

Clinical Profile of Addison's Disease in a Tertiary Care Institute, Southern India – The Changing Landscape

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Abstract

Aims and Objectives: Clinical, biochemical, and radiological profiles of Addison's disease and to assess the various etiological spectrum of primary adrenal insufficiency (PAI) in adults. **Materials and Methods:** A retrospective cohort study was carried out in the Department of Endocrinology, Madurai Medical College, Madurai between January 2014 and January 2021 over a 7-year period. **Inclusion Criteria:** All the patients with clinical symptoms and or signs of suspected PAI, such as hyperpigmentation, weight loss, persistent nausea or vomiting, fatigue, and hypotension, were recruited. All suspected cases underwent measurement of 8-AM plasma ACTH and cortisol levels. In possible cases and equivocal cortisol levels, patients underwent Co-syntropin/ACTH stimulation test. To know the underlying etiology of PAI, 21-hydroxylase autoantibodies (21OHAb), thyroid function test, Anti TPO, calcium, parathyroid hormone (PTH), LH and FSH, CT of chest and abdomen, and sputum AFB based on the clinical pattern of involvement were performed. **Exclusion Criteria:** Patients with onset of PAI at infancy and childhood, secondary adrenal insufficiency or exogenous Cushing's syndrome, and central hypocortisolism, including Sheehan's syndrome, were excluded. **Results:** Thirty-six patients were diagnosed with PAI in this study; 19 (53%) were females and 17 were males (47%). The median age of diagnosis was 35 years. Patients were divided into acute presentation and subacute presentation. Twenty-six patients presented with acute presentation and ten were presented with progressive evolved symptoms. Non-tuberculous etiology was the predominant finding noted in our cohort study (87%, 31 out of 36 patients). The other causes of Addison disease included isolated auto-immune PAI, polyglandular autoimmune syndrome type 1 and II, APLA Syndrome, and adrenal metastasis. **Conclusion:** Non-tuberculous causes of PAI are the leading etiology in our retrospective study. Autoimmune PAI and Polyglandular autoimmune syndromes are increasingly being recognized as the cause of Addison's disease. PAI individuals require lifelong surveillance for possible development of coexisting autoimmune syndromes and need for glucocorticoid/mineralocorticoid therapy.

Keywords: Addison's disease, adrenal crisis, autoimmune polyendocrine syndrome, Nikshay, primary adrenal insufficiency

INTRODUCTION

Primary adrenal insufficiency (PAI) is a rare disorder with an estimated prevalence of 100 to 140 cases per million according to the western literature.^[1,2] It is characterized by the inability of the adrenal cortex to produce glucocorticoids and/or mineralocorticoids, leading to a severe and potentially life-threatening adrenal crisis if unrecognized and/or untreated. It was first described by Thomas Addison, hence commonly termed as Addison's disease (AD).^[3]

The various etiologies of PAI can be classified into two categories. First is adrenal dysgenesis/impaired steroidogenesis, usually genetic with autosomal recessive inheritance and neonatal/childhood onset. The second category

of adrenal destruction is, usually has its onset in adulthood due to autoimmunity or following adrenal hemorrhage, adrenalectomy, neoplasia, and metastatic adrenal failures.^[4,5] It also happens when the majority of the adrenal cortex is destroyed or infiltrated by the hematogenous/lymphatic spread of tuberculosis (TB) or fungal infections.^[6-8]

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When Thomas Addison first described hypoadrenalism, TB accounted for 80% of the cases.^[1] Due to the effective anti-tuberculosis therapy (ATT) regimen, the incidence of TB-related clinical hypoadrenalism has dropped worldwide. Currently, autoimmune adrenalitis is the most common cause of PAI worldwide.^[5] In India, the most common etiology of AD is due to TB from the previously published Indian literature.^[9-11] However, there are no recent publications from the Indian subcontinent regarding the etiological profile of AD for more than two decades after the improvement in the daily and drug-sensitive ATT regimen by various TB elimination programs.^[12] Hence, this study is planned to assess the various etiological spectrum of PAI in adults.

