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RESEARCH ARTICLE

THE POSSIBLE LINK BETWEEN VITAMIN D LEVELS AND RESTLESS LEG SYNDROME: A HOSPITAL-BASED CASE-CONTROL STUDY FROM KASHMIR, INDIA

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Abstract

Background & Objectives: Various pathophysiological mechanisms and risk factors have been identified in patients with restless leg syndrome and there exist other factors also that are yet to be identified and are under-researched. Evidence suggests a possible link between Vitamin D deficiency and Restless leg syndrome. The aim was to study the Vitamin D levels in patients diagnosed with RLS and to find a correlation between Vitamin D and RLS.

Methods: This was a case-control study carried out in the outpatient department of the Institute of Mental Health and Neurosciences Kashmir. A total of 144 subjects were enrolled in the study. Fifty-one were diagnosed cases of RLS and 93 were healthy controls. The Vitamin D levels were analysed by the chemiluminescent immunoassay method in both cases as well as controls. The descriptive statistics were used for various socio-demographic and clinical variables. The data were analysed by chi-square test, t-test and multivariate logistic regression analysis.

Results: The vitamin D levels were significantly low in the RLS group in comparison to the control group. There was a significant correlation between vitamin D levels, vitamin D deficiency and restless leg syndrome (OR= 1.01, p-value 0.005 and OR= 5.40, p-value <0.0001 respectively).

Interpretation & conclusions: Vitamin D levels were low in patients with RLS. This signifies vitamin D may have some role in the pathophysiology of RLS. Vitamin D regulates the nervous system development and function therefore, its use can be considered in the management of RLS when other modalities cannot prove as a promising agent.

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Introduction:-

Restless leg syndrome though a neurological sensorimotor disorder is a common clinical presentation in the psychiatric outpatient department. [1] Also known as Willis Ekblom's syndrome, and is characterized by sensorimotor abnormality leading to an irresistible urge to move the limbs.[2] The prevalence of this disorder ranges from 3 to 10%, with a higher rate of occurrence in females and older aged patients. [3] Restless leg syndrome severely affects patients sleep at night thereby impairs their daily life activities. [4, 5] Various psychiatric comorbidities like depression, anxiety disorders, ADHD have been found in Restless leg syndrome. [6, 7] Dopaminergic agents are considered to be the first-line treatment for RLS, while as different supplementary therapies have also been tried for Restless leg syndrome. [8]

Various biochemical factors like Iron, Dopamine and vitamin B12 have been studied in Restless leg syndrome but there is less supportive evidence regarding levels of vitamin D in Restless leg syndrome. [9] The present study was aimed to find the plasma levels of Vitamin D in individuals between 18-60 years of age with and without restless leg syndrome.

Material & Methods:-**Study design**

It was a case-control study.

Settings and variables

The study was conducted in the Institute of Mental Health and Neurosciences, Kashmir an associated hospital of Government Medical College, Srinagar from march 2020 to march 2021. The Cases and controls were recruited from the outpatient department. We enrolled 51 patients with RLS as cases and 93 participants without RLS as controls between 18-60 years of age. Informed consent for participation in the study was obtained from all the participants. The detailed medical history, psychiatric and neurological examination was performed to rule out pregnancy, medical causes e.g hypothyroidism, psychiatric causes, physical causes, and drugs causing RLS. The family history of restless leg syndrome was ruled out in all the participants. To remove the bias the cases and controls were matched in most of the confounding variables. Like we took age and sex-matched cases and controls. We also took a maximum of two controls against each case from the same family especially first degree relative from the same socioeconomic class. The cases and controls were all with average body mass index. The restless leg syndrome was diagnosed according to the International RLS Study Group (IRLSSG) diagnostic criteria.[10] The symptom severity was assessed using the IRLSSG rating. [11] Vitamin D was measured by Chemiluminescence Method without any pre-test preparation.

