

# Spectrum of Addison's Disease in Children

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## ABSTRACT

**Objective:** To determine the clinical presentation of Addison's disease in order to increase the awareness of presentation in Pakistani children.

**Study Design:** Observational study.

**Place and Duration of Study:** Department of Diabetes and Endocrinology, National Institute of Child Health, Karachi, Pakistan, from 2015 to 2019.

**Methodology:** Sixty-three children of Addison's disease were enrolled in the study, who have visited and facilitated from the services of National Institute of Child Health from urban and rural region of the Sindh province. Diagnosis were made through biochemical analysis and detailed examination of acute and chronic symptoms. Study was initiated after taking the approval from Institutional Review Board. Moreover, written informed consents were also taken from each of the study participant.

**Results:** There were 36 boys and 27 girls with a mean age at diagnosis of 3.92 and 4.96 years, respectively. Twelve patients were presented with an adrenal crisis following an acute illness. All of them had hyponatraemia; however, 10 had a hyperkalaemia and 8 had been reported with hypoglycaemia. Increased skin pigmentation was observed in 45 children with other identifiable features including weight loss, lethargy, and poor response in activities. Moreover 15 of them were identified with associated disorder (autoimmune polyendocrinopathy syndrome (APS), Allgrove or triple A syndrome, and adrenoleukodystrophy).

**Conclusion:** Typical and atypical presentations of Addison's disease in children of Pakistani population are defined in this study which may assist in better management of Addison's patients.

**Key Words:** Adrenal crisis, Hyponatremia, Hyperkalemia, APS, Allgrove, Adrenoleukodystrophy.

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## INTRODUCTION

Addison's disease is relatively uncommon but lifelong chronic endocrine disorder. Prevalence in western countries is reported as 39 per million.<sup>1</sup> Addison's disease is rare in children with frequency 1:10,000. Most common cause of Addison's disease is autoimmune destruction of adrenal cortex leading to decrease in glucocorticoids, mineralocorticoids, and adrenal androgens; consequently low serum cortisol and aldosterone. These hormones are essential for survival during stressful condition, other less common causes include infection like tuberculosis. Adrenal hemorrhage and metastatic cancer can also affect adrenal gland. There is familial incidence also and females are more affected.<sup>2,3</sup>

Autoimmunity is also a proven etiology of Addison disease as, other autoimmune disorders like autoimmune polyglandular syndrome (APS), Allgrove syndrome (Triple A syndrome) (Addison disease, achalasia, and alachremia and adrenal leukodystrophy) also associated with Addison's disease.

Clinical manifestation is highly variable, potentially life-threatening condition is adrenal crisis due to severe infection, trauma, dehydration or surgery. The adrenal crises manifested with volume depletion, hypotension, shock hypoglycemic seizures, marked electrolytes and metabolic abnormalities of hyponatremic, hyperkalemic, hypoglycemic and metabolic acidosis. Only prompt diagnosis and early initiation of treatment can save the life of children. On the other hand, the chorionic manifestations are often subtle, nonspecific including fatigue, lethargy, muscular weakness, abdominal pain, joint pain, vomiting, anorexia, and weight loss may be easily missed. The dark pigmentation of skin of recent onset is strong clinical clue to suspect Addison's disease.<sup>5</sup> Spontaneous progression of tiredness and muscular weakness certainly may be the important evidence of Addison's disease.<sup>4</sup> Psychological stress was also reported among young children with Addison's disease (anorexia, fatigue and anxiety).<sup>5</sup>

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Addison's disease is treatable though requiring lifelong replacement of steroids. High index of suspicion, based on clinical manifestation is required for early diagnosis and treatment. The misdiagnosis or delayed diagnosis of Addison's disease may lead to high risk of morbidity and mortality, especially in children.<sup>6</sup>

It is a fact that the facility of pediatric endocrine is sparse in Pakistan and clinical research on the subject has not been done in our population. However, it has significant importance among endocrine disorders known for high rate of death. Only few centres are there to register and follow pediatric endocrine patients. To make awareness among the residents, family physicians and pediatrician for Addison's disease about variable clinical and laboratory findings. This study was conducted at Pediatric Endocrinology Department, National Institute of Child Health, with the aim of presenting the clinical spectrum in children with Addison's disease.

