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Primary adrenal insufficiency among Sri Lankan adults: A cross-sectional study in National Hospital Colombo, Sri Lanka

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Abstract

Background:

Clinical, biochemical & radiological characteristics and aetiologies of primary adrenal insufficiency (PAI) among Sri Lankan adults are not known.

Aims:

To describe the clinical features, aetiology, diagnostic and treatment outcomes of patients with PAI in Sri Lanka.

Methods:

A cross-sectional study was conducted in Endocrine clinics of National Hospital of Sri Lanka. We screened prescription records to identify patients with PAI. Data was collected using a structured interviewer administered questionnaire and by reviewing clinic records, during their scheduled clinic visit.

Results:

Forty patients were recruited (median age 38 (IQR 27-52), men 35%, 361 patient-years follow up). Adrenal tuberculosis was the aetiology in 10/40. Cause was unknown in 29/40, among whom 16 had an associated other organ autoimmune dysfunction. Delay in presentation, diagnosis and presentations with Addisonian crisis were less in patients who presented after 2010 compared to those before (9 vs 18 months, 6 vs 12 months and 5/12 vs 3/28 respectively).

Hyperpigmentation (39/40), weight loss (32/40) and postural lightheadedness (27/40) were the common manifestations. Adrenal atrophy and adrenal calcification were seen in 20/30 and 6/30 respectively. All patients were on hydrocortisone, 31/40 were on fludrocortisone and none were on androgen replacement. Incidence of Addisonian crisis was 7.5 per 100 patient-years: commonest cause was lapses in medication adherence (14 of 24 events).

Conclusion:

Tuberculosis was the cause of PAI in 25% of adult patients. Aetiology in others is presently unknown. Delay in presentation and diagnosis has shortened over time. Addisonian crisis after diagnosis is commonly due to non-adherence.

Keywords: Primary adrenal insufficiency, Addison disease, adrenalitis, adrenal crisis, South Asia

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Introduction

Primary adrenal insufficiency (PAI) is a rare disease with an estimated incidence of 4.4-6.2 new cases per million population per year 1,2 and prevalence of 39 – 221 per million population.3 Almost all the data are from Europe. Its epidemiology in South Asia is less well described. PAI is a commonly overlooked, potentially life-threatening but easily treatable disease. Many advances have been made in the last couple of decades in diagnosis, treatment and follow-up. With improved treatment of PAI, increased longevity of the patients has exposed other problems related to quality of life, bone health, metabolic and cardiovascular disease and evolving autoimmune co-morbidities.

Despite these advances, data on aetiology, disease presentation, clinical, biochemical and radiological characteristics, treatment practices and clinical outcomes are scarce, particularly from South Asian and developing countries. To the best of our knowledge, data from Sri Lanka has not been reported before. We aimed to describe the above characteristics in a cohort of patients with PAI followed up in a tertiary care referral centre for endocrinology in Colombo, Sri Lanka.

Methods

We conducted a descriptive cross-sectional study on adults with primary adrenal insufficiency followed up at the Diabetes and Endocrine Clinic of National Hospital Colombo and University Medical Unit Endocrine Clinic at the same institution. Prescription records of the clinics were manually screened between October to December 2019 to identify patients with primary adrenal insufficiency who were being followed up in the clinics since their inception (these records contained the contact details, diagnosis and current medication). Patients were contacted over the phone and were followed up to the next visit where past investigations and follow up records were reviewed to gather additional information.

Clinical history, laboratory and radiological investigations were retrieved by reviewing the medical records (held with the patient) and interview, based on a structured interviewer administered questionnaire. All data collection was done by the principal investigator. The diagnosis of primary adrenal insufficiency was established based on clinical features, short synacthen test and increased ACTH level whenever available. Short synacthen test was performed after injection on 250 mcg of synacthen and checking cortisol levels before and 30 and 60 minutes after the injection, using immunoassay method (Advia Centaur or Abbot Architect i2000 platforms) and peak value below 550 nmol/L was considered diagnostic of adrenal insufficiency. When ACTH assays were not available, clinical judgement (hyperpigmentation, absence of clinical or other laboratory features predictive of secondary or tertiary cortisol insufficiency) was exercised to establish the diagnosis. Aetiology was determined based on radiological and clinical evidence. Patients with PAI, enlarged adrenals on imaging and clinical response to anti-tuberculous therapy were retrospectively diagnosed to have tuberculous adrenalitis.

