

A STUDY ON CONCOMITANT OCCURRENCE OF SUBCLINICAL HYPOTHYROIDISM AND REDUCED GROWTH HORMONE SECRETION ON FIBROMYALGIA

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ABSTRACT: Fibromyalgia, the abnormal pain perception by an individual has a complex etiopathogenesis with multifactorial involvement. The current study was conducted in 39 clinically diagnosed cases of fibromyalgia in NEIGRIHMS shilling from September 2013 to March 2014. Data from the cases when compared with 25 numbers of age matched control revealed a non-significance of growth hormone in fibromyalgia with p value >0.05. The study also showed a significant difference in TSH concentration among cases and control as indicated by a p value of <0.05.

KEYWORDS: Fibromyalgia, Human Growth hormone (hGH), Thyroid Stimulating Hormone (TSH).

INTRODUCTION: Fibromyalgia is commonly characterized by chronic widespread musculoskeletal pain with stiffness, paraesthesia and disturbed sleep. Often individuals complain of easy fatigability along with multiple, widely and symmetrically distributed painful tender points. The male to female ratio of occurrence of the fibromyalgia is 1:9 which is found in most of the countries, most prevalent among different ethnic groups in all types of climates. Different factors have been considered as a factor of abnormal pain perception in fibromyalgia including several abnormalities of the central nervous system. It is seen that fibromyalgia symptoms can be induced in a healthy individual by disrupting the stage IV NREM (Non Rapid Eye Movement) sleep by induced α wave intrusions. Reduced Growth hormone secretion, decreased cortisol response to stress, chronic emotional disturbances may be the other factors. The growth hormone is required for the proper nourishing of the muscles. The fact related to the growth hormone association may be because growth hormone is secreted at the stage IV of sleep.⁽¹⁾

However, most of the patients of fibromyalgia have a normal thyroid function but some study shows that there is evidence of the occurrence of abnormal TRH secretion in fibromyalgia. Moreover, it has been observed that the values of thyroid hormones are usually normal even if patients show some signs of hypothyroidism.⁽²⁾ Also Low urinary free cortisol and a diminished cortisol response to corticotrophin-releasing hormone suggest an abnormal hypothalamic-pituitary-adrenal axis.⁽³⁾ Due to these multiple etiopathogenesis it is often difficult to find out the exact aetiology in an individual of fibromyalgia which is a major hurdle in management of fibromyalgia patient. The current study was undertaken in an effort to understand the significance of TSH and Growth hormone (GH) in patients with fibromyalgia symptoms in our

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setting with due consideration of constraints in the resources of directly estimating the Thyroid releasing hormone (TRH).

OBJECTIVE OF THE STUDY: To find out the association of elevated Thyroid stimulating hormone (TSH) concentration and reduced Growth hormone in fibromyalgia.

MATERIALS & METHODS: The cases were selected from the patients attending the Medicine, Orthopaedic and Obstetrics and Gynecology Outpatient Departments of NEIGRIHMS, Shillong with the symptoms of fibromyalgia. The study was conducted from the month of September 2013 to March 2014. Most of the Cases presented one or more symptoms of persistent body ache with muscle cramp, chronic headache, history of increased fatigability, sleeps disturbance and menstrual irregularities. Cases were diagnosed clinically based on the criteria set by American College of Rheumatology, 1990 which is based on the demonstration of significant tenderness or pain in at least 11 of the 18 tender point sites on digital palpation.⁽¹⁾ To compare the findings we had taken age-matched subjects without any fibromyalgia symptoms as control group from the individuals attending for routine health checkup for fitness. Growth hormone, TSH along with unbound free T4 was done in all cases and control. Data of the control group were used to test the significance of the data collected from the cases. Cases and controls with the history of Rheumatoid arthritis, SLE, endocrine disorders like diabetes mellitus, metabolic syndrome were excluded from the study. Institutional ethics committee approved the study and samples were collected after informed consent of the study subjects.

