. The mean age of diagnosis of 21-OH deficiency CAH was at 4 months of age while the mean age of onset of signs and symptoms was at almost 2 months of age. The diagnosis could have been made earlier by newborn CAH screening, which is unavailable in Thailand.

12.9% of the presented patients with $1°$ AI were diagnosed with non-CAH causes, which were familial glucocorticoid deficiency (FGD) in two siblings, Triple A syndrome in one. The definite diagnoses were not made in 8.1% of patients with $1°$ AI.

The present findings are quite similar to the previous study by Perry et al who reported that CAH was the most common cause of $1°$ AI in children (71.8%) while 6% of their patients did not have definite diagnoses.

Triple A or Allgrove syndrome, a rare cause of $1°$ AI was diagnosed in a boy who presented with classic triads consisting achalasia, alacrima and ACTH-resistant adrenal insufficiency. Achalasia is usually the initial symptom that brings the patient to medical attention. Interestingly, our patient initially presented with $1°$ AI at a very young age (3 months). Alacrima and achalasia appeared much later. AAAS gene localized at 12q13 is responsible for this disorder. The product of this gene is called ALADIN (Alacrima-Achalasia-adrenal Insufficiency-Neurological disorder) protein.

The diagnosis of FGD was made in a pair of siblings (a boy and a girl). Both presented with recurrent hypoglycemic seizures and hyperpigmentation. Both of them were proved to have cortisol deficiency without MC deficiency. FGD is an autosomal recessive disorder in which unresponsiveness to ACTH leads to deficient secretion of cortisol. Although the authors did not perform a molecular analysis of ACTH receptor gene, the authors made a diagnosis based on clinical presentation, the history of two affected siblings and the evidence of cortisol deficiency without MC deficiency. Since MC production is mainly regulated by the renin-angiotensin-aldosterone system, it is rarely affected. Mutation of the ACTH receptor is responsible for this condition.

Among children with $1°$ AI whom the final diagnosis could not be determined (8.1%), based on clinical presentation and clinical course of each patient, the authors speculated that their differential diagnoses could be autoimmune adrenalitis, adrenal leukodystrophy (ALD), adrenal hypoplasia congenita (AHC), and FGD.

Autoimmune adrenalitis can be an isolated entity or a part of an autoimmune polyendocrinopathy syndrome (APS). It was suspected in patient no. 2, 3, and 5 who presented with $1°$ AI with or without signs of MC deficiency. Circulating autoantibodies against side-chain cleavage enzyme (SCC) and 17α-hydroxylase are relatively specific for APS patients. However, these biochemical markers are not widely available in Thailand.

X-linked adrenoleukodystrophy (ALD) was highly suspected in a boy (patient no. 4) since he had $1°$ AI and progressive neurological impairment. Mutations have been found in the ALD gene encoding a membrane transport protein, which is involved in the import of VLCFA coenzyme A synthetase into the peroxisome. ALD is associated with demyelination of the central or peripheral nervous system with or without A110. MRI of the brain should be worthwhile in this particular patient to evaluate the presence of cerebral white matter disease. Since $1°$ AI may precede neurological function, X-linked ALD cannot be totally excluded in patient no. 2, 3, and 5.
AHC should be considered in a girl (patient no.1) and a boy (patient no.2) since both presented with combined GC and MC deficiency (salt wasting) during infancy and childhood. AHC is a rare inherited disorder that occurs in two distinct forms: X-linked and autosomal recessive. The X-linked recessive form is characterized by lack of the permanent adult cortical zone\(^{(12)}\) whereas, the autosomal recessive form is characterized by small adrenal glands composed almost entirely of permanent cortex with normal histology\(^{(13)}\). Patients frequently developed salt wasting and GC deficiency during infancy but these can present later in life\(^{(14)}\).

FGD should be considered in two boys (patient no. 3 and 5) who presented with hyperpigmentation, hypoglycemia due to hypocortisolemia without signs of MC deficiency. The details of FGD were discussed earlier.

In the present study, panhypopituitarism associated with structural brain anomalies was the most common cause of \(1^\circ\) AI. In contrast, previous data suggested that abrupt discontinuation of glucocorticoid therapy was the most common cause of \(2^\circ\) AI\(^{(15)}\). This observed difference could be accounted for by the limited numbers of the presented patients with \(2^\circ\) AI together with the fact that children with mild non-specific symptoms of AI may not come to medical attention.

Isolated ACTH deficiency, a very rare disorder was suspected in a boy who presented with hypocortisolism without any hyperpigmentation or electrolyte disturbance. Unfortunately, serum ACTH was not performed in this patient. During the follow up period, he did not have evidence of other pituitary hormone deficiencies. Clinical onset of isolated ACTH deficiency can vary from just after birth to 8 years of age\(^{(16)}\).