Written informed consent was obtained from all the participants. The study was approved by the Ethics Review Committee of National Hospital of Sri Lanka. Data was analysed using SPSS software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Descriptive statistics of non-parametric continuous variables are presented as median and interquartile range. Missing data were excluded case-wise in the analysis.

Results

Population characteristics

Screening of prescription records in the two endocrine clinics at National Hospital of Colombo, Sri Lanka identified 60 patients with primary adrenal insufficiency. Among them, data from 40 patients were available for the analysis. Others were uncontactable for consenting, interview and data collection. Available data amounted to 361 patient-years of follow up. Clinical & epidemiological characteristics of the participants are summarized in table 1.

Clinical presentation

Majority of the patients were referred to the clinic from medical units of the same hospital (18/40) or other hospitals (17/40) while the others were self-referrals.

Hyperpigmentation was the commonest clinical feature noted at presentation. It was first noticed by the patient him/herself in 12/39, by a family member or a friend in 14/39 or by the healthcare provider in 14/39. Addisonian crisis was commoner as a presentation among patients who were diagnosed before 2010, compared to those after (5/12 vs 3/28). Other clinical features are summarized in table 2.

Median delay in patient presentation (from the time of earliest symptom onset to first healthcare contact) was 12 months (range 2 - 36) & the delay in diagnosis

(time from first healthcare contact to confirmation of the diagnosis and commencement of glucocorticoid replacement) was 5 months (range immediate to 24 months).

Median number of healthcare teams that evaluated the patient between first presentation and confirmation of the diagnosis was 2 (range 1 to 6).

Table 1: Characteristics of the study population

Parameter	Diagnosed before 2010	Diagnosed after 2010	Total cohort
Number	12	28	40
Age (median, IQR)	39 (25-55)	38 (29-49)	38 (27 – 52)
Males, number (%)	5 (41.7)	9 (32.1)	14 (35)
Level of education (%)			
No formal education	2 (16.7)	1 (3.6)	3 (7.5)
Primary school	2 (16.7)	2 (7.2)	4 (10.0)
Secondary school	4 (33.3)	13 (46.4)	17 (42.5)
Passed Ordinary level	2 (16.7)	6 (21.4)	8 (20.0)
Passed Advanced level	1 (8.3)	1 (3.6)	2 (5.0)
Vocational training	1 (8.3)	5 (17.9)	6 (15.0)
Graduate or above	0	0	0
Monthly family income in SLR x 103, median (IQR)*	38 (23-54)	41 (27-50)	40 (25 – 52)
Age at diagnosis of PAI in years, median (IQR)	34 (18 - 48)	28 (22-36)	30 (20 – 40)
Duration of receiving treatment in years, median (IQR)	13.0 (9.5-16.0)	4.1 (1.0-8.4)	5.0 (2.3 – 11.5)
Delay in presentation in months, median (IQR)	18.0 (7.1-28.9)	9.2 (2.5-16.3)	12.0 (6.1 – 19.3)
Delay in diagnosis after healthcare contact in months, median (IQR)	12.0 (6.0-18.4)	6.0 (2.0-11.1)	5 (2 – 12)
Aetiology, number (%)			
Tuberculous adrenalitis	4 (33.3)	6 (21.4)	10 (25.0)
Autoimmune adrenalitis	NK	NK	NK
Other	0	1 (3.6)	1 (2.5)
Unconfirmed	8*(66.7)	2 (7.2)	29 (72.5)
Co-morbidities, number (%)			
Hypothyroidism	5 (41.7)	5 (17.9)	10 (25.0)
Hypertension	2 (16.7)	4 (14.5)	6 (15.0)
Hypergonadotrophic hypogonadism	2 (16.7)	2 (7.2)	4 (10.0)
Type 1 diabetes	1 (8.3)	2 (7.2)	3 (7.5)
Dyslipidaemia	1 (8.3)	2 (7.2)	3 (7.5)
ASCVD	0	0	3 (7.5)
Type 2 diabetes	1 (8.3)	1 (3.6)	2 (5.0)
Treatment, number (%)			
Hydrocortisone	12 (100.0)	28 (100.0)	40 (100.0)
Prednisolone	0	0	0
Fludrocortisone	11 (91.7)	20 (72.0)	31 (77.5)

