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# Clinical and Biochemical Parameters at Presentation of Patients with Adrenal Insufficiency Attending a Tertiary Care Hospital

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**Abstract:** Background: Adrenal insufficiency is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency of mineralocorticoids and adrenal androgens. It results from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis. Patients often have nonspecific symptoms such as weakness, fatigue, lethargy, anorexia, nausea, vomiting, fever, confusion or coma. Without appropriate therapy, shock progresses to coma and death. The aim of the study was to evaluate the clinical and biochemical parameters at presentation in patients admitted with adrenal insufficiency. Methods: Patients diagnosed with adrenal insufficiency fulfilling the diagnostic criteria were considered as study population. Purposive consecutive type of sampling method was applied. Data was collected in a structured questionnaire. All the data were analysed by SPSS V 22.0. Results: A total of 100 patients of adrenal insufficiency were included in the study. The most were in the age group of 51-60 years (33%), mean age ± SD was 50.82±13.51 years & 38% were male. In our study, 100% patients had generalized weakness, 88% had GI symptoms, 41% had vertigo and 18% had weight loss. Most of them (83%) had vomiting, 70% had nausea and only 17% had anorexia. 38% patients were anaemic and 23% had shock and 33% patients presented with adrenal crisis. In this study, 82% patient were hypotensive, 46% had postural hypotension. In our study, 56% had puffy face, 49% had history of weight gain, 26% had skin thinning. Mean Hb was 10.96 gm/dl, 25% had a serum creatinine of>1.2 mg/dl. Hypoglycaemia was present in 7%, 12% had high blood urea nitrogen, 71% had hyponatraemia, 39% had hyperkalaemia, 12% had hypercalcaemia and 20% had acidosis. Conclusion: Adrenal insufficiency presented with non-specific features like fatigue, weakness, vertigo, GI symptoms, unexplained fever or weight loss and specific pattern of biochemical findings like hyponatraemia, hyperkalaemia, mild acidosis, hypercalcaemia & hypoglycaemia. So, these features should raise the suspicion of adrenal insufficiency.

**Keywords:** Clinical Parameters, Biochemical Parameters, Presentation, Adrenal Insufficiency

## 1. Introduction

Adrenal insufficiency is the clinical manifestation of deficient production or action of glucocorticoids, with or without deficiency of mineralocorticoids and adrenal androgens. It is a disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary axis. [1] The cardinal clinical

symptoms of adrenocortical insufficiency, as first described by Thomas Addison in 1855, include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, and salt craving; characteristic hyperpigmentation of the skin occurs with primary adrenal failure. [2]

Whatever the cause, adrenal insufficiency was invariably fatal until 1949, when cortisone was first synthesized, and glucocorticoid replacement treatment became available [3]. However, despite this breakthrough, the diagnosis and treatment of patients with the disorder remain challenging. According to the underlying mechanism, adrenal insufficiency is classified as primary and secondary. Primary adrenal insufficiency results from inability to produce steroid by adrenal cortex. Secondary adrenal insufficiency is caused by impaired production or action of corticotropin (ACTH) or impaired release of corticotropin realizing hormone (CRH). In Europe, the prevalence of chronic primary adrenal insufficiency has increased from 40–70 cases per million people in the 1960s [4, 5] to 93–144 cases per million by the end of the 20th century, [6, 7] with an estimated incidence now of 4.4–6.0 new cases per million population per year. [6] Autoimmune adrenal insufficiency has become the most common form in the later part of the 20th century. [7]