MATERIALS AND METHODS

A retrospective cohort study was carried out in the Department of Endocrinology, Government Rajaji Hospital, a 3500-bed tertiary care hospital in Madurai, Southern India, between January 2014 and January 2021, over a 6-year period. Patients aged more than 12 years with clinical symptoms and or signs of AD like hyperpigmentation, weight loss, persistent nausea or vomiting, fatigue, and hypotension were recruited. Patients with onset of PAI in infancy or childhood, secondary adrenal insufficiency due to Exogenous Cushing's or alternative medicine, Sheehan's syndrome, or central cortisol deficiency were excluded. The detailed study algorithm has been detailed in Figure 1.

All suspected cases underwent measurement of 8-AM plasma adrenocorticotrophic hormone (ACTH) and cortisol levels. The diagnosis of AD was confirmed with a combination of classical clinical presentation along with supportive biochemical evidence like random or 8 AM cortisol level of less than 2 mcg/dL or 50 nmol/L, hyponatremia, and/or hyperkalemia. When cortisol level of more than 2 mcg/dL, patient underwent Co-syntropin/ACTH Stimulation Test.^[5] Since Synacthen is not marketed in India, Acton Prolongatum was used as ACTH stimulation test. After overnight fast blood sample was taken for serum cortisol estimation between 8–9 AM, injection Acton Prolongatum of 25 units (16 Units in 40 IU insulin syringe) was injected intra muscularly; second blood sample was collected after 60 minutes for cortisol estimation.^[13] Post ACTH stimulation, cortisol level greater than 500 nmol/L or a rise of more than 250 nmol/L from baseline level usually indicates adequate adrenal reserve. When patient presented with features of adrenal crisis, blood sample was taken before giving injection hydrocortisone and ACTH sample was taken on next day morning.

Apart from the sputm AFB in symptomatic individuals, contrast-enhanced computed tomography (CECT) Chest and abdomen were done in all PAI patients to exclude the etiology of TB, disseminated fungal infections, mass lesions, and adrenal hemorrhage. 21-hydroxylase autoantibodies (21OHA_b) were used in selected subgroup of AD patients depends upon the availability. Blood levels of cortisol, ACTH, Free T4, TSH,

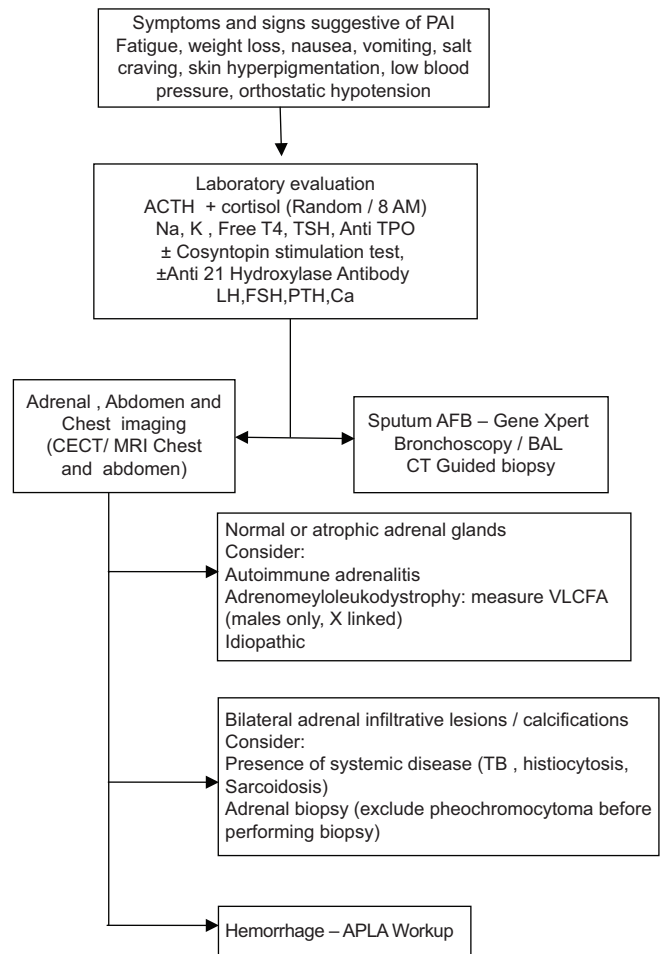


Figure 1: Detailed study algorithm of suspected Addison's disease

Anti TPO and PTH were estimated depend upon the underlying clinical presentation using electrochemiluminescence immunoassay (ELECSYS 2010, Roche Diagnostics, Mannheim, Germany).