## METHODOLOGY

In this cross-sectional study of Pakistani children 63, cases of Addison's disease (aged from 1-15 years) were included, who were registered in Pediatric Endocrinology Department, National Institute of Child Health, Karachi, Pakistan, and facilitated with institutional services from 2015 and 2019. The sample size was calculated as 16 through the formula:

$$Z_{1-\alpha/2}^2 p(1-p)/d^2$$

Where  $Z_{1-\alpha/2}^2 = 1.96$  (standard normal variate),  $p$  = expected proportion in population and  $d$  = absolute error or precision.

Convenient sampling technique was applied for the recruitment. These patients were referred for the evaluation of unexplained weight loss, persistent diarrhea, electrolytes imbalance, loss of appetite and failure to thrive suspected for Addison's disease. Approval to conduct the study was attained from the IERB and informed consent to participate in the study was obtained from the parents. Children with normal ACTH and Cortisol level were excluded. Every patient was critically examined by the experienced physician and approved by the two of the authors, who are pediatric endocrinologist. Data was composed by taking physical examination of patient and evaluating the biochemical analysis with history; including age at diagnosis, comprehensive clinical features and presence of any complication at the time of enrolment.

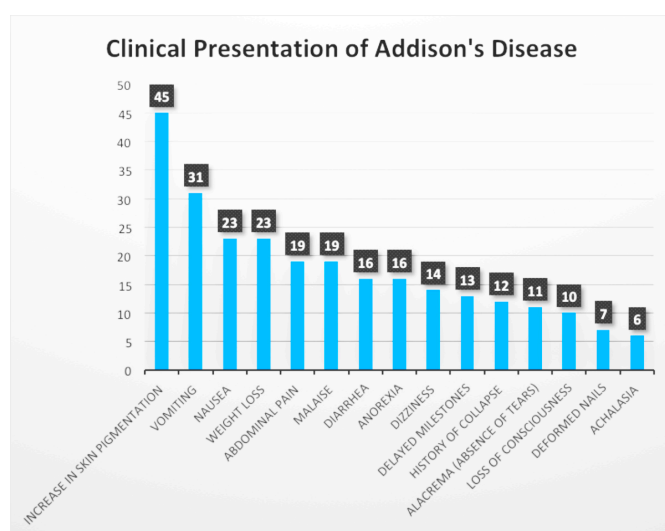
Diagnostic confirmation was made on the basis of the suggestive clinical presentation (especially hyperpigmentation, which is usually generalised over the entire body and can be found in palmar creases, buccal mucosa, vermilion border of the lips, and around scars and nipples), low basal cortisol, and elevated adrenocorticotrophic hormones (ACTH). Patients with congenital adrenal hyperplasia (CAH) were excluded by evaluating their 17OHP levels; moreover patients with precocious puberty and genital ambiguity were also excluded. Descriptive statistics were applied to the gathered data for measures of central tendency and dispersion.

**Table I: Mean age, weight, and height of the children.**

Gender	Age (years) Mean $\pm$ SD	Weight (kg) Mean $\pm$ SD	Height (cm) Mean $\pm$ SD
Male	8.03 $\pm$ 3.92	18.19 $\pm$ 7.18	105.33 $\pm$ 20.64
Female	8.67 $\pm$ 4.96	21.67 $\pm$ 12.75	108.35 $\pm$ 21.80

**Table II: Biochemical profile of the children.**

Laboratory profile, Addison's disease	n (%)
ACTH (>110 pg/ml)	53 (84.1)
Sodium (135-145 mmol/l)	51 (80.9)
Hyperreninemia	46 (73)
Basal cortisol (<171 nmol/l)	27 (42.8)
Potassium (3.5-5.0 mmol/l)	26 (41.2)
Short Synacthen (<50 nmol/l)	26 (41.2)
Hyponatremia (106-106-127 mmol/l)	12 (19)
Anemia	12 (19)
Hyperkalemia (5.6-7.6 mmol/l)	10 (15.87)
Acidosis ( $\text{HCO}_3^-$ <15 mmol/l)	9 (14.28)
Hypoglycemia	8 (12.69)



**Figure 1: Graphical presentation of the Addison's patient clinical features.**

## RESULTS

Majority of the enrolled patients belonged to Karachi (77%), whereas remaining were identified as rural population of Sindh. There were 36 boys and 27 girls among the enrolled children; their mean age, height and weight are described in Table I. Clinical manifestations of the children are mentioned in Figure 1. Biochemical profile is described in Table II, which includes the electrolytes, random blood sugar level, cortisol, ACTH and short synacthen test. However, cortisol level was low in 27, hyponatremia was found in 12, hyperkalemia in 10 and hypoglycemia was found in 8 children. ACTH and short synacthen was done for the reconfirmation, these test were performed on 53 and 26 patients respectively.