* At the time of data collection (2019/2020)
ASCVD: Atherosclerotic cardiovascular disease, IQR: Inter-quartile range, NK: not known, SLR: Sri Lankan Rupees

Table 2: Clinical features at presentation (N = 40)

Clinical manifestation	Number of patients	Percentage
Increased skin pigmentation		
Generalized	28	70.0
Localized	11	27.5
Total	39	97.5
Weight loss	32	80.0
Anorexia	30	75.0
Nausea and/or vomiting	27	67.5
Postural dizziness	23	57.5
Symptoms suggestive of recurrent hypoglycaemia	16	40.0
Abdominal pain	10	25.0
Addisonian crisis	8	20.0
Diarrhea	7	17.5
Salt craving	3	7.5

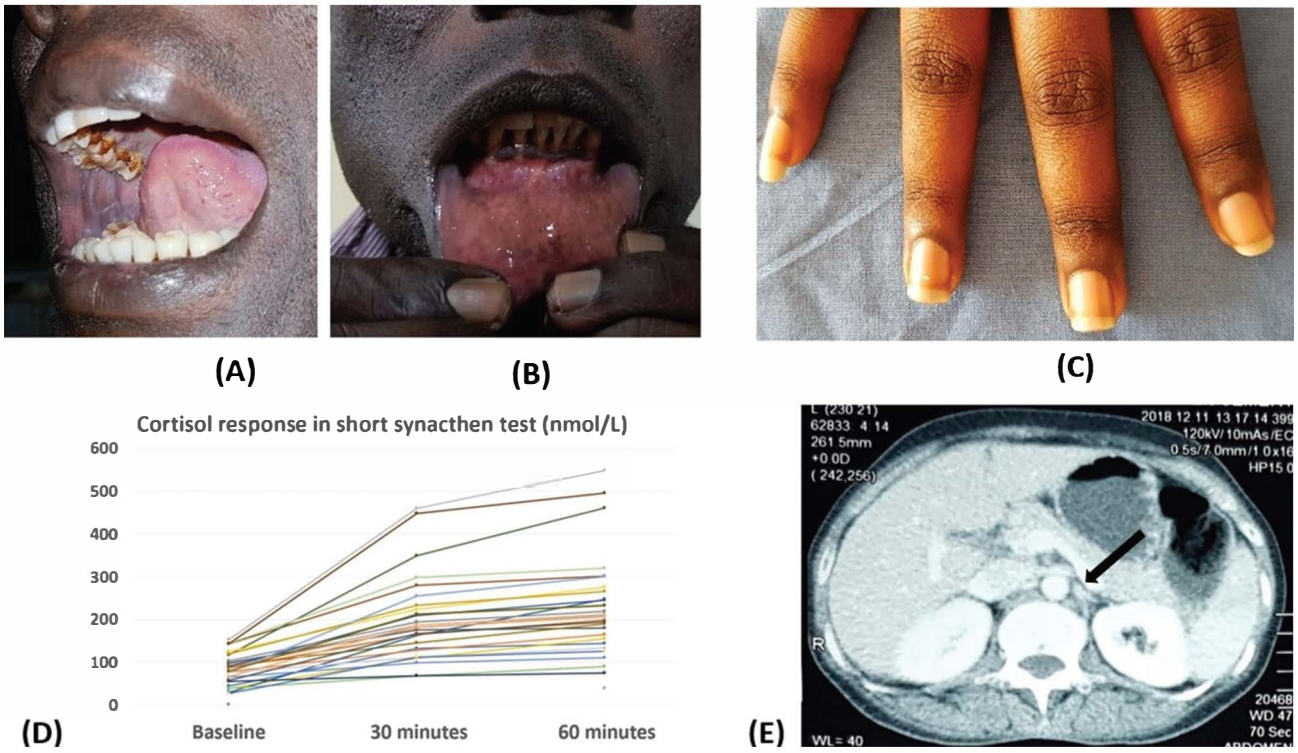

Figure 1. (A) Hyperpigmentation in buccal mucosa, lips and face
(B) Hyperpigmentation in gingiva, nails and fingers
(A and B from a patient who had generalized hyperpigmentation).
(C) hyperpigmentation of knuckles and nail bed,
(D) Cortisol response to synacthen in short synacthen test. Serum total cortisol levels (in nmol/L) in venous blood were determined before and 30 & 60 minutes after the injection of 250 micrograms of synacthen.
(E) Atrophied calcified right adrenal on abdominal CT scan

Compared to patients who were diagnosed before 2010, those diagnosed after 2010 had a shorter delay in presentation (median 9 vs 18 months) and a shorter delay in diagnosis (median 6 vs 12 months).

Investigation findings

In our cohort, records of short synacthen test were available in 35 patients. Median (and IQR) cortisol values at baseline, 30 minutes and 60 minutes were 79 (45 – 105) nmol/L, 182 (120 – 218) nmol/L and 208 (142 – 252) nmol/L respectively. The median difference from 0 to 30 minutes and 30 minutes to 60 minutes were 92 (62 – 129) nmol/L and 25 (20 – 40) nmol/L respectively. Peak cortisol levels were observed at 60 minutes in all participants. The median peak rise was 117 (86 – 156) nmol/L. Greater than 150 nmol/L rise from the baseline was observed in 10/35 (28.6%) of patients (Figure 1D). A peak serum total cortisol level of 550 nmol/L or more was cut off to exclude the diagnosis of adrenal insufficiency. Three patients had a peak cortisol level close to 500 nmol/L. The diagnosis was established based on clinical assessment, and they remained to be on hydrocortisone long term. These patients required long term hydrocortisone replacement.