After collection, the samples were analyzed in the department of Biochemistry, NEIGRIHMS as per the assay protocol. Serum fasting growth hormone was accessed by Beckman coulter Access 2 Immunoassay system (USA). In this test, a sample was added to a reaction vessel along with polyclonal goat anti-hGH alkaline phosphatase conjugate, and paramagnetic particles coated with mouse monoclonal anti-hGH antibody. The serum hGH binds to the monoclonal anti-hGH on the solid phase, while the goat anti-hGH-alkaline phosphatase conjugate reacts with a different antigenic site on the serum hGH. After incubation in a reaction vessel, materials bound to the solid phase were held in a magnetic field while unbound materials were washed away. The chemiluminescent substrate Lumi-Phos 530 was then added to the vessel and light generated by the reaction was measured with a luminometer. The light production is directly proportional to the concentration of hGH in the sample. The amount of analyte in the sample was determined from a stored, multi-point calibration curve.^(4,5,6)

The thyroid-stimulating hormone (TSH) was measured by Beckman coulter Access 2 Immunoassay system (USA). This test was based on the principle of chemiluminescence. Here patient sample was added to a reaction vessel along with goat anti-hTSH-alkaline phosphatase conjugate, buffered protein solution, and paramagnetic particles coated with immobilized mouse monoclonal anti-hTSH antibody. The hTSH binds to the immobilized monoclonal anti-hTSH on the solid phase while the goat anti-hTSH-alkaline phosphatase conjugate reacts with a different antigenic site on the hTSH. After incubation in a reaction vessel, materials bound to the solid phase were held in a magnetic field while unbound materials were washed away. Then, the chemiluminescent substrate Lumi-Phos 530 was added to the vessel and light generated by the

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reaction is measured with a luminometer. The light production is directly proportional to the concentration of human thyroid-stimulating hormone in the sample.^(7,8,9)

Unbound Free T4 was estimated to assist the thyroid status of the cases and control by chemiluminescence technique using Beckman coulter Access 2 Immunoassay system (USA). The test principle was based on the Competition of thyroxin in sample and alkaline phosphatase tagged T3 for binding to biotinylated T4 antibody producing chemiluminescence, which could be compared from a stored, multi-point calibration curve.⁽¹⁰⁾

A null hypothesis was formulated with the confidence interval of 95% and permissible α error of 5%. Unpaired 't' test for unequal variance with 2 tailed distributions was used to test the level of significance and all the statistical analysis was done by Microsoft excel 2007 statistical tool.

RESULT & OBSERVATION: Out of the total 39 cases, many of them were presented with more than two symptoms of fibromyalgia with highest frequency being the experience of increased fatigability (21 out of 39, Figure 1). Among the cases 21 individual (53.8%) showed a reduced level of Growth hormone than the normal reference range (Figure 2, Table 1). In control group, only three individuals had showed the reduced Growth hormone in comparison to the standard reference range (0.01 to 3.607ng/ml) (Figure 2, Table 1). In the present study, it was observed that TSH was elevated in seven (18%) individuals out of 39 cases whereas in the control group only one (4%) individual out of 25 showed an elevation in TSH level (Figure 3, Table 1).

DISCUSSION: In the present study, 21 cases out of total 39(53.8%) showed a reduced growth hormone secretion than the standard reference range while in the control group only 3 individuals out of total 25(12%) had showed reduce growth hormone level. However, statistical analysis between the control group and cases showed a p value of 4.56. (Table 2) Hence, we will accept the null hypothesis. The finding may be because the growth hormone is secreted in pulsatile manner under the influence of very complex regulation mechanism. The growth hormone secretion is reduced along with the muscle mass on advancement of age. GH secretion is also reduced in obese individuals, though IGF-I levels may not be suppressed, suggesting a change in the set point for feedback control. Elevated GH levels occur within an hour of deep sleep onset as well as after exercise, physical stress, trauma, and during sepsis. It is reported that the growth hormone secretion is higher in females. Even in the 50% of the day time samples obtained from healthy and obese individual the growth hormone is not detectable.⁽¹¹⁾

