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Management of Acromegaly associated Late-onset hypogonadism by Siddha medicine: A case report

Case Report

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Abstract

Male Hypogonadism is the condition diagnosed in men with signs and symptoms of testosterone deficiency. Hypogonadism may be further classified as primary or secondary caused due to organic or functional pathology. This classification has significant therapeutic implications for instituting gonadotropin therapy to restore testosterone levels, spermatogenesis and so fertility is possible in secondary hypogonadism but not in primary hypogonadism. Testosterone replacement therapy (TRT) remains the mainstay and primary therapeutic option in the treatment of hypogonadism. In this case report, we discuss acromegaly associated Late-onset hypogonadism (LOH) treated successfully with Siddha medicine regimen on screening with Androgen deficiency in aging male (ADAM's) Questionnaire, laboratory investigation of total testosterone level and evaluated the patient's quality of life using the Aging Male's symptoms scale (AMS) for prognosis. Siddha treatment regimen such as *Poonaikali vidhai chooranam* with *Amukkra chooranam* was administered for one year. Total testosterone level improved from 70 ng/dl to 172 ng/dl and ADAM's score reduced from 49 to 27, while AMS score reduced from 5 to 1 indicating an alternative ray of hope to TRT.

Key Words: Testosterone deficiency, *Poonaikali vidhai choornam, Amukkra choornam*, ADAM's score, AMS scale.

Introduction

Hypogonadism is defined as a clinical syndrome caused by the failure of the testes to produce physiological concentrations of testosterone and or spermatozoa count within normal range due to pathology at the level of hypothalamic-pituitary-testicular axis level. Hypogonadism is the testosterone deficiency that may occur due to primary (Testicular) or secondary (hypothalamic-pituitary axis -HPA) cause. The clinical features of testosterone deficiency are non-specific and modified by age, co-morbid illness, severity, and duration of testosterone deficiency. Non-specific clinical signs and symptoms are decreased energy, feeling sad, depressed mood, poor concentration and memory, increased sleepiness, reduced muscle bulk or strength (1). The diagnosis of Late-onset hypogonadism (LOH) is made with symptoms and signs consistent with Total testosterone deficiency (2). Normal physiological range of Total testosterone is 300-1493 ng/dl (3). This is the first case report to shed light on the acromegaly associated with late-onset secondary hypogonadism with the previous history of pituitary tumor resection in young adulthood and successful management by Siddha medicine. Acromegaly is a condition caused by excessive secretion of growth hormone (GH) and increased secretion of Insulin-like growth factor (IGF-I), primarily caused by GH-secreting pituitary adenoma (Leandro kasuki 2019). This case report is written as per CARE Guidelines for Case reporting.

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Case Description

A middle-aged gigantic man of 48 years old with a height of 195 cm, a weight of 115.1 kg, and body mass index (BMI) of 30.3 visited the hospital with complaints of suffering from backache, fatigue for the past 3 months. The Patient was the tallest in the family. He was with sparse facial hair, large hands, and feet with mild prognathism. Regular medications prescribed elsewhere by the physician for backaches such as muscle relaxant or pain killers did not yield any benefit. Further, his non-specific symptoms like backaches and fatigue had intrigued the consulting physician, the patient was referred to the endocrinologist as the patient had a significant medical history and underwent surgical procedure for removal of Pituitary adenoma 27 years back. Any major illness or surgical procedure may suppress the central axis and may lead to secondary hypogonadism (4). Gradual decline in serum total testosterone level occurs at the mid-'30s and progresses at an average rate of 1.6% every year (5). Currently, the patient has no co-morbidity of metabolic syndromes such as Diabetes mellitus, hypertension, dyslipidaemia or hypertension which were common risk factors or co-morbidities for late-onset testosterone deficiency. His

blood pressure was 120/70mmHg. The patient was under no regular medication for any illness. On screening for Insulin-like growth factor (IGF-1) Total and free testosterone levels, prolactin, Dehydroepiandrosterone sulphate (DHEAS), concluded with a diagnosis of testosterone deficiency and treatment commenced in this direction through Testosterone replacement therapy (TRT). Patient was administered a testosterone injection of 100mg once in 3 weeks for two doses and re-tested for serum concentration for improvement of total testosterone, but remained persistently very low. Laboratory parameters of Follicle-stimulating hormone (FSH) was 19.67 mIU/ml, Cortisol 12.96 ug/dl, Total Testosterone was 70ng/dl, T_4 was 1.02, TSH level was 2.47, Hba1c was 5.7%, Growth hormone -0.58 ng/dl, IGF-I (Somatomedin C) was 241ng/ml.