ACTH levels had been selectively performed only when secondary adrenal insufficiency was clinical suspected (5 patients). Similarly, when clinically indicated 17-hydroxy progesterone levels were performed to rule out non-classic congenital adrenal hyperplasia (3 patients). Aldosterone renin ratio was not performed in any of the patients included. The lower use of these investigation is a result of unavailability and/or high cost of these investigations in our setting. Blood glucose, serum electrolytes and blood gas analyses prior to treatment commencement was not available in most patients.

Radiological imaging was performed in most patients (30/40). Majority had plain X-ray radiograph (27/40), ultrasonography of the abdomen (25/40) or both (22/40). Six patients had undergone CT of the abdomen (Figure 1E). Adrenal atrophy was a common finding (20/30). Adrenal calcifications were noted only in 6/30.

Aetiology

Among our study population, five had confirmed tuberculous adrenalitis. Five of the others had a presumptive diagnosis of adrenal tuberculosis made based on past history of tuberculosis and clinical presentation. One patient had developed primary adrenal insufficiency after starting highly active anti-retroviral treatment. Rest of the cohort had no definite cause established. Notably, none were investigated for autoimmune adrenalitis. However, autoimmune thyroiditis, hypergonadotrophic hypogonadism (Turner syndrome and Klinefelter syndrome excluded), type 1 diabetes and vitiligo were present 10/40, 4/40, 3/40 and 2/40 patients respectively suggesting a possible autoimmune aetiology. Overall, 16/40 patients had an associated autoimmune disease. None of the patients had mucocutaneous candidiasis or neoplastic aetiologies.

Co-morbidities

In addition to the auto-immune co-morbidities listed above other chronic diseases were also prevalent in this population. These included hypertension (6/40), type 2 diabetes (2/40), dyslipidaemia (3/40) and ischaemic heart disease (3/40).

Treatment, outcomes and adherence

All patients were on hydrocortisone for glucocorticoid replacement. Majority (30/40) received 20 mg a day in 2 to 3 divided doses, while the others required higher (22.5 mg/day in two patients, 25 mg/day in three, 30 mg/day in one patient) or lower (15 mg/day in two patients, 17.5 mg/day in two patients) doses. When adjusted to body weight, the median requirement was 0.34 mg/kg/day (0.32 – 0.39). Thirty one (out of forty) required fludrocortisone therapy. The dose ranged from 25 to 100 micrograms per day. None were on androgen replacement.

