Original Article

Endocrine dysfunction in patients of leprosy

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ABSTRACT

Background: Leprosy is a chronic granulomatous disease and affects many internal organs in addition to the skin and peripheral nerves. Endocrine dysfunction is often silent and is often missed in patients of leprosy leading to significant morbidity. We studied the presence of occult endocrine disorders in leprosy patients and compared the same with disease parameters. **Materials and Methods:** We evaluated 40 patients of leprosy (aged 18–70 years, any duration) in this cross-sectional, observational study. All subjects were assessed for pituitary, thyroid, adrenal, gonadal function, and dynamic testing was done when deemed necessary. The participants were divided into two groups: Group 1 (Leprosy, $n = 40$) and Group 2 (Controls, $n = 20$) and the data were analyzed with appropriate statistical tests. **Results:** The study participants (35 males, 5 females) had a mean age of 36.4 ± 11.3 years, and duration of the disease was 2.5 ± 5.5 years. Eleven out of 40 patients showed results consistent with an endocrine disorder, including subclinical hypothyroidism ($n = 4$), sick euthyroid syndrome ($n = 3$), growth hormone (GH) deficiency ($n = 2$), primary hypogonadism ($n = 2$) and secondary hypogonadism in one patient. One patient had partial hypopituitarism (GH deficiency and secondary hypogonadism) and none of the controls showed any hormonal dysfunction. Testosterone levels showed inverse correlation with the number of skin patches ($P = 0.0006$). **Conclusion:** Occult endocrine dysfunction is seen in a quarter of patients with leprosy. Thyroid and gonadal axes abnormalities are common, and the severity is more in lepromatous forms of the disease. Further large studies are required to confirm the findings observed in our study.

Key words: Endocrinology, hypogonadism, hypothyroidism, lepromatous, leprosy

Introduction

Leprosy is a chronic, granulomatous disease prevalent in India and other third world countries.[1] Leprosy and tuberculosis are the two common mycobacterial diseases leading to significant morbidity and mortality in our country.[2] The presence of leprosy in India has been documented in the older medical treaties like *Charaka Samhita and Sushruta*.[3] The improvement in sanitation and hygiene practices has reduced the burden of leprosy over the past few years. However, the social stigma attached to the disease persists despite a lot of advances in the management of the disease. The disfigurement and disabilities are the major reasons behind the social stigma of the disease.[4] The disease is caused by mycobacterium leprae and the classical sites of involvement are skin and peripheral nerves.[5] Though the disease manifests predominantly in peripherally visible organs, it involves other internal organs also. Endocrine disorders are often silent, unreported and remain undiagnosed in patients of leprosy.[6]

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Endocrine disorders in leprosy result from the direct involvement of the tissue or due to the alteration in immune response. Infection with lepra bacilli is characterized by the changing immune response as a spectrum of the disease activity.[7] The commonly reported endocrine disorders in leprosy include hypogonadism, infertility and osteoporosis.[6] These disorders usually occur late in the course of the disease and are often asymptomatic. The pathogenic mechanism of tissue destruction includes the altered immune response mediated by the inflammatory cytokines and local changes due to endarteritis and fibrosis.[8] Hypogonadism and infertility

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are the common observations in patients of leprosy. The gonadal involvement is common because testes may act as the reservoir for the lepra bacilli. Osteoporosis is also described more in leprosy and is usually secondary to the hypogonadism. The involvement of other hormonal axes is not widely studied, and there is limited research on this subject from India.[9,10] Hence, we conducted this study to assess the prevalence of occult endocrine dysfunction in patients with leprosy and also correlated the same with important disease-related parameters.