Past Medical History

At the age of 21 years old, the patient had suffered from headaches, mostly occipital occurring once in 15-20 days for one year. Headache was not associated with vomiting or visual disturbances was reported with increased frequency over the past 6 months. Follicle stimulating hormone (FSH) 6 mIU/ml, Growth hormone (GH) >30ng/ml, Luteinizing hormone (LH) <1 mIU/ml, Cortisol-8.6 ug/dl, Prolactin-33.3ng/dl. On further investigation like CT (Plain & Contrast) revealed on lab workup. A rounded hypodense lesion enhancing minimally with contrast lesion extending suprasellar and into the right parasellar region. The Ventricular system and Basal cistern were normal. And Magnetic resonance imaging (MRI) of the Brain showed a large dense mass lesion seen in the Sella extending into the suprasellar cistern. The lesion had parasellar extension mostly on the right side without any pressure over optic chiasma. So, Trans ethmo-sphenoidal approach to the sellar, total tumour removal was done. Post-operative visual assessment was normal. The post-operative was uneventful. Followed by, histopathological examination of the specimen confirmed it as pituitary (macro) adenoma.

Testosterone Replacement therapy (TRT): Indication, contraindication and its adverse effects

Testosterone level analysis and prescriptions had escalated triple times as per the Evaluation and management of testosterone deficiency AUA guideline. TRT is contraindicated in patients planning fertility in the near term or having any of the following conditions such as breast or prostate cancer (PSA level >4 ng/ml) and erythrocytosis (Haematocrit >54%) severe obstructive sleep apnoea, Heart failure, Myocardial infarction or stroke within the last 6 months or Thrombophilia(1). Ideally, the therapy should provide physiological testosterone levels typically in the range of 300-800 ng/dl (AACE Hypogonadism 2002 update). In 2015, the U.S food and drug administration issued a warning alert that TRT may increase the risk of cardiac attack and stroke, although systematic review had reported inconclusive. Conversely, low testosterone itself poses cardiovascular (CVD) risk and increased mortality risk (Laughlin, G. A et al. 2008). Other potential adverse effects include decreased sperm production, decreased testicular size, increased mood changes, headache, breast tenderness and growth, acne, and other skin reactions. Given the above conditions, safer alternatives for non-hormonal testosterone regulation therapy are to be investigated. Furthermore, various guidelines suggest monitoring testosterone levels once in 3-6 months after treatment, and later annually in those undergoing TRT (Raymond C 2018). Evaluating patients on TRT is if the patient had responded to treatment, compliance, and adverse effects if any, incurs high economic healthcare costs (1).