The increase in the frequency of primary adrenal insufficiency over the past few decades, associated with a decline in the prevalence of tuberculosis, is indicative of the rising proportion of cases of autoimmune adrenal insufficiency. [8] In a series of 615 patients with Addison's disease, studied between 1969 and 2009, the autoimmune form was diagnosed in 82% of cases, the tuberculosis related form in 9%, and other causes in about 8% of cases. [9] Primary adrenal insufficiency occurs more frequently in women than in men, and can present at any age, although most often appears between the ages of 30 and 50 years. [10] Secondary adrenal insufficiency is more common than primary adrenal insufficiency. It has an estimated prevalence of 150–280 per million and affects women more frequently than men. [11, 12] A systematic review and meta-analysis of reported prevalence of hypopituitarism in adult patients who had received cranial irradiation for non-pituitary tumors showed that the point prevalence of any degree of hypopituitarism was 0.66 (95% CI 0.55–0.76) and the prevalence of corticotropin deficiency was 0.22 (0.15–0.30). [13] The most common cause of adrenal insufficiency is long-term administration of exogenous glucocorticoids, which leads to prolonged suppression of hypothalamic secretion of corticotropin releasing hormone. [14]

The symptoms and signs of adrenal insufficiency depend upon the rate and extent of loss of adrenal function and the degree of stress. The onset of adrenal insufficiency is often very gradual and it may go undetected until an illness or other stress precipitates adrenal crisis. In primary adrenal insufficiency, adrenal crisis most commonly presents as shock [15] but the patients often have nonspecific symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion or coma. Hypoglycemia is a rare presenting manifestation of acute adrenal insufficiency; it is more common in secondary adrenal insufficiency caused by isolated corticotropin (ACTH) deficiency. [16] Patients with long-standing adrenal insufficiency who present in crisis may be hyperpigmented (due to chronic ACTH hypersecretion) and have weight loss, serum electrolyte abnormalities, and other manifestations of chronic adrenal insufficiency. [17] Patients with chronic primary adrenal insufficiency may have symptoms and signs of glucocorticoid, mineralocorticoid, and in women, androgen deficiency. In contrast, patients with secondary adrenal insufficiency usually have normal mineralocorticoid function.

The most common clinical features of chronic primary adrenal insufficiency are - weakness, tiredness, fatigue (100%), anorexia (100%), nausea (86%), vomiting (75%), constipation (33%), abdominal pain (31%), diarrhea (16%), salt craving (16%), postural dizziness (12%), muscle or joint pains (6-13%), weight loss (100%), hyperpigmentation (94%), hypotension (systolic BP<110 mmHg) (88-94%), vitiligo (10-20%). [17, 18] Hyperpigmentation, which is evident in nearly all patients with primary adrenal insufficiency, is the most characteristic physical finding. [19] Amenorrhea develops in about 25 percent of women. [20] Diffuse myalgia and arthralgia are frequent symptoms in patients with adrenal insufficiency.[20] Many patients with severe or long-standing adrenal insufficiency have psychiatric symptoms, including - confusion, delirium, and stupor, depression and psychosis. [21]

The clinical features of secondary adrenal insufficiency are similar to those of primary adrenal insufficiency, with a few major exceptions. Weakness, fatigability, myalgia, arthralgia, and psychiatric symptoms all can occur in patients with secondary adrenal insufficiency, indicating that these symptoms are caused by glucocorticoid rather than mineralocorticoid deficiency. The major exceptions are hyperpigmentation which is not present because ACTH secretion is not increased. Dehydration is not present, and hypotension is less prominent. [17] Hyponatremia (88%), hyperkalemia (64%), hypercalcemia (6%), azotemia (55%) and anemia (40%) may present in adrenal insufficiency. [17, 18] Hyponatremia can occur early in the disease and may be the initial manifestation. Hyperkalemia is not present, reflecting the presence of aldosterone. Hypoglycemia is more common in secondary adrenal insufficiency. [17, 22] Hypoglycemia may occur after prolonged fasting or, rarely, several hours after a high-carbohydrate meal. [18] Because adrenal crisis is difficult to recognize clinically, it must be considered whenever these symptoms develop in a patient with one or more risk factors. Without appropriate therapy, shock progresses to coma and death. [23]