In the current study, TSH was also used as a parameter to test the significance in fibromyalgia. Seven numbers (18%) of cases out of 39 had the evidence of hypothyroidism as indicated by the elevated levels of Serum TSH. Statistically significant difference in the TSH concentration was noted among the study groups. The cases had a mean TSH concentration of $3.952 \mu\text{IU/ml} \pm 3.676 \mu\text{IU/ml}$ against $2.559 \pm 1.461 \mu\text{IU/ml}$ in control group with 2-tailed distribution. Statistical computation generated a p-value of 0.04 (<0.05). This may be because of the similarity of symptoms of hypothyroidism with that of fibromyalgia. Auto immune Hypothyroidism is also common in females in comparison to males and may be present with impairment of muscle function with stiffness, cramps, pain and slow relaxation of tendon reflexes, besides the

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normal symptoms of weight gain, cold intolerance, constipation, impairment of memory and concentration.⁽¹²⁾ However our study did not showed a significant difference in the mean unbound free T4 concentration, which is often used as marker for thyroid hormone reserve. The case had a concentration mean value of 0.878 ± 0.869 ng/dl against the control with 0.856 ± 0.149 ng/dl. Which showed no significant difference in cases as indicated by a p-value of 0.875 (>0.05 , with C.I of 95% with 2 tailed distribution). This may be due to the fact that Free T4 is not a very reliable marker for thyroid hormone reserve and in case of subclinical hypothyroidism the free T4 may be normal even with elevated TSH levels.⁽¹³⁾ The similar type of finding was also noted by Eda Demir Onal et al in their study with 40 individuals. They found that one (2.5%) patient had subclinical hyperthyroidism and one (2.5%) had subclinical hypothyroidism, whereas one (2.5%) control had hyperthyroidism.⁽¹⁴⁾

CONCLUSION: In our study, it was seen that subclinical hypothyroidism was probably presented with separate entity but diagnosed to be fibromyalgia due to similar symptoms. Hence, we would like to conclude that Fibromyalgia has to be diagnosed mainly by exclusion of differential diagnosis of subclinical hypothyroidism.

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Fig. 1: Frequency of symptoms among cases in the study conducted from September, 2013 to March, 2014 in NEIGRIHMS, Shillong.

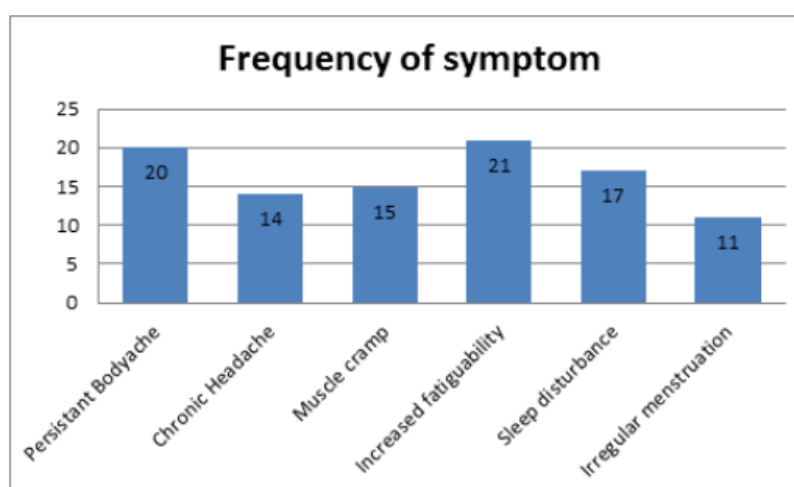


Fig. 1

Fig. 2: Number of cases and controls having normal & reduced Growth hormone in the study conducted from September 2013 to March 2014 in NEIGRIHMS, Shillong.

