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Assessment and prediction of restless leg syndrome (RLS) in patients with diabetes mellitus type II through artificial intelligence (AI)

Sadaf Iftikhar[1], Saman Shahid[2]*, Muhammad Umar Hassan[1] and Mamoona Ghias[3]
[1]Department of Neurology, King Edward Medical University (KEMU), Mayo Hospital Lahore Pakistan
[2]Department of Sciences & Humanities, National University of Computer and Emerging Sciences (NUCES), FAST Lahore Campus, Pakistan
[3]Department of Medicine, King Edward Medical University (KEMU), Mayo Hospital Lahore Pakistan

Abstract: This study aimed to diagnose the incidence of restless leg syndrome (RLS) in patients with diabetes mellitus (DM) type-2, thorough artificial intelligence based multilayer perceptron (MLP). 300 cases of diabetes mellitus type-2, of age between 18-80 years were included. Point-biserial correlation/Pearson Chi-Square correlations were conducted between RLS and risk factors. We trained a backpropagation MLP via. supervised learning algorithm to predict clinical outcome for RLS. Majority of the patients were having hypertension (63%) and with peripheral neuropathy (69%). Two mostly reported scaled parameters were: 18% ‘tiredness’ and 14%, ‘impact on mood’. A significant correlation was found in RLS with smoking, hypertension and chronic renal failure (CRF). MLP model achieved more than 95% accuracy in predicting the outcome with cross entropy error 0.5%. Following scaled symptomatic variables: ‘need/urge to move’ (100%) achieved the highest normalized importance, followed by ‘relief by moving’ (85.7%), ‘sleep disturbance’ (62%) and ‘impact on mood’ (51.3%). Artificial intelligence based models can help physicians to identify the pre diagnose RLS, so that active measures can be taken in time to avoid further complications.

Keywords: Restless leg syndrome, multilayer perceptron, diabetes mellitus, sleep disturbance, urge to move.

INTRODUCTION

Restless leg syndrome (RLS) is a common movement disorder denoted by a strong, irresistible, urge to move the legs, which usually felt on taking rest especially in the evening or night time. It reduces with different movements of arms or legs (Allen *et al* 2014). Based on a population-based survey, the prevalence of RLS was 3% between ages 18 and 29, 10% between ages 30 and 79 and 19% in people older than 80 years of age. This disorder affects women more frequently and is associated with significant morbidity. The principal abnormality in RLS appears as dopamine deficiency and brain iron dysregulation (Bollu *et al.,* 2018). RLS is frequently found in patients with diabetes mellitus type 2 patients (Lopes *et al.,* 2005; Akın *et al.,* 2018), who are often reported to have a peripheral neuropathy (Lopes *et al.,* 2005), hypertension (Sabic *et al.,* 2016), glycosylated hemoglobin (HBA1c) (Modarresnia *et al.,* 2018) and chronic renal failure (CRF) (Cuellar and Ratcliffe 2008). Siddiqi *et al.,* (2015) reported a 55.8% prevalence of RLS in DM type 2. The prevalence of RLS significantly increases with age (Nichols 2003). In another community-based study, the overall prevalence of RLS was reported 10.6% (Hogl, 2005). In a Pakistani study, the prevalence of RLS was found to be 23.6% (Mahmood, 2015). Diabetes mellitus type 2 (DM2) accounts for the majority (90%) of total diabetes prevalence. About 1 in 11 adults worldwide have DM (Zheng, 2018). The International Diabetes Federation (IDF) estimated diabetic patients will be increased in the world to 592 million by 2035, with the majority in developing countries (Shi. 2014). Many studies have shown a significant association of RLS in DM2 (Akin, 2018). Besides polyneuropathy, diabetes alters the central and peripheral catecholaminergic systems by reducing the nigrostriatal dopaminergic system activity that is crucial for the RLS circuitry (Gallego, 2003). The recurrent high blood pressure during night time, can progress in the day time as well, and becomes a risk factor of stroke and heart diseases (Walters, 2009). It has been suggested the with the aid of artificial intelligence (AI), neurological and psychological conditions’ predictions and classifications can be made from the existing data on complex clinical symptoms and risk factors for an effective treatment (Mitchell, 1997; Bzdok *et al.,* 2018). This study aimed to predict the prevalence of RLS with associated risk factors in patients with diabetes mellitus (DM) type-2, thorough building a multilayer perceptron (MLP)-an artificial neural network (ANN) model.