This study focuses on providing the clinician with new insights into presentation of adrenal insufficiency. The clinical diagnosis of chronic adrenal insufficiency at times is difficult to identify unless there is clinical awareness of the disease. Diagnosis is often obvious when classic symptoms and signs are present. However, early symptoms such as lassitude and fatigability are nonspecific. [17] Suppression of hypothalamic-pituitary-adrenal function with chronic administration of high doses of glucocorticoids is the most common cause of adrenal

insufficiency. [24] Many medical illnesses have been treated with systemic steroid; adrenal insufficiencies have been reported in most of them when the use exceeded more than a month. [25] We usually overlook this problem because the presenting symptoms are insidious and non-specific, hence, there should be a high index of suspicion, therefore a good history and examination should be conducted on all patients on prolonged steroid therapy. The objective of the study was to evaluate the clinical and biochemical presentation of patients with adrenal insufficiency.

# 2. Methods

This cross-sectional observational study was conducted at the inpatient department of BIRDEM General Hospital from January 2018 to August 2019. Patients diagnosed as adrenal insufficiency (primary or secondary) of more than 18 years who were willing to give voluntary consent were included in the study. Patients having congenital adrenal hyperplasia, pregnancy or any kind of liver, kidney or heart disease and those who refused to give voluntary consent were excluded from the study. Purposive consecutive type of sampling method was applied. After full explanation, informed written consent was taken. A detailed history was obtained. Demographic, clinical and biochemical parameters were recorded at presentation. Data was collected in a structured questionnaire.

### *2.1. Operational Definitions*

Adrenal insufficiency (AI): Deficient adrenal production of glucocorticoids with or without mineralocorticoids results in adrenocortical insufficiency which is either the consequences of adrenal cortex (primary adrenal insufficiency) or secondary to deficient pituitary ACTH secretion (secondary adrenal insufficiency). [26]

Shock: Shock is the clinical syndrome that results from inadequate tissue perfusion. Irrespective of cause, the hypoperfusion-induced imbalance between the delivery and requirements for oxygen and substrate leads to cellular dysfunction. [27]

Clinical feature of shock:

1) Altered consciousness, confusion, irritability.
2) Pallor, cool skin, sweating.
3) Heart rate > 100 bpm
4) Hypotension (SBP < 90 mm Hg)
5) Respiratory rate > 30 breaths/ min
6) Oliguria (urine output <0.5- 1 ml/kg/h)

Hypotension: A systolic blood pressure of less than 90 millimeters of mercury (mm Hg) or diastolic of less than 60 mm Hg is generally considered to be hypotension. [28]

Postural hypotension: Orthostatic hypotension is defined as a fall of at least 30 mm Hg in systolic blood pressure or a fall of at least 10 mm Hg in diastolic blood pressure within 3 minutes of standing. [29]

Weight loss: Loss of weight 3 kg or more within 6 months. [30]

Hypoglycemia: Random blood glucose < 3.9 mmol/L. (ADA-2017)

Hyponatremia: Defined as a plasma Na + concentration < 135mmol/L. [21]

Hyperkalemia: Defined as a plasma potassium level 5.5 mmol/L or more. [31]

Hypercalcemia: Defined as a serum corrected calcium more than 10.5 mg/dl. [32]

### *2.2. Statistics*

After collection of all the required data, they were checked, verified for consistency and then tabulated into the computer using the SPSS v22.0. Statistical analysis was done by Statistical Package for Social Sciences version 22.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Variables were expressed as frequencies and percentages. A p-value of<0.05 was considered as significant.

# 3. Results

Result of our study is expressed through the following tables and diagrams.