Statistical Analysis

Data were analysed statistically by using SPSS V.21 computer program. The Statistical Package for the Social Sciences is a software package of a comprehensive system for analysing data. The descriptive statistics were used for various socio-demographic and clinical variables. The Chi-square and t-test were used as prime statistics to get the interpretations from the data available. The Odds ratio was calculated by multivariate logistic regression analyses between RLS and non-RLS to find the correlation between different variables. The results were taken significantly at a P-Value of <0.05.

Ethical Clearance

The study was approved by Institutional Ethical Committee with code of ethic CDSCO U/P No: ECR/1422/Inst/JK/2021.

Results:-**Case group (RLS group)**

A total of 51 patients with RLS were enrolled in the study. The mean age of the patients was 38.10±13.70 years. The male and females were in the ratio of 1: 9.2. The mild RLS was found in 18 (35.29%) patients followed by moderate, severe and very severe RLS in 16 (31.37%), 11 (21.56%) and 06 (11.76%) patients respectively. Out of 51 patients with RLS, 26 (50.98%) had vitamin D levels <20ng/dl and 25 (49.01%) had more than 20ng/dl of vitamin D levels. Details are shown in Table 1

Control group (non-RLS group)

A total of 93 healthy controls without RLS were enrolled in the study. The mean age of the patients was 40.32±11.65years. The male and females were in the ratio of 1: 9.3. Out of 93 healthy controls without RLS, 16.12% had vitamin D levels <20ng/dl and 83.87% had more than 20ng/dl of vitamin D levels. Details are shown in Table 1.

Table 1:- Comparison of different Variables among RLS and non-RLS Group.

Variable	RLS Group N=51	Healthy controls or non-RLS Group N=93	statistics	p-value
Age (Mean ± SD)	38.10±13.70	40.32±11.65	t-value 1.02	0.30
Sex			Chi-square value	0.98
Male	05 (9.8%)	09 (9.67%)	0.0727	
Female	46 (90.19%)	84 (90.32%)		
RLS				
Mild	18 (35.29%)			
Moderate	16 (31.37%)			
Severe	11 (21.56%)			
Very severe	06 (11.76%)			
VIT D			Chi-square value	0.00001**
<20ng/ml	26 (50.98%)	15 (16.12%)	19.6442	
>20ng/ml	25 (49.01%)	78 (83.87%)		

Table 1** Statistically significant values

From table 1, it is evident that vitamin D levels were low in the RLS group than the non-RLS group and results were statistically significant with a Chi-square value of 19.6442 and a p-value of 0.00001.

Table 2:- Vitamin D Levels in Cases with Restless Leg Syndrome.

Severity of RLS	N (%)	Levels of Vitamin D	N=51 (%)
Mild 0-10	18 (35.29)	<20ng/dl	07 (13.72)
		>20ng/dl	11 (21.56)
Moderate 11-20	16 (31.37)	<20mg/dl	08 (15.68)
		>20ng/dl	08 (15.68)
Severe 21-30	11 (21.56)	<20ng/dl	07 (13.72)
		>20ng/dl	04 (7.84)
Very severe 31-40	06 (11.76)	<20ng/dl	04 (7.84)
		>20ng/dl	02 (3.92)

Out of 18/51 patients with mild RLS, 07 patients had vitamin D levels of <20ng/dl and 11 patients had > 20ng/dl of vitamin D levels. Similarly, out of 16/51 patients with moderate RLS, 8 patients were with <20ng/dl of vitamin D levels and 8 were with >20ng/dl of Vitamin D levels. Among 11/51 patients with severe RLS, 07 patients had <20ng/dl of vitamin D levels and 04 patients had >20ng/dl of Vitamin D levels. Out of 06/51 patients with severe RLS, 04 patients had <20ng/dl of vitamin D levels and 02 patients had >20ng/dl of Vitamin D levels. Details are shown in Table2

Table 3:- The Multivariate Logistic Regression analysis of Age, Sex, Vitamin D levels and Vitamin D deficiency associated with RLS

Variable	OR	P-value	95% CI
Age	0.98	0.7903	0.22 to 3.46
Sex	1.01	0.9804	0.32 to 3.20
VIT D Deficiency	5.40	<0.0001**	2.48 to 11.78
Serum VIT D ng/dl	1.01	0.005**	1.04 to 1.07