**Corresponding author:* e-mail: drshahidsaman@gmail.com

MATERIALS AND METHODS

A cross-sectional study was designed to find out the prevalence of restless leg syndrome (RLS) along with its risk factors. An artificial neural network (ANN) model (multilayer perceptron) was developed to predict the prevalence of RLS in patients with DM type-2 confirmed according to the American Diabetes Association diagnosis criteria. The patients (n=300) from indoor and outdoor of Neurology & Endocrinology departments, Mayo Hospital, Lahore Pakistan were included on informed consents. The study was approved from the institutional review board (IRB) and advanced studies & research board (ASRB) of King Edward Medical University (KEMU), Lahore Pakistan. The study conducted for three months from 1st Dec 2019 to 29th February 2020. The calculated sample size is 300 cases, with 95% confidence level, 5% margin of error and taking an expected percentage of 27% RLS (Lopes *et al.,* 2005) in patients with DM type 2. The sampling technique as non-probability consecutive sampling was considered.

Inclusion and exclusion criteria

All cases of diabetes mellitus type-2, of age between 18-80 years and both genders were included. Following conditions were excluded on the basis of history, clinical examination and investigations: peripheral artery disease, nocturnal leg cramps, neuroleptic-induced akathisias, myalgias, rheumatoid arthritis, venous stasis and leg edema, painful legs and moving toes syndrome, meralgia paresthetica and habitual foot tapping.

Data collection parameters

All patients' background and clinical information were collected on following: age, gender, intake of alcohol (yes/no), use of cigarette smoking (yes/no), restless leg syndrome (present/absent), hypertension (present/absent), duration of diabetes mellitus (DM) type-2 (years), intake of SSRI (selective serotonin reuptake inhibitors), peripheral neuropathy (present/absent), chronic liver disease -CLD (present/absent), chronic renal failure -CRF (present/absent).

Neurological assessments

All patients were assessed by the same neurologist for RLS. It was diagnosed using the criteria of the International RLS Study Group (Allen *et al* 2014), and severity of RLS was assessed using the International RLS Study Group Rating Scale (Walters-Group IRLSS, 2003). Total 10 scaled symptomatic parameters (RLS discomfort, need/urge to move the arm(s)/leg(s), relief from moving the arm(s)/leg(s), sleep disturbance, tiredness, severity of RLS, frequency of RLS symptoms, RLS symptoms per day, impact on daily activities (social, professional, home, family etc.) and mood disturbance (angry, sad, depressed, anxious or irritable) were filled and recorded on the pre-designed proforma for each patient by the neurologist. All scaled parameters were assessed according to the scale: 1: none; 2: mild; 3: moderate; 4: severe; 5: very severe and derived from the questionnaires of the proforma. The scaled parameter 'frequency of symptoms' was assessed on the following scale: 0: occasional; 1: sometimes; 2: often; 3: very often. The mimicking conditions such as peripheral artery disease, myalgia, venous stasis, leg edema, arthritis, nocturnal leg cramps, meralgia paresthetica, painful legs and moving toes syndrome, positional discomfort and habitual foot tapping were carefully investigated and excluded.