***Table 1.*** *Demographic profile of the study subjects (n=100).*

| | Frequency (n) | Percentage (%) |
|---|---|---|
| Age (years) [mean ± SD] | 50.82±13.51 (21-78) | |
| Gender | | |
| Male | 38 | 38.0 |
| Female | 62 | 62.0 |
| Level of education | | |
| Graduate | 37 | 37.0 |
| Under graduate | 53 | 53.0 |
| Illiterate | 10 | 10.0 |
| Occupation | | |
| Service | 22 | 22.0 |
| Day labor | 10 | 10.0 |
| Business | 9 | 9.0 |
| Housewife | 50 | 50.0 |
| Unemployed | 9 | 9.0 |
| Socioeconomic status | | |
| Low | 31 | 31.0 |
| Middle | 44 | 44.0 |
| High | 25 | 25.0 |

***Table 2.*** *GI symptoms of the study subjects (n=100).*

| GI symptoms | Frequency (n) | Percentage (%) |
|---|---|---|
| Anorexia | 17 | 17.0 |
| Nausea | 70 | 70.0 |
| Vomiting | 83 | 83.0 |
| Diarrhea | 23 | 23.0 |
| Abdominal pain | 26 | 26.0 |
| Constipation | 11 | 11.0 |

***Table 3.*** *Clinical presentations of the study subjects (n=100).*

| Signs | Frequency (n) | Percentage (%) |
|---|---|---|
| Adrenal crisis | 33 | 33.0 |
| Shock | 23 | 23.0 |
| Hypotension | 82 | 82.0 |
| Postural hypotension | 46 | 46.0 |
| Altered consciousness | 8 | 08.0 |
| Anemia | 38 | 38.0 |
| Vitiligo | 5 | 05.0 |
| Psychiatric illness | 11 | 11.0 |