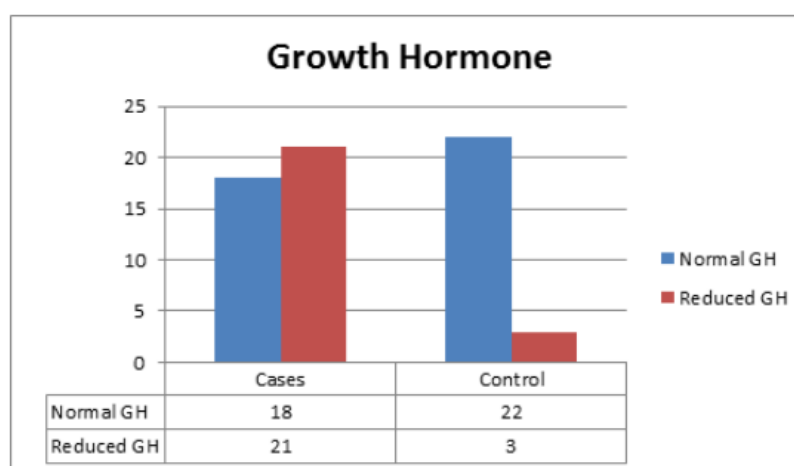


Fig. 2

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Fig. 3: Number of cases and controls having normal and reduced TSH in the study conducted from September 2013 to March 2014 in NEIGRIHMS, Shillong.

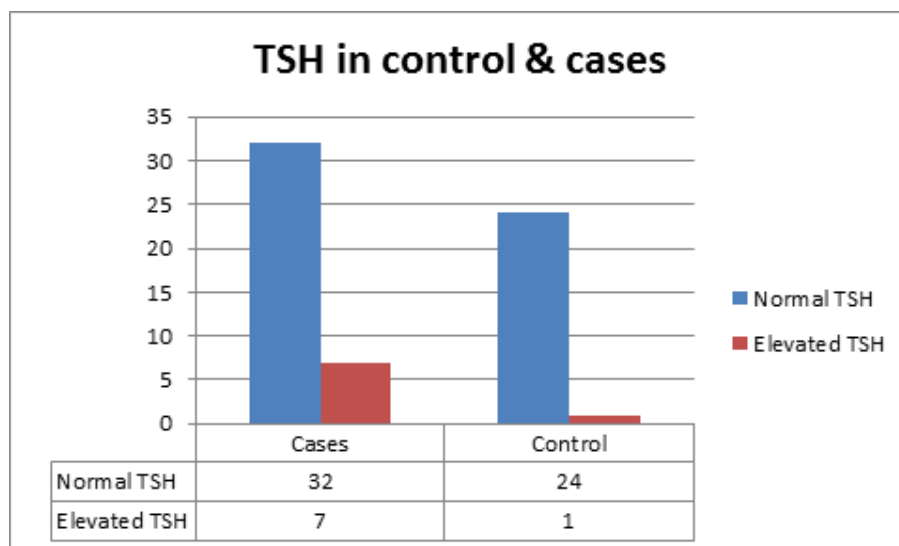


Fig. 3

Percentage of cases & control with abnormal TSH & Growth hormone concentration					
	Growth hormone		TSH		
	Cases (39)	Control (25)		Cases (39)	Control (25)
Normal	18 (46.2 %)	22 (88 %)	Normal	32 (82 %)	24 (96 %)
Reduced	21 (53.8 %)	3 (12%)	Elevated	7 (18 %)	1 (4 %)

Table 1: Percentages of cases & control with an abnormal hormone concentration study conducted from September 2013 to March 2014 in NEIGRIHMS, Shillong

Parameter	Study group	Mean	Standard Deviation	Significance
Growth Hormone (ng/ml)	Cases	0.137	0.232	4.56 Not significant
	Control	1.130	0.845	
TSH (μ IU/ml)	Cases	3.952	3.676	0.04 P<0.05
	Control	2.559	1.461	
Free T4 (ng/dL)	Cases	0.878	0.869	0.875 Not significant
	Control	0.856	0.149	

Table 2: Test of significance using unpaired t test for unequal variance in the study conducted from September 2013 to March 2014 in NEIGRIHMS, Shillong

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