Materials and Methods

We conducted this cross-sectional, observational study at a tertiary level referral hospital in India. All patients with a known diagnosis of leprosy (aged 18–70 years) under follow up at our hospital were included in the study. We included newly diagnosed patients and also the patients on regular follow-up. Leprosy was diagnosed based on the presentation, clinical examination, and skin biopsy findings. For the study purpose, the disease has been classified as per the consensus classification of the Indian Association of Leprologists into five types (tuberculoid, borderline tuberculoid, borderline lepromatous, lepromatous and pure neuritic leprosy).[11] The cases of indeterminate leprosy were excluded because of vague clinical and histopathological features pending confirmation of the diagnosis. All the patients with known thyroid or endocrine disorders, previous exposure to head and neck radiation were excluded from the study. All the participants were divided into two groups: Group 1 (Leprosy patients, $n = 40$) and Group 2 (Controls, $n = 20$). The age and sex matched controls were selected from the relatives of the patients attending the hospital.

A detailed history was obtained from all the participants, and the specific features include the duration, type of the leprosy, smear status, presence of lepra reactions, corticosteroid use and the anti-mycobacterial regime used. Systemic examination of the patients is focused more on endocrine glands, including goiter, testicular size, gynecomastia and loss of secondary sexual characteristics. A detailed dermatological examination was carried out to include the number of cutaneous lesions and the peripheral nerves involved. The presence of long term neurologic complications like claw hand and permanent deformities in the pure neuritic form of leprosy were noted from the study participants. All patients were explained about the aims and objectives of the study. The local Ethics Committee approved the trial protocol, and all patients provided written informed consent.

A fasting blood sample was collected from each participant at 0800 h in fasting state, and the serum was separated and stored at −80°C. All the samples were analyzed for pituitary profile (Growth hormone [GH], insulin-like growth facor-1 [IGF-1], luteinizing hormone [LH], follicle stimulating hormone [FSH], prolactin, adrenocorticotrophic hormone [ACTH]), thyroid profile (Free triiodothyronine, free thyroxine [FT4], total triiodothyronine [T3], total thyroxine [T4], thyroid stimulating hormone [TSH]) and adreno-gonadal profile (cortisol, total testosterone, estradiol [E2], dehydroepiandrosterone [DHEA], DFEA sulfate [DHEAS]). Patients with morning cortisol <200 nmol/L were subjected to modified ACTH stimulation test.[12] We did not perform any dynamic testing for the somatoform, gonadal and thyroid axes evaluation. The entire hormonal panel was evaluated using electrochemiluminescence assay barring IGF-1 and testosterone, which were measured by the enzyme immunoassay method.

Primary hypothyroidism is defined as low FT4 (normal, 0.8–2.1 ng/ml) with elevated TSH (normal, 0.5–6.5 μIU/ml) and subclinical hypothyroidism as normal FT4 with raised TSH. The sick euthyroid syndrome was defined by the presence of low T3 and T4 along with normal TSH levels. Primary hyperthyroidism is defined as elevated FT4 with low TSH and subclinical hyperthyroidism as normal FT4 with suppressed TSH. Hypogonadism was defined in males with testosterone <300 ng/dL (normal 310–1200 ng/dL) and amenorrhea along with E2 <30 pg/mL in females. The hypogonadism was termed as primary (elevated LH and FSH) or secondary (low or normal LH/FSH). Adrenal insufficiency was diagnosed when 8 AM cortisol is <100 nmol/L and stimulated cortisol is below 500 nmol/L. An IGF-1 level below the range specific for the age is considered as diagnostic of GH deficiency, and we did not do GH stimulation test in these individuals. A diagnosis of complete hypopituitarism was made with dysfunction of more than or equal to three hormonal axes and partial hypopituitarism with two hormonal axes abnormalities.

Data are presented as mean ± standard deviation and a comparison between the groups was done using non parametric (Mann–Whitney U-test) and Fisher's exact tests. Spearman's correlation test was used for correlation between numerical variables, and a $P < 0.05$ was considered significant. The statistical analysis and graph generation were done using the Graph Pad Prism Software, Version 6 (Graph Pad Software, San Deigo, CA, USA).