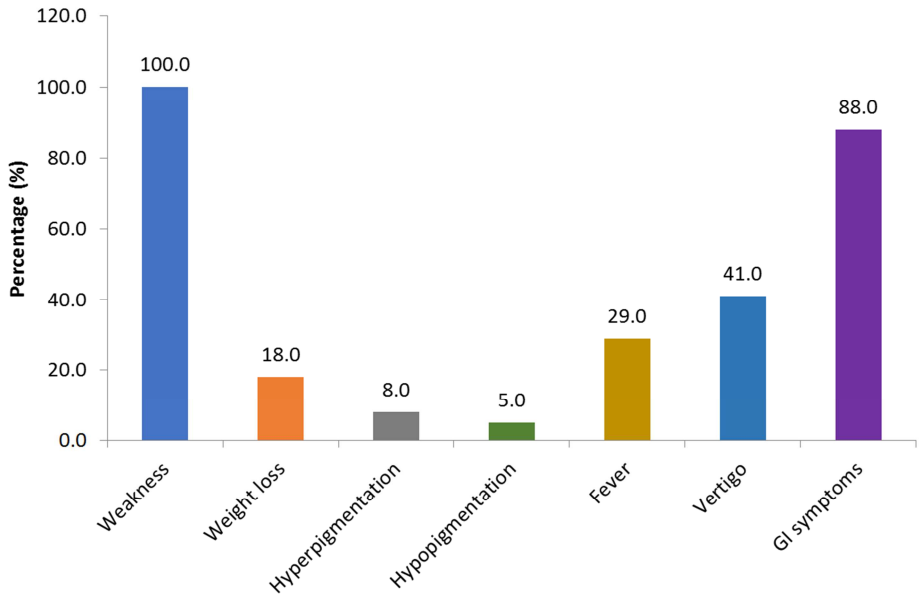


***Figure 1.*** *Bar diagram showing frequency of various symptoms of adrenal insufficiency (n=100).*

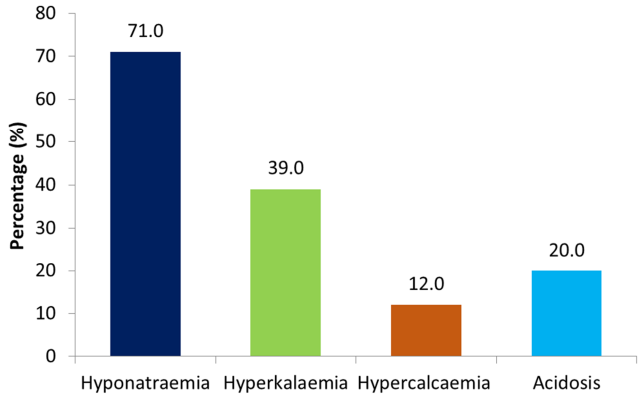


***Figure 2.*** *Pattern of electrolyte imbalance in study subjects at presentation (n=100).*

***Table 4.*** *Pattern of blood pressure distribution among the study subjects (n=100).*

| Blood pressure | Mean ± SD | Min-Max |
|---|---|---|
| Systolic blood pressure (mmHg) | 84.6±19.32 | 60-170 |
| Diastolic blood pressure (mmHg) | 57.11±15.82 | 35-90 |

***Table 5.*** *Associated features of the study population (n=100).*

| Features | Frequency (n) | Percentage (%) |
|---|---|---|
| Weight gain | 39 | 39.0 |
| Puffy face | 36 | 36.0 |
| Skin thinning | 26 | 26.0 |

***Table 6.*** *Distribution of the study subjects according to variation in BMI (According to Asia-pacific obesity guideline) (n=100).*

| BMI (kg/m$^2$) | Frequency (n) | Percentage (%) |
|---|---|---|
| Underweight (<18.5) | 08 | 08.0 |
| Normal weight (18.5 - 22.9) | 38 | 38.0 |
| Overweight (23.0 - 24.9) | 35 | 35.0 |
| Obese (>25.0) | 19 | 19.0 |
| Mean ± SD | 23.38±4.22 | |

***Table 7.*** *Lab parameters of the study subjects (n=100).*

| Parameter | (Mean ± SD) | Frequency | Percentage (%) |
|---|---|---|---|
| Hb. (gm/dl) | 10.96±1.81 | | |
| Male (<13) | | 12 | 31 |
| Female (<11) | | 26 | 41.9 |
| S/creatinine (>1.2mg/dl) | 1.14±0.41 | 25 | 25 |
| Blood urea (>40 mg/dl) | 26.87±8.02 | 12 | 12 |
| RBS (<3.9 mmol/L) | 9.47±4.30 | 07 | 07 |

# 4. Discussion

The cardinal clinical symptoms of adrenocortical insufficiency include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension and salt craving; characteristic hyperpigmentation of the skin occurs with primary adrenal failure. Biochemical disturbances such as hyponatremia, hyperkalemia, hypoglycemia, hypercalcemia and anemia have all been described in adrenal insufficiency. In our study, total one hundred patients of adrenal insufficiency were included. Among them 62 were female (62%) and rests were male (38%). The highest percentage (33%) of the patients belonged to the age group of 51 to 60 years. Kong MF et al. in 1994 showed that adrenal insufficiency occurs more frequently in women than in men, and can present at any age, although most often appears between the ages of 30 and 50 years.[10] Nilsson et al. in 2000 conducted a study in Sweden and has found the similar result.[27] So, our study coincides with these studies. The female to male ratio in the survey was 1.6, which is comparable to our earlier report and to those from Italy, the United Kingdom and Denmark.[27]

This study found no statistically significant differences in presentation in between demographic distributions; however adrenal insufficiency was much higher (53%) in less educated persons than who are highly educated (37%). Social

status might have also some impact on adrenal insufficiency. In our study, it was shown that middle income families were more (44%) affected than low (31%) and high (25%) income families. There is a local belief on herbal product that it is non -toxic, efficacious, easily available and cheap. So, it is used by the common people and exposed to steroid and its hazards. In this study, we found that 100% patient had generalized weakness. Charmandari et al. in Greece found the same finding in their study. [33] Neary et al. in 2010 stated that generalized weakness and malaise were most common features of adrenal insufficiency [1]. Erichsen et al. in 2009 showed that 95% of patients had fatigue. [7] These findings are consistent with our study.