The clinical manifestations, leading to associated disorder, were achalasia, alacremia, nail dystrophy and regression of mile stone. Associated diseases included APS (autoimmune

polyendocrinopathy syndrome) and Allgrove syndrome in six patients each, adrenoleukodystrophy in three and congenital hypoplasia patients.

## DISCUSSION

The current study revealed variable clinical spectrum of Addison's disease in children; ranging from chronic non-specific symptoms to life-threatening acute adrenal crisis. In the recent study, 63 confirmed Addison's patients were recruited, with a high impact due to the maximum possible clinical symptom. All of the enrolled patients were categorised in different groups, according to their clinical presentation and laboratory profile.

Among all of the patients, 48 were grouped in Addison's disease with the chronic manifestation of classical symptoms, *i.e.* increase in skin pigmentation; reported in 71.4% of the total patients (along with palm and buccal mucosal pigmentation),<sup>1,7,8</sup> while vomiting and nausea were in 49.2 and 36.5% patients respectively. Complaint of weight loss and abdominal pain was found among 6.5%. This was supported by an earlier study by Hsieh and White in 2011 who found the complain of gastrointestinal symptoms in approximately 89% of total subjects.<sup>9</sup>

In a recent study by Ross and Levitt, conducted at Arabian South Sahara, on increase skin pigmentation was described in 76% of patients followed by other chronic nonspecific symptoms (fatigue, lethargy, unexplained weight loss, muscular weakness, nausea, vomiting and abdominal pain) in more than 40% cases.<sup>10</sup> Additionally, diagnostic confirmation was done through laboratory profile. In the present study, similar biochemical profile was observed with ACTH level >110 pg/ml in 84.1% patients, basal cortisol <171 nmol/l in 42.8% and Sodium 135-145 mmol/l in 51% patients.

Other group of this study interestingly were labelled as Addison's disease with associated autoimmune disorder including APS (autoimmune endocrinopathy syndrome) in six patients with major symptoms of deformity in nails, hypocalcemia and vitiligo,<sup>11</sup> Allgrove (triple A syndrome) presented along with alacremia, and achalasia in 6 patients, adrenoleukodystrophy in 3 patients with regression of mile stones, and 2 patients had congenital adrenal hypoplasia as seen by other researches.<sup>12</sup> Similar number of patients in each group with almost same symptoms were observed by Hsieh and White in 2011 as well.<sup>9</sup>

In spite of mentioned groups, there were some patients who landed in emergency room of the hospital with acute adrenal crisis, presented with vomiting, diarrhea, dehydration, seizures, hypotension and shock. They were found to have hyponatremia, hyperkalemia, hypoglycemia and metabolic acidosis. Cortet *et al.* stated comparable symptoms in children with adrenal insufficiency.<sup>13</sup>

It has always been challenging to diagnose Addison's disease in children and adolescent in regards of weight loss because initial symptoms are usually indistinguishable.<sup>14</sup> Sheikh *et al.* presented a case of six years old Addison's boy who was misdiagnosed earlier due to non-specific symptoms of the

disease.<sup>4</sup> Another recent example of misdiagnosis of Addison's disease was reported by Feeney and Buell: the patient was misdiagnosed and treated for anorexia nervosa and some other depressive disorder.<sup>15,16</sup> Similarly, a child was mistreated for syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as reported by Pintaldi *et al.*<sup>17</sup> Even though the disease can be recognised considering alike symptoms with characteristic physical features and evaluation of biochemical tests, For instance, presence of hypernatremia is crucial for the ratification of Addison's disease among children because of aldosterone deficiency. The reported ratio of hyponatremia is 90% of cases followed by hyperkalemia (50%) and hypoglycemia (30%) of the cases. In this study, patients reported with the same laboratory finding with highest ratio of hyponatremia and least number of hypoglycemia.

## CONCLUSION

Addison's disease is often misdiagnosed or delayed which leads to high morbidity and mortality in children. Awareness about typical and atypical presentation of Addison's disease among health professionals is highly crucial and need of the time to avoid the escape of Addison's disease.

### ETHICAL APPROVAL:

This study was conducted after the approval of Institutional Ethical Review Committee.

### CONFLICT OF INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

TML: Conception and design of study, manuscript editing for important intellectual content.

MNI: Conception and design, manuscript editing.

ZK, MN: Conception and acquisition of data.

MIH: Design of study, acquisition of data, manuscript writing.

JR: Conception and design, final approval of the manuscript version to be published.

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