Three low birth weight (LBW) infants were diagnosed with immaturity of hypothalamic-pituitary adrenal axis. All of them required glucocorticoid treatment for the treatment of hypoglycemia. Glucocorticoid replacement was discontinued in two patients without any recurrence of hypoglycemia. Weaning of glucocorticoid treatment should be considered in the other patient. In premature infants, HPA axis is relatively hypoactive when compared to full-term infants. Pituitary ACTH response to stress may be immature. Moreover, the sensitivity of the adrenal glands to ACTH may be reduced in preterm infants\(^{(17)}\). All of these increase risks of hypoglycemia after birth.

In summary, CAH was the most common cause of \(1^\circ\) AI while panhypopituitarism was the most common cause of \(2^\circ\) AI in the present study. The other causes of AI were relatively rare. Determination of definite causes of AI can be a great challenge to physicians. Clinical observation and special tests including biochemical and molecular studies in children with unidentified causes of AI are warranted for diagnosis and prognostic importance.

References

สาเหตุของการต่อมหมวกไตทำงานน้อยในเด็กไทย 73 ราย: ประสบการณ์ 20 ปี

ประพารัตน์ โอสุวรรณรัตน์, สาโรช นิมกาญจน์, สุภาวดี ลิขิตมาศกุล, จีรันดา สันติประภพ, ไพรัลยา สวัสดิพานิช

ภูมิหลัง: การต่อมหมวกไตทำงานน้อยเป็นภาวะผิดปกติที่เกิดจากต่อมหมวกไตหลั่งฮอร์โมนออกมาไม่พอป้องกันภาวะต่อต้านการแข่งขันหรือฮอร์โมนที่หลั่งออกมาไม่สามารถออกฤทธิ์ได้ตามปกติ การต่อมหมวกไตทำงานน้อยแบ่งออกเป็นชนิดปฐมภูมิ(เกิดจากความผิดปกติของต่อมหมวกไต, 1°) และทุติยภูมิ(เกิดจากความผิดปกติของไฮโปทาลามัส และ/หรือต่อมใต้สมอง, 2°)

วัตถุประสงค์: เพื่อประเมินสาเหตุของการต่อมหมวกไตทำงานน้อยในผู้ป่วยเด็กไทย

วิสัยและวิธีการ: เป็นการศึกษาและวิเคราะห์ข้อมูลของผู้ป่วยเด็กที่มีอาการแสดงของการต่อมหมวกไตทำงานน้อยที่มารับการตรวจรักษาที่ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ตั้งแต่ปี พ.ศ. 2525-2545 (20 ปี)

ผลการศึกษา: มีผู้ป่วยเด็ก 73 ราย (เด็กชาย 31 ราย เด็กหญิง 42 ราย)ได้รับการวินิจฉัยว่ามีการต่อมหมวกไตทำงานน้อย โดยพบว่าการต่อมหมวกไตทำงานน้อยอยู่ในระดับ 62 ราย (84.9%) มีการต่อมหมวกไตทำงานน้อยชนิดปฐมภูมิ ขณะที่ 11 ราย (15.5%) มีการต่อมหมวกไตทำงานน้อยชนิดทุติยภูมิ ผู้ป่วยที่มีภาวะต่อมหมวกไตทำงานน้อยชนิดปฐมภูมิ พบในหน่วย (87.1%) เกิดจาก CAH สาเหตุที่พบบ่อย 4.8% พบ ACTH unresponsiveness 8.5% และที่ไม่ทราบสาเหตุ 8.5% ผู้ป่วยมีภาวะต่อมหมวกไตทำงานน้อยชนิดปฐมภูมิ พบในเด็กทารกที่มีน้ำหนักต่ำกว่า 2.5 กก. ผู้ป่วยที่มีภาวะต่อมหมวกไตทำงานน้อยชนิดทุติยภูมิมีดังนี้ panhypopituitarism (63.6%), Isolated ACTH deficiency (9.1%) ทำให้เกิดอาการรวมถึงการต่อมหมวกไตทำงานน้อย 27.3%

สรุป: ในกรณีศึกษา CAH เป็นสาเหตุที่พบบ่อยที่สุด ในผู้ป่วยที่มีภาวะต่อมหมวกไตทำงานน้อยชนิดปฐมภูมิ ซึ่ง panhypopituitarism เป็นสาเหตุที่พบบ่อยที่สุดของการต่อมหมวกไตทำงานน้อยชนิดทุติยภูมิ สาเหตุอื่น ๆ ของการต่อมหมวกไตทำงานน้อยชายของอายุต่ำกว่า 10 ปี พบในผู้ป่วยที่มีภาวะต่อมหมวกไตทำงานน้อยที่มีสาเหตุทางคลินิกและการตรวจพิเศษ เช่น การตรวจทางพันธุกรรม เพื่อการวินิจฉัยเฉพาะและเพื่อการพบอาการโรคต่อไป