Results

The study participants consist of 35 males and 5 females with a mean age of 36.4 ± 11.3 years and disease duration of 2.5 ± 5.5 years. Twenty-eight (70%) patients had BT leprosy, six borderline lepromatous, four lepromatous leprosy, and the remaining two had pure neuritic disease. The majority (34/40) of the patients were smear negative, and the remaining six had smear positivity. The leprosy related complications like permanent deformities and lepra reactions were seen in 21 patients. Anesthetic skin patches were seen from a single to multiple numbers extending up to a maximum of 50 in a patient of lepromatous type. The number of peripheral nerves involved ranges from none to 6 and the nerve thickening was observed in 35 patients. Gynecomastia was observed in nine patients out of 35 males, and none of the patients had testicular atrophy and loss of secondary sexual characteristics. All the patients received three drug regime and only two patients had completed their course of therapy and are being followed up without therapy.

Eleven out of 40 patients showed results consistent with an endocrine disorder, including subclinical hypothyroidism (n = 4), sick euthyroid syndrome (n = 3), GH deficiency (n = 2), primary hypogonadism (n = 2) and secondary hypogonadism in one patient. One patient had partial hypopituitarism (GH deficiency and secondary hypogonadism), and none of the participants showed features of complete hypopituitarism. None of the patients had primary hypothyroidism, hyperthyroidism, hypocortisolism, and none of the controls showed any hormonal dysfunction.

The comparison between the groups regarding the clinical profile and hormonal parameters is given in Table 1. Briefly, the findings include low levels of thyroid hormones and testosterone in patients with leprosy when compared to control population. Adrenal and pituitary hormones did not show any alteration between both the groups. We performed a univariate correlation analysis with all hormonal parameters and parameters (age of the patient, duration of disease and a number of skin patches) of leprosy. Testosterone concentration showed an inverse correlation with the number of skin patches [Figure 1] and none of the other hormones have shown significant correlations with other evaluated parameters.

Discussion

Our study revealed the presence of endocrine disorders in 28% (11 out of 40) of the leprosy patients. Previous studies revealed involvement of adrenal axis in 30% of patients, hypogonadism in 50% and metabolic bone disease in 40% of patients.[6,13,14] Our data are not comparable to the previous studies as we have evaluated the entire hormonal panel in the same patients and not individually for each hypothalamic pituitary axis.

Thyroid disorders are the most common finding observed in our study. The prevalence of subclinical hypothyroidism was seen in 10–20% of the population and are more

Table 1: Comparison between 2 groups regarding their clinical and hormonal profiles

Feature	Units	Group 1 (leprosy) *n*=40	Group 2 (controls) *n*=20	*P*
Age	Years	36.4 (11.3)	34.2 (10.6)	0.7651
Sex	Male/ female	35/5	15/5	0.8929
Pituitary profile				
Growth hormone	ng/mL	9.5 (4.9)	10.4 (7.3)	0.9475
IGF-1	µg/L	216.1 (102.7)	238.5 (98.6)	0.6313
LH	IU/L	7.8 (5.1)	4.7 (3.3)	0.5483
FSH	IU/L	6.2 (4.6)	9.2 (6.8)	0.5160
Prolactin	pmol/L	465.8 (186)	428 (97.4)	0.5708
ACTH	pmol/L	5.3 (3.8)	4.6 (3.7)	0.6269
Thyroid profile				
T3	nmol/L	0.68 (0.28)	0.93 (0.17)	0.0068
T4	µg/dL	4.8 (1.2)	7.4 (2.3)	0.1182
FT3	pmol/L	1.2 (0.6)	1.8 (0.5)	0.1997
FT4	ng/dL	0.68 (0.18)	1.1 (0.2)	0.0037
TSH	mIU/L	2.5 (1.4)	2.2 (0.7)	0.3597
Adreno-gonadal profile				
Cortisol (8 am)	nmol/L	291.3 (91.5)	257.3 (94.2)	0.7675
DHEA	ng/dL	268.5 (105.6)	360.3 (123.2)	0.5521
DHEAS	µg/dL	204.7 (114.8)	183.8 (86.7)	0.4465
Total testosterone (8 am)	ng/dL	418.6 (184.2)	649.6 (210.7)	0.0253
Estradiol	pmol/L	118.4 (110.3)	102.2 (134)	0.7193