We found that only 18 out of 100 patients presented with weight loss. Dunlop et al. stated that the weight loss is primarily due to anorexia, but dehydration may contribute. [29] The amount of weight lost can vary from 2 to as much as 15 kg and may not become evident until adrenal failure is advanced. Erichsen et al. found that 73% patients had weight loss. [7] This finding had significant disparity with our finding. Ross et al. [34] in south Africa (2010) found that 25% patients presented with weight loss, which is similar to our study. In this study, 8% patients had hyperpigmentation. And 5% patients had hypopigmentation and all of them had primary adrenal insufficiency. Erichsen et al. in Norway found that 11% patients had hypopigmentation [7], but all this patient enrolled in that study was primary adrenal insufficiency. In the same study 74% patients had hyperpigmentation at diagnosis. In our study, we considered both primary and secondary adrenal insufficiency. So, this disparity may be present.

29% patients in our study presented with fever. Nieman et al. stated that, it should be assumed that fever indicates infection that must be identified and treated [35]. The combination of abdominal pain and fever may lead to the incorrect diagnosis of an acute surgical abdomen with potentially catastrophic surgical exploration. Alexandraki et al. showed that 66% patients present with fever, which was more common in primary than in secondary adrenal insufficiency [36]. It is much more than our finding. Lee et al. found that 33% patients presented with fever which is much closer to our finding. [37] Gastrointestinal symptoms were most common in our study, where 83% patients presented with vomiting, 70% with nausea, 17% with anorexia, 23% with diarrhoea, 11% with constipation and 26% with abdominal pain. Charmandari et al. described that 92% patients presented with gastrointestinal symptoms and it is more common in primary adrenal insufficiency. [33] Tobin et al. stated that gastrointestinal symptoms, usually nausea, occasionally vomiting, abdominal pain, or diarrhea that may alternate with constipation, are common and correlate with the severity of adrenal insufficiency.[30] Vomiting and abdominal pain often herald adrenal crisis, and the fluid loss due to vomiting or diarrhea may precipitate the crisis. Alexandraki et al. found that 86% patients had GI symptoms, among them 47% had nausea & vomiting. [36] This finding is little bit less than our finding. Erichsen et al. showed that 62% patients presented with anorexia, nausea, vomiting. [7] It is approximately close to our findings. Ross et al. stated that 51% patients suffer from nausea, 43% from vomiting, 21% from abdominal pain and 15% from diarrhea. These findings more or less coincide with our study.

In this study, 41% patients presented with vertigo. Charmandari et al. shown 12% present with vertigo. [33] This difference with our study was due to presence of other comorbidities. In our study, 33% patients presented with adrenal crisis and 23% patients presented with shock. Nieman et al. showed that, the predominant manifestation of adrenal crisis was shock. [35] Ross et al. showed that 5% patient with primary adrenal insufficiency presented with shock.[34] We did not differentiate primary or secondary adrenal insufficiency, this may be the cause of discrepancy with our finding. We found that 8% patients presented with altered consciousness. Alexandraki et al. found 42% patients present with neuropsychiatric symptoms like confusion, lethargy, disorientation & coma. [36] In this study, neuropsychiatric symptoms were included with coma, so the percentage was so high than our study. Leigh et al. stated that many patients with severe or long-standing adrenal insufficiency had psychiatric symptoms, [21] including mild to moderate organic brain syndrome in 5 to 20 percent. This study coincides with our finding. 11% patient in our study had psychiatric illness. Burke et al. described that psychiatric symptoms (memory impairment, depression, anxiety, psychosis, reduced consciousness, delirium) were present in 12% patients with adrenal insufficiency which is more or less similar to our study.