Data analysis and correlation analysis

All the data was analyzed by using IBM SPSS version 23. The frequency and descriptive of each above mentioned parameters/variables were calculated. Mean/SD, minimum and maximum values were calculated for the continuous variables (age, duration of DM). Frequency and percentage were calculated for each nominal/ordinal parameter (gender, RLS, SSRI, alcohol, smoking, hypertension, peripheral neuropathy, CLD and CRF) and for each scaled symptomatic parameters (RLS discomfort, need/urge to move the arm(s)/leg(s), relief from moving the arm (s)/leg(s), sleep disturbance, tiredness, severity of RLS, frequency of RLS symptoms, RLS symptoms per day, impact on daily activities and mood disturbance). Correlation analyses were conducted to measure and the strength between dependent variable RLS (restless leg syndrome) and independent variables as risk factors (age, gender, hypertension, peripheral neuropathy, duration of DM, smoking, CLD & CRF). Point-biserial correlation was applied for nominal-continuous variables, whereas, Pearson Chi-Square correlation for association were applied for nominal-nominal variables. Phi and Cramer's V values were observed to see the strengths of the association in Pearson Chi-Square correlations. A p value of less than 0.050 was considered for the significant results. Kendall'tau (b) was also applied for additional verification of the significant parameters.

Multilayer perceptron-neural network

An artificial neural network (ANN) based model of a multilayer perceptron (MLP) was built which predicts the presence or absence of restless leg syndrome (RLS) in DM type-2 patients, by the analyzed data of the recoded scaled-variables. We built a three-layered network artificial neural network (ANN), through a supervised learning algorithm with batch training to classify input data (factors/covariates) into output categories as clinical outcome (RLS: present/absent). The MLP model was trained with supervised, back-propagation learning algorithm. The network included the scaled conjugate gradient in order to reduce the error function. Following four RLS predictors as factors were considered: 'need/urge to move', 'relief by moving', 'sleep disturbance' and 'impact on mood' and following three covariates were also considered: 'age', 'tiredness' and 'impact on activities' in the MLP ANN model. We randomly assigned the cases based on relative numbers of cases. 208 (69.3%) samples were used as training, whereas, 92 (30.7%) samples were used as testing. The training set of data was used to find out the weights, whereas, the testing set of data was used to fig. out the errors and to prevent from overtraining.

There was only one hidden layer in the network with a number of 7 hidden units. Hyperbolic tangent as

Table 1: Percentages and frequencies in categorical parameters (n=300)

Sr. #	Parameter	*Yes/Present (n)*	*No/Absent (n)*
1	Restless Leg Syndrome (RLS)	83 (27.7%)	217 (72.3%)
2	Intake of Selective Serotonin Reuptake Inhibitors (SSRI)	2 (0.7%)	298 (99.3%)
3	Intake of Alcohol	0 (0%)	300 (100%)
4	Smoking	33 (11%)	267 (89%)
5	Hypertension	190 (63.3%)	110 (36.7%)
6	Peripheral Neuropathy	206 (68.7%)	94 (31.3%)
7	Chronic Liver Disease (CLD)	0 (0%)	300 (100%)
8	Chronic Renal Failure (CRF)	7 (2.7%)	292 (97.3%)

Table 2: Percentages and frequencies in scaled parameters (n=300)

Sr. #	Parameter	None (n)	Mild (n)	Moderate (n)	Severe (n)
1	RLS Discomfort	218 (72.7%)	35 (11.7%)	37 (12.3%)	10 (3.3%)
2	Need to Move	218 (72.7%)	35 (11.7%)	41 (13.7%)	6 (2%)
3	Relief by Moving	218 (72.7%)	34 (11.3%)	40 (13.3%)	8 (2.7%)
4	Sleep Disturbance	219 (73%)	40 (13.3%)	38 (12.7%)	3 (1%)
5	Severity	218 (72.7%)	38 (12.7%)	36 (12%)	8 (2.7%)
6	Impact on Activities	218 (72.7%)	37 (12.3%)	41 (13.6%)	4 (1.3%)
7	Impact on Mood	219 (73%)	32 (10.6%)	43 (14.3%)	6 (2%)
8	Tiredness	219 (73%)	55 (18.3%)	26 (8.6%)	0 (0%)
9	RLS as Whole	221 (73.7%)	32 (10.7%)	37 (12.3%)	10 (3.3%)
	Parameter	Occasional	Sometimes	Often	Very Often
10	Frequency of Symptoms	219 (73%)	31 (10.3%)	42 (14%)	8 (2.7%)