Adherence to therapy was satisfactory in the majority. All reported taking the morning dose of hydrocortisone on all days, while 12/40 reported missing mid-day and/evening doses infrequently. The main challenge for sustained adherence was unavailability of the medication from time to time. Incidence of acute adrenal crisis was 7.5 per 100 patient years (24 events per 321 follow up years). Commonest precipitating factors were lapses in adherence to glucocorticoid replacement (14/24) and infections (acute gastroenteritis 6/24, cellulitis 2/24 and pneumonia 2/24).

Majority of the patients who had pigmentation on presentation reported subjective perception of reduction in hyperpigmentation (36/39). Improvement in other symptoms (postural dizziness, vomiting) weight regain were consistent features of response to therapy. Most had achieved good resolution of symptoms at their first follow up visit (36/39), which usually took place in 1 to 2 months.

Patient awareness and concerns

All patients were aware of the timing of hydrocortisone. 30/40 could specify the dose they were using. Majority (35/40) were aware that the dose should be increased / doubled in case of acute illness.

However, only 18/40 could mention the steps to take in case of intractable vomiting. Commonest concerns were irregularities in availability of medication and its cost. None of the patients were on injectable hydrocortisone, which is not available in Sri Lanka. Thirty-five patients had received 'steroid card' at some point in time. But only 25 of them carried the card with them. The others were not aware its need and importance.

Discussion

Primary adrenal insufficiency is a rare disease. Its prevalence ranges between 4 to 11 per 100 000 population[3], but with significant geographical variation, ranging from 39-221 cases per million in Europe to 5 cases per million in Japan.[4,5] There is limited data on its prevalence in South Asia. To the best of our knowledge, this is the first report on primary adrenal insufficiency from Sri Lanka and adds to the limited literature from other South Asian countries. This unravels several important knowledge gaps.

Conventionally, infectious aetiologies were thought to be the leading cause for primary adrenal insufficiency in low-middle income countries in Asia/Africa while autoimmune adrenalitis was thought to predominate in the high income countries in the West. In Europe 75-96% of cases are due to autoimmune adrenalitis while in Japan tuberculosis was the aetiology in 37% of cases.[4,5] Among those with autoimmune adrenalitis other autoimmune organ involvement is seen in about two thirds.[6] Ten of the 40 patients (25%) in our cohort were thought to have tuberculous adrenalitis. This was confirmed in five and considered highly likely in the rest. This is less than what was reported from India in 2003, (47%)[7], but comparable to more recent studies where tuberculosis was the cause only in 13% (5/36) to 15% (13/89).[8,9] Patients in two retrospective cohort studies. Interestingly, in one of these studies, adrenal histoplasmosis was the commonest cause for primary adrenal insufficiency affecting 45% of their patients (40/89).[9] Histolplasmosis is rare, but known to occur in Sri Lanka, largely outside Western Province[10] where most of the patients in our cohort were residing. Forty percent (16/40) of patients in our cohort had concomitant autoimmune involvement of other organs, suggesting possible autoimmune aetiology. Unfortunately, adrenal autoantibodies were not performed due to non-availability. Autoimmune adrenalitis was thought to account for up to 25% of patients with primary adrenal insufficiency in India.[9] Aetiology of PAI in most of our patients is not known and this warrants further studies.

The diagnosis of adrenal insufficiency was confirmed with short synacthen test in most of the patients. This was performed by sampling venous blood for serum total cortisol at baseline and 30 and 60 minutes after the injection of synacthen. All patients achieved the peak cortisol response at 60 minutes after injection. This is comparable with several other studies.[11, 12] In fact some patients who failed the test at 30 minutes may passed at 60 minutes.[11] Therefore, in settings with limitations on assay availability or cost concerns, testing the baseline and 60-minute response will be a reasonable alternative to three-point testing. However, given the retrospective, non-comparative nature of this study, it is not possible to draw a definitive conclusion. Our prescribing practices are like that of other series reported in the past and with current international guidelines.[13] However, the decisions were clinically justified with limited biochemical evaluation. It is unclear if the outcomes would be different if dose titrations were based on clinical as well as biochemical criteria.