After the diagnosis of AD, all were treated with two-three daily doses of hydrocortisone (HC-15-25 mg/day) or oral prednisolone (5-10 mg/dl) and with fludrocortisone (0.05-0.1 mg/day).^[5,14] All PAI patients and family members were educated regarding the sick day rules like double-triple the glucocorticoids dose in the case of fever or infections and to switch to injectable glucocorticoids in the case of vomiting, diarrhea or acute hypotension.

RESULTS

Thirty-six patients were diagnosed as PAI in this study, 19 (53%) were Females and 17 were males (47%), median age of diagnosis was 35 years. Female:Male ratio, 1.1:1. Patients were divided into acute presentation and sub-acute presentation. Twenty-six patients presented with acute presentation and ten presented with progressively evolving symptoms. Non Tuberculous etiology was the predominant finding noted in our cohort study (31 out of thirty-six patients). The most common symptoms noted in our study cohort were

hyperpigmentation followed by weight loss and nausea/vomiting. The clinical features were detailed in Table 1. Except in one family, where both siblings had APS type 1, no family history of AD was documented in the present cohort.

The different etiological profiles noted in this study are described in Table 2. The diagnosis of autoimmune polyendocrine syndrome type 1 (APS1) was made later on the follow-up, when carpal spasm noted due to hypoparathyroidism, and oral candidiasis documented retrospectively. Primary hypothyroidism, vitiligo, and premature ovarian insufficiency were the most common association in autoimmune polyendocrine syndrome type 2 (APS 2). The bilateral adrenal metastasis-related PAI was due to small cell carcinoma in both the cases. The clinical photographs of AD noted in our cohort are shown in Figure 2. The interesting imaging pictures in the present study are shown in Figure 3.

DISCUSSION

In contrast to the previously published literature from India,^[9-11] this study shows that non Tuberculous etiology is the most common cause of PAI or AD. In the current cohort only 13% of AD was due to TB. When the PAI has been confirmed at the biochemical and hormonal level it is important for therapeutic reasons to identify the underlying etiology of AD.^[5] The appropriate etiological diagnosis of AD allows screening of other associated clinical features like polyglandular syndromes and careful monitoring of additional endocrine and non-endocrine systemic manifestations that may be diagnosed after years of AD onset.^[14]

High index of clinical suspicion is required to identify a case of PAI in countries like India. Hyperpigmentation is one of the most specific sign and symptoms of PAI, followed by weight loss and low normal blood pressure to ortho-static hypotension. Hyperpigmentation must be compared with the

patient's background pigmentation such as that in sibling and with previous photographs. The reduction in cortisol causes increased ACTH and MSH production, which acts on the melanocytes resulting in hyperpigmentation. Differential diagnoses of hyperpigmentation are hyperthyroidism, B12 deficiency, and cancer chemotherapy related. Depending on the rate of destruction of adrenal glands, clinical symptoms may manifest as insidious into rapid onset generalized weakness, fatigue, weight loss, anorexia, nausea, vomiting, depression and postural dizziness.^[5,14] 8 AM cortisol or random serum cortisol (in emergency situations) is the single most important test to diagnose PAI before initiating any hormonal therapy.