The association between age and sex with RLS was insignificant (p-value of 0.7903 and 0.9804 respectively). However, serum vitamin D levels and Vitamin D deficiency were significantly associated with RLS (OR= 1.01, p-value 0.005 and OR= 5.40, p-value <0.0001 respectively) Table 3

Discussion:-

Restless Leg Syndrome a most distressing disorder interrupts one's sleep and impairs the daily routine life of an individual. [4, 5] Various pathophysiology mechanisms causing Restless Leg Syndrome have been established. One of the most proven pathophysiological mechanisms of RLS is dopaminergic dysfunction in the striatum which too is supported by different imaging studies.[12, 13]

The severity and higher incidence of RLS in neurological disorders like Huntington's disease, Tourette syndrome, and essential tremor has been explained by the reduction of D2 receptors in different brain areas, adequate replacement, results in significant improvement in symptoms.[14] Nevertheless, the underlying mechanisms remain unclear.

There is accumulating evidence that the dopaminergic system plays an important role in the pathophysiology of RLS.[15,16] Moreover, vitamin D appears to have a key function in the dopaminergic system; indeed, this vitamin participates in regulating nervous system development and function. It has been reported that vitamin D affects the nigrostriatal dopaminergic pathway by increasing the levels of dopamine or its metabolites and by protecting dopaminergic neurons against toxins.[17, 18] Low doses of 1-alpha,25-dihydroxyvitamin D₃—1, 25-(OH) 2D₃— (the hormonally active form of vitamin D) can protect mesencephalic dopaminergic neurons against toxins that cause a decrease in the glutathione content, which when decreased may lead to selective dopaminergic neuron death.[19,20] A recent publication also concluded that vitamin D deficiency may lead to an increased risk of central nervous system diseases, such as parkinsonism, schizophrenia, and multiple sclerosis.[21]

In our study, the risk for the development of RLS was significantly higher in vitamin D deficient cases compared to those who are vitamin D sufficient. Additionally, the mean serum 25(OH) vitamin D level was significantly lower in patients with RLS than in normal controls. The association between vitamin D deficiency and RLS remained significant after adjusting for all other significant factors.

Our results were also in agreement with several recent studies examining the role of vitamin D in the aetiology of RLS. Balaban et al conducted a hospital-based study and evaluated 25(OH) vitamin D levels in female patients with and without RLS, reporting significantly lower serum levels in the former. However, the study was limited to patients with idiopathic and non-familial RLS.[22] The cross-sectional study conducted by Oran et al. examined the prevalence of RLS in subjects with and without vitamin D deficiency; an increased prevalence of RLS was observed in the vitamin D deficiency group, suggesting an association between serum vitamin D level and RLS.

Taking into consideration, the dopaminergic effects of vitamin D, it supports our observation that low vitamin D levels are an etiological factor for restless leg syndrome.

Restless legs syndrome (RLS) is one cause of disturbed sleep was observed to be somewhat more common among women than men in Ekblom's 1945 seminal series of clinical cases with the disease. [19] He, however, reported this gender difference mainly for those with more severe symptoms. The same finding has been reiterated by our study that shows a female preponderance.

Some limitations of the present study should be mentioned. Evaluation of disorders that are frequent in RLS patients, such as periodic limb movements during sleep, would be useful to support RLS diagnosis; however, we did not evaluate these because a variety of disorders have been argued to be frequent in RLS patients. Also, it would have been better to calculate a sample size estimation for each group; instead, we included all patients who had adequate inclusion and exclusion criteria. This might be considered as another limitation. One more limitation of our study was that we did not check other chemical variables like Serum Ferritin, Vitamin B12 and serum Folate levels.

Conclusion:-

From our study, we conclude that like other neurochemical agents e.g, dopamine Vitamin D also have some role in the pathophysiology of RLS. The RLS was more prevalent in those who had deficient vitamin D levels than with sufficient vitamin D levels.

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Conflicts of interest

There are no conflicts of interest.

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