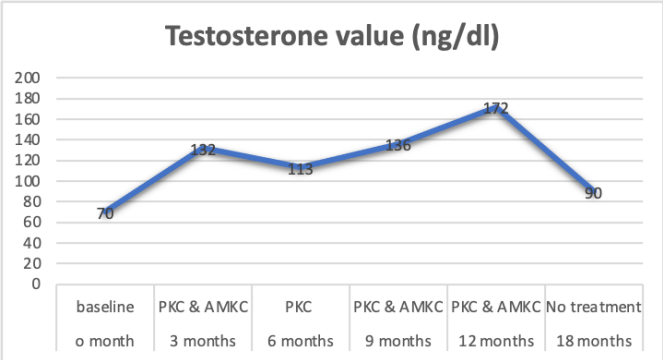
Interventional Siddha medicine

According to *Siddhar* Yugi Muni, this condition of male infertility was described as "*Aan maladu*", under which he describes the quality of *sukkilam* (semen) as absence of virility and buoyancy in water. *Poonaikali vidhai choornam* and *Amukkra choornam* drugs are commonly used drugs as aphrodisiac in the treatment of male infertility and nervine tonic. Non-specific clinical symptoms such as fatigue, backache had not improved following TRT. At this juncture patient sought Siddha treatment for any relief, it may provide for testosterone deficiency state. He was administered *Poonaikali vidhai choornam* of 2 grams twice a day with 10 ml of milk as adjuvant after food and *Amukkra choornam* of 2 grams twice a day with 10 ml of milk as adjuvant after food for 3 months initially and followed-up for 1 year. *Poonaikali choornam* is an official formulation in the Siddha formulary of India, part-I which contains only ingredient as *Poonaikali* (*Mucuna pruriens (L). DC.* Seeds. This medicine is indicated for nervous debility, tremors, particularly in Parkinsonism, diarrhoea with bleeding, leucorrhoea and hemiparesis. *Mucuna pruriens (L). DC.* is a major source of the phenolic content of L-3,4, dihydroxyphenylalanine(L-DOPA), its metabolite may stimulate hypothalamic-pituitary-gonadal axis, to secrete Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) causing increased the synthesis of testosterone by Leydig cells of the testes (6). Mucuna seeds are safe to use as in Traditional Siddha medicine for no acute systemic toxicity was observed in a study(7).

Amukkra choornam is also an official formulation in Siddha Formulary of India, Part I, indicated for gastric disorders, hepatomegaly, leucorrhoea, anaemia, wheezing, tuberculosis, peripheral neuritis and anabolic activity. Its constituents are *kirambu* (*Eugenia caryophyllata Thunb.*), *Cirunagapoo (Mesua ferrea L.), Elam (Elettaria cardamom L.), milagu (Piper nigrum L.), Thippili (Piper longum L.), Chukku (Zingiber officinale Roscoe), Amukkra (Withania somnifera (L) Dunal. Amukkra kizhangu is* a commonly used drug in the Siddha system of medicine for aphrodisiac, rejuvenating medicine, nervine tonic, infertility in various formulations. A clinical study revealed increased testosterone level, increase in serum LH concentration thereby improving semen parameters (Ambiye V.R.et al.2013). The non-

oxidative mechanism of *Amukkra* exerts its action on HPG axis and its anti-stress activity on Hypothalamic-pituitary-adrenal (HPA) axis by its major constituents Withaferin A and Withanolide-D (8). Laboratory investigations showed improvement in free serum testosterone levels of about 172 ng/dl from the baseline of 70ng/dl.

Figure 1. Timeline of treatment effects on serum testosterone (T) level with *Poonakali choornam* (PKC) and *Amukkra choornam* (AMKC)



The Aging Male's Symptoms Scale (AMS)

The Aging Male's symptoms scale (AMS) is the most commonly used scale worldwide to predict androgen deficiency. It is also used to evaluate the quality of life in patients with testosterone deficiency, to assess the severity of symptoms clinically, and to measure the prognosis before and after testosterone replacement therapy (9). This questionnaire is based on 17 factors and each item is rated on a scale 1 to 5. The maximum score is 85 and the minimum is 17. In this case, pre-treatment the score was 49, and post-treatment with Siddha medicine intervention the score of 27 was reported.

Androgen deficiency in the ageing male (ADAM'S) Questionnaire

The Saint Louis University Androgen deficiency in the ageing male qualitative and quantitative (ADAM) Questionnaire had been widely in use for screening androgen deficiency, particularly in late-onset hypogonadism(10). This questionnaire comprises 10 questions related to androgen deficiency of dichotomous natured answers as yes or no type. The sensitivity of ADAM Questionnaire may be as high as 83.3% to 97% and specificity as 19.7% to 36.6%. (Bernie et al. 2014). The high sensitivity of this questionnaire makes it a reliable screening test in androgen deficiency. Answering, affirmatively for more than three questions is said to be the positive score. This patient had answered affirmatively to 5 questions in ADAM questionnaire such as he had decreased strength, was sad, noticed a decreased enjoyment of life, fell asleep, and had recent deterioration in his work performance. Followed by treatment patient had answered only 1 as positive, hence negative for ADAM's score.

Discussion

This case report had emphasized that the importance of careful history taking and suspect late-onset hypogonadism in primary care settings. The Siddha medicines classified as nervine tonics were believed to improve the hypothalamic-pituitary-endocrine feedback mechanism. This postulates a hypothesis for further study that *Amukkra chooranam* in combination with *Poonaikali chooranam* if beneficial significantly rather than *Poonakali chooranam* alone.

Conclusion

This insight may be extrapolated to provide hypotheses for clinical research in the Siddha system of medicine in place of TRT. There were no adverse effects observed during the treatment period.

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