When Thomas Addison first described hypoadrenalism, TB accounted for 80% of the cases.^[3] This is the result from hematogenous/lymphatic spread of infection from the primary site that affects both the adrenal gland function. More than 90% of adrenal tissue must be destroyed before symptoms manifest.^[6-8] Imaging studies usually reveal an enlarged adrenal gland due to the inflammatory process at the initial stage followed by fibrosis, with or without calcification replacing

Table 1: Clinical Features of Primary Adrenal Insufficiency

Features	Frequency (%)
Symptoms	
Fatigue and Weakness	100
Nausea and vomiting	86
Diarrhea	14
Abdominal Pain	22
Postural Dizziness	14
Muscle or Joint pains	16
Signs	
Weight loss	100
Hyperpigmentation	100
Postural Hypotension	86
Vitiligo	14
Alopecia	6
Carpal Spasm	8
Laboratory Parameters	
Hyponatremia	78
Hyperkalemia	67

Table 2: Etiology of Primary Adrenal Insufficiency noted in this study

Etiology	No (%)	Female: Male
Pulmonary Tuberculosis	5	2:3
Possible Auto immune PAI	12	8:4
Poly glandular auto immune syndrome type 1	3	1:2
Poly glandular auto immune syndrome type 2	4	4:0
Allgroove syndrome	3	1:2
Anti-Phospholipid Antibody Syndrome (APLA)	4	1:3
AdrenoLeukodystrophy	2	0:2
Adrenal metastasis	2	1:1
Post Bilateral Adrenalectomy	1	1:0



Figure 2: (a) Mucosal pigmentation. (b) Hyperpigmentation over the palm and skin crease along comparison with sibling. (c) Vitiligo with hyperpigmentation in AAD. (d) Alopecia in APS Type 1

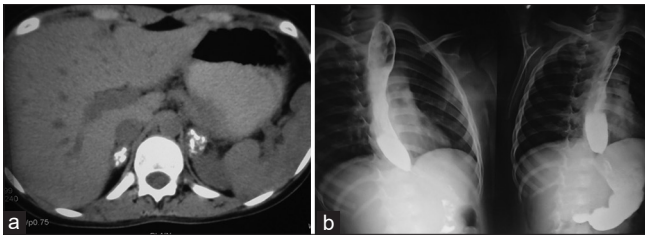


Figure 3: (a) CT Adrenal showed bilateral adrenal calcification in tuberculous AD. (b) Barium meal study showed fluid-filled dilated thoracic esophagus suggestive of achalasia cardia in AAA syndrome

normal gland tissue. Many reports in the Indian literature have documented the relationship of TB and sub-clinical adrenal deficiency and reversal with anti-TB treatment.^[15] While some of the studies have contradicted it.^[16]

The possible explanation why PAI due to TB is less common etiology in this study are both improvements in diagnostic techniques as well as effective implementation of TB eradication program.^[12] The Indian Government Central TB Division developed a case-based and web-based system called “Nikshay”. This centralized system helped with the reporting of all TB cases, whether they diagnosed in government hospitals or private sectors.^[17] The effective implementation of this plan, led to improved access to rapid molecular tests such as Gene Xpert MTB and line-probe assays and availability of imaging techniques to diagnose pulmonary and extrapulmonary TB. This also follows the switch, from intermittent therapy to an internationally accepted supervised daily regimen with drug-susceptible TB treatment. Access to new drugs and regimens for Multi drug-resistant TB (MDR-TB) through the Revised National TB Control Programme (RNTCP) as well as National Strategic Plan (2017-2025) leads to achieve the goal of Ending TB by 2025.^[12,18] Due to the effective implementation of the anti TB therapy (ATT), AD due to TB is less commonly seen in the India currently. Even though TB has not been eradicated from India, physicians are needed to be vigilant to identify the modern risk factors of TB like uncontrolled diabetes mellitus and HIV infection even in absence of fever with significant weight loss.

Among the adult population, autoimmune Addison's disease (AAD) is the most common cause of PAI worldwide.^[4,5] Presence of 21-hydroxylase autoantibodies (21OHAb) or autoantibodies against CYP21A2 identifies subjects with ongoing clinical or pre-clinical adrenal autoimmunity.^[19] The limitations for adrenal autoantibodies are they are not standardized, subject to wide methods variation and limited availability.^[20] Hence in our cohort only three were diagnosed as AAD based on the antibody reports. Hence antibodies against other associated autoimmune diseases like Anti TPO, GAD65, and parietal cell antibody are more important and will be compliment to diagnose AAD.^[19] Autoimmunity precedes over AD by years, as in many autoimmune disorders. AAD is a major component of autoimmune polyendocrine syndrome type 1 (APS1) and type 2 (APS2).^[21,22] Recognition of the APS and early

detection of the associated disorders can contribute to prevention of morbidity and mortality.