The study has a few limitations. It was limited to two clinics in one tertiary endocrine referral centre. Endocrinology clinical service is now available in almost all provinces in the country and our findings may not reflect the status of other regions where sociocultural status and incidence of tuberculosis are different. Retrospective nature of the study introduced limitations due to recall bias and missing data (eg: data on clinical and biochemical results at presentation, route of synacthen administration and assay methods, response to treatment, quality of life). Cross sectional design meant that we could not evaluate the performance of diagnostic tests. Our cohort did not include any patients with hypoadrenalism due to metastatic malignancies. Furthermore, we could not assess the mortality data. Status of the patients who could not be contacted remains unknown. Fourth, we did not have data on route of synacthen administration in most patients. Finally, limited availability of biochemical investigations prevents drawing conclusions about their utility in diagnosis and monitoring.

Nevertheless, comparison of patient profiles who were diagnosed within last ten years compared those who were diagnosed before that provides useful insights into the evolution of dedicated endocrinology service in Sri Lanka. The Diabetes and Endocrine Clinic at the National Hospital of Sri Lanka was the first such dedicated service, started in year 2004. Notably, presentation in Addisonian crisis, delay in presentation and diagnosis have been less after 2010 compared to before. Overall, the median delay to diagnosis in our cohort is comparable to that from some European centres.[14] Yet, the delay

remains a concern. For example, in a cohort from Poland, patients who presented with Addisonian crisis, had a longer delay (6 months vs 3 months) indicating the need for early diagnosis. It highlights the need for raised awareness among health care providers at primary care level for early recognition and appropriate referral of patients with features of adrenal insufficiency.

Furthermore, we identified several practices that needs reconsideration. Firstly, routine performance of serum ACTH, 17-hydroxyprpogesterone and aldosterone renin ratio are useful in excluding the differential diagnosis and determining the need for fludrocortisone therapy. Their underutilization reflects the limited availability and high cost of those biochemical investigations which even in today's practice are reserved for essential circumstance based on clinical judgement. Secondly, all our patients were on hydrocortisone for glucocorticoid replacement, administered in two to three divided doses. Although the level of adherence to therapy was satisfactory, use of prednisolone, which can be administered once a day, may be a useful strategy with better patient convenience and enhanced adherence without an increase in the risk of iatrogenic hypercortisolism.[15] It is also a less expensive option. For example, annual cost for hydrocortisone 20 mg/day was 10117.80 SLR (49.79 USD) compared to 923.45 SLR (4.50 USD) for an equivalent dose (5mg/day) of prednisolone in 2022. However, the major limitation is the unavailability of 1 mg prednisolone tablets without which finer dose titrations are not feasible. In fact, higher doses of prednisolone may increase the risk of cardiovascular disease,[14] hence the need for optimum dosing. Alternatively, dual release hydrocortisone tablets are useful in preventing recurrent peaks of cortisol.[16,17] However, this is a more expensive strategy, currently not available in Sri Lanka and in most developing countries. Thirdly, the aetiology of PAI remains unknown in the majority of patient. If autoimmune aetiology is identified, periodic focused screening for other common organ autoimmunity and dysfunction will be possible. Fourthly, more efforts are needed to educate the patients on sick-day rules and use of steroid cards, which can further reduce the incidence of adrenal crisis. Finally, greater attention to other aspects of care such as addressing psychosocial concerns, bone health & non-communicable diseases should be considered.[4,13]

Conclusions

Aetiology of PAI is not established in most patients. Tuberculosis and adrenal autoimmunity may be the cause in a significant proportion of patients. A significant reduction in Addisonian crisis and delays in presentation and diagnosis is observed in the last decade. Management of PAI is mostly guided by clinical assessment and cost-effectiveness of additional biochemical indices for diagnosis and monitoring need to be studied further. Improving patient education and introducing 1 mg strength prednisolone tablets may improve the adherence, treatment outcomes and cost.

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