Table 3: Pearson chi-square test (Significant Correlations)

Correlation	Pearson Chi-Square	df	*p* value	Phi	Cramer's V
RLS & Smoking	4.035	1	0.045	0.116	0.116
RLS & Hypertension	3.963	1	0.047	0.115	0.115
RLS & CRF	7.241	2	0.027	0.155	0.155

Table 4: Multilayer perceptron (MLP): Performance and errors

	Cross entropy error	Percent incorrect predictions	Overall correct predictions
Training	6.096	0.5%	99.5%
Testing	0.218	0.0%	100%

activation function was used for the hidden layer. The output layer was consisted of two units with Softmax as an activation function. Cross-entropy was used as an error function. A batch training mode was selected with scaled conjugate gradient as optimized algorithm to regulate the synaptic weights. The other training values are as follows: initial learning rate: 0.4; momentum: 0.9; interval center: 0 and interval offset: ±0.5; maximum number of epochs: 500, minimum relative change in training error: 0.0001; minimum relative change in the training error ratio: 0.001 and maximum steps without a decrease in error: 1. Percentage normalized importance was calculated in seven independent predictor variables.

RESULTS

Frequencies and Prevalence

Total 300 patients with DM type-2 were assessed for the restless leg syndrome. Mean age of the patients was 50.27±11.90 years, with minimum age 26 years and maximum age was 75 years. There were 114 (38%) male patients, whereas, 186 (62%) were female patients. The mean time for the duration of DM was 10.21±5.859 years. The other parameters' frequencies and percentages are shown in table 1. The restless leg syndrome was present in around 28% of patients. 63.3% patients were having hypertension and 68% were having peripheral neuropathy. No patient was found with chronic liver disease (CLD), whereas, only 2.7% were having chronic renal failure (CRF). 11% patients were smokers. Table 2 describes frequencies of 10 scaled symptomatic parameters. 73-74 % patients did not report the severity with 'none' response in all of the scaled symptomatic parameters. 10-8% reported the 'mild' conditions in all scaled parameters. The 'moderate' response was from 8-14%, whereas, the severe response was only up to 3.3%. Following were mostly reported scaled parameters were: 'tiredness' (18.3% in mild level), 'impact on mood'

(14.3% in moderate level), ‘sleep disturbance’ (13.3% in mild level) and as ‘relief by moving’ (13.3% in moderate level).

Table 5: Independent variable importance

Factors/Covariates	Normalized Importance
Need to move	100.0%
Relief by moving	85.7%
Sleep disturbance	62.1%
Impact on mood	51.3%
Age	23.0%
Tiredness	20.9%
Impact on activities	22.8%

Correlation Analyses

These correlations (weak-negative) were found insignificant. Pearson Chi-Square correlation for association were applied for RLS & gender; RLS & smoking; RLS & hypertension; RLS & CLD; RLS & CRF; RLS & peripheral neuropathy; RLS & intake of SSRI. Table 3 shows the detail of the statistical results for the correlations. The restless leg syndrome (RLS) was found in a significant association with smoking ($p=0.045$), hypertension ($p=0.047$) and chronic renal failure (CRF) ($p=0.027$). According to the Phi and Cramer's V values, these significant associations were however, having weak-positive associations.

Model-Multilayer Perceptron

A trained, supervised back-propagation MLP model was successfully built which predicted the outcome of RLS (as present or absent). The model properties for training and testing part is shown in table 4. The model achieved 99-100% success in correctly predicting the outcome with reduced cross entropy error up to 0.5%. Table 5 provides the impact of each independent predictor in the MLP ANN model in terms of relative and normalized importance. The scaled symptomatic variable ‘need/urge to