As per the recommendations by the Endocrine Society Clinical Practice Guidelines,^[5] all CYP21A2 negative individuals with unknown etiology of AD, should undergo CT scan of Adrenal/abdomen and chest to identify the disseminated infections like pulmonary and extrapulmonary TB, fungal infections, malignancies and adrenal metastasis. Apart from TB, our cohort did not find other infectious causes of PAI like Cryptococcus and histoplasmosis. All were extensively evaluated with careful history, clinical examination and imaging. CT guided adrenal biopsy is required for confirmation of rare fungal infection and metastasis of unknown primary after ruling out pheochromocytoma.

Four of our patients had acute onset adrenal insufficiency with deep venous thrombosis, subsequently diagnosed as Antiphospholipid syndrome (APS). PAI in APS occurs due to adrenal hemorrhage or hemorrhagic infarction related to adrenal vein thrombosis and another possible mechanism is autoimmune failure. Hence serological tests for lupus anticoagulant and anti cardiolipin antibodies are mandatory in all cases of adrenal hemorrhage and/or infarction.^[23]

Adrenoleukodystrophy (ALD) with coexisting AD was noted in two of this study cohort. One was cerebral ALD, and other was adrenomyeloneuropathic form of ALD. PAI may precede, coexist or develop after neurological manifestations.^[24] The diagnosis was confirmed by significant high levels of very long chain fatty acid and MRI imaging of demyelination pattern.

Two of our patients had gastrointestinal symptoms suggestive of dysphagia and vomiting while on optimal doses of hormonal therapy for AD. On detailed evaluation by upper gastrointestinal endoscopy, barium swallow, and CT abdomen, they were diagnosed to have achalasia cardia. Subsequent history of cry without tears since their childhood and detailed ophthalmological evaluation revealed bilateral dry eye with schirmer test report of alacrima. Hence, diagnosis of AAA syndrome or Allgrove syndrome was made. It is a rare autosomal recessive disorder characterized by ACTH resistant adrenal insufficiency, achalasia, and alacrimia.^[25]

The appropriate etiological diagnosis of adrenal insufficiency allows screening of other associated clinical features and reduces the risk of life-threatening complications. The clinical features may evolve over time; we recommend regular examinations for development of related features in all PAI of non-TB etiology.^[26]

The hormonal replacement therapy of PAI is similar regardless of the etiology. More than 90% of patients with AD require both glucocorticoids and mineralocorticoids.^[4,5] The lowest possible HC dose must be identified according to clinical and biochemical parameters to minimize long-term complications that include osteoporosis and cardiovascular and metabolic alterations.

The strength of this cohort study was that a large number of AD cases were included. This study revealed various etiological spectrum and clinical presentation of PAI noted in India, along with endocrine and non-endocrine syndromic associations. The study was done in a period where no recent evidences available regarding the etiological profile of AD in India, more than a decade after improvement in TB management strategies. This study is not without limitations. This study was conducted in a tertiary care referral center in patients with only symptoms and signs of AD, hence selection bias can't be ruled out. Adrenal functions including ACTH stimulation test were not evaluated in all TB patients, hence subclinical AD due to TB might have been missed. Extrapulmonary TB like TB meningitis and skeletal TB were not included, since many were already on glucocorticoids. Anti-adrenal antibodies were commercially available only in later part of the study hence we could not do in all possible cases of AAD. Renin and aldosterone levels were not measured to determine the presence of mineralocorticoid deficiency, and may be a predictor of subclinical or early AD.

CONCLUSION

Our study shows that TB is no longer the leading cause of AD in India. Autoimmune PAI and Polyglandular autoimmune syndromes are increasingly being recognized as cause of AD. PAI individuals require lifelong surveillance for possible development of coexisting autoimmune syndromes and need for glucocorticoid/mineralocorticoid therapy.

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Conflicts of interest

There are no conflicts of interest.

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