Mean (SD). SD: Standard deviation, IGF-1: Insulin-like growth facor-1, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, ACTH: Adrenocorticotrophic hormone, T3: Total triiodothyronine, T4: Total thyroxine, FT3: Free triiodothyronine, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, DHEA: Dehydroepiandrosterone, DHEAS: Dehydroepiandrosterone sulfate

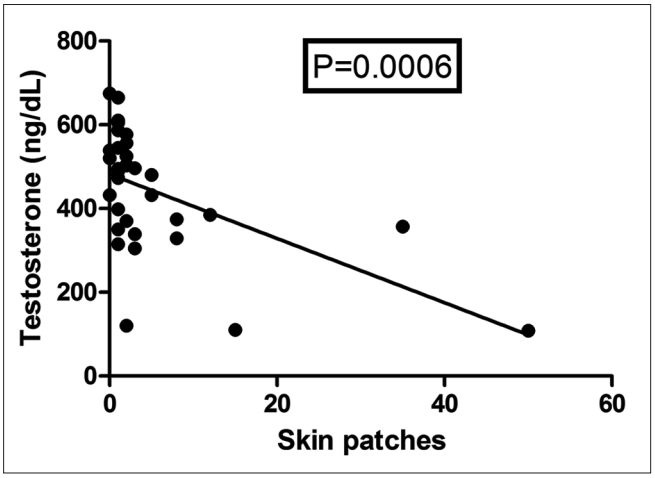

Figure 1: Correlation between the number of skin patches and testosterone

common due to the presence of autoimmune thyroid disease. The presence of leprosy could alter the immune response and predispose the individuals to develop autoimmune thyroid disease.[15] However, we did not perform thyroid antibody testing in our patients to confirm the presence of autoimmune thyroid disease. Previous reports suggest conflicting results and the majority of studies confirms the presence of the sick euthyroid syndrome.[16] Clinically significant thyroid dysfunction is not commonly seen after leprosy, and none of our patients had primary hypothyroidism.

Hypogonadism is observed in 10–80% of patients of leprosy as described by different authors.[6] The gonadal involvement observed in leprosy is restricted to testes and one of our patients had features of secondary hypogonadism. This patient aged 65-years-old had leprosy for 34 years and finished his therapy 18 years back. The observed secondary hypogonadism could have been due to the advanced age of the patient rather than due to the bacillary involvement. Figure 1 shows that the gonadal involvement is more severe in lepromatous form of the disease, and the same has been reported earlier.[17] None of the female participants had gonadal dysfunction and previous reports suggest menstrual abnormalities in 30% of patients. The low prevalence of hypogonadism (2/35 males) seen in our study could be due to the shorter duration of the disease and young age of the patients in our study.

Two patients in our study had GH deficiency and one of the patients also had secondary hypogonadism as described previously. The involvement of GH abnormalities has not been studied earlier. Leprosy is seen predominantly in young adults and middle age and is rarely described in children.[18] This could be the reason for the lack of comparable data about the effects of lepra bacilli on GH axis. The lack of adrenal involvement in our study could be due to the cross-sectional nature of the hormonal estimation and lack of stimulatory testing in all the participants. Previous reports suggest that the adrenal androgen, DHEAS is significantly low in leprosy patients due to higher levels of inflammatory cytokines.[19,20] The strength of our study includes an assessment of all hormonal axes in leprosy patients, and no such study has been conducted earlier from our country. The limitations of our study include the cross-sectional nature of the study, small sample size, failure to perform dynamic testing and the lack of evaluation of bone health. Our data preclude comparison of endocrine dysfunction between lepromatous and tuberculoid forms of leprosy due to small sample size.

Conclusion

Occult endocrine dysfunction is common in patients with leprosy and is seen in a quarter of patients. Thyroid and gonadal axes abnormalities are identified in the majority of patients. The endocrine dysfunction is related to the severity of the disease and is more common in lepromatous forms of the disease. Further large scale studies with more number of patients are required to confirm the findings observed in our study.

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