In our study, only 5% patient had vitiligo. All of them had primary adrenal insufficiency. Erichsen et al. found 8.5% patients presented with vitiligo, which was slightly higher than our finding. [7]

In our study, 46% patient had postural hypotension. In several studies it is showed that, in most patients the blood pressure is low, but some have only postural hypotension. Glucocorticoids are necessary for adrenal medullary epinephrine synthesis, and patients with adrenal insufficiency have decreased serum epinephrine and compensatory increases in serum norepinephrine concentrations. This may cause slightly lower basal systolic blood pressure and an exaggerated increase in pulse rate in response to upright posture. Alexandraki et al. stated that, hypotension (<110mmHg systolic) and syncope/ shock (>90%) were present in significant number of patients.[36] Charmandari et al. showed that, low blood pressure, postural hypotension, dehydration (pronounced in primary adrenal insufficiency) was present in 88-92%.[33] These findings are higher than our study. But Erichsen et al. [7] have the similar result (56%) with our study.

In our study, only 8% patient were under-weight where only 35% patient were overweight and 19% were obese. 38% patient were anemic. Erichsen et al. [7] showed only 13% patient were anemic, which was much lower than our finding. This is most probably due to ethnic difference, poverty in our

country, lack of knowledge about the content of food & nutritional deficiency and presence of other chronic illness etc. Patients with secondary adrenal insufficiency commonly have associated cushingoid features like- skin thinning, puffy face and weight gain, that suggest diagnosis and indicate history of glucocorticoid use. In this study, 36% patients had puffy face, 39% had weight gain & 26% had skin thinning as associated features where exogenous glucocorticoid is the cause of adrenal insufficiency. In our study, 12% patient had high blood urea, 25% had high creatinine and 7% patient had hypoglycemia. Charmandari et al. showed that increased serum creatinine was found in primary adrenal insufficiency. [33] Lee et al. found that the mean serum creatinine in adrenal insufficiency was 1.29 mg/dl. [37] Increased age and presence of other comorbidity may explain the high serum creatinine in our study.

Nieman et al. showed that hypoglycemia was more common in infants and children with primary adrenal insufficiency, patients with secondary adrenal insufficiency caused by isolated ACTH deficiency and in patients with type 1 diabetes mellitus who developed adrenal insufficiency. In our study, total 71% patient had hyponatremia. Hyperkaliemia was found in 39% patients. Raised serum calcium was found in 12% patients. Acidosis was present in 20% of the population. Charmandari et al. [33] and Husebye et al. [38] found that 90% had reduced level of sodium at diagnosis. Nieman et al. and Alexandraki et al. found 85-90% had hyponatremia in their study. [35, 36] Charmandari et al. showed that 88% patient had hyponatremia. [33] These findings coincided with our finding. Naidoo et al. showed 62% patients had hyponatremia.[39] This is less than our finding. Charmandari et al. found in their study that, at diagnosis 50% patient had hyperkaliemia [33] and Alexandraki et al. found 60-65% patient had hyperkalemia [36] which were very high than our finding. This may be due to our failure to classify the findings between primary & secondary adrenal insufficiency, whereas Charmandari et al. showed only the finding of primary adrenal insufficiency. Naidoo et al. found 35% had hyperkalemia [39] which was also double than our finding. Charmandari et al. [33] showed that 6.6% patients had hyperkalemia only in primary adrenal insufficiency which was lower than our finding. Again, Charmandari et al. found that calcium level was raised in 10-20% of newly diagnosed cases of primary adrenal insufficiency [33] which was similar with our finding.

## 5. Conclusion

Adrenal insufficiency presents with non-specific features like fatigue, weakness, vertigo, GI symptoms, unexplained fever or weight loss and specific pattern of biochemical findings like hyponatremia, hyperkalemia, mild acidosis, hypercalcemia & hypoglycemia. So, these features should raise the suspicion of adrenal insufficiency which may endanger the life if diagnosis is delayed. As it is a treatable condition, potentially life-saving measures can be taken promptly by the physicians to prevent life threatening situations by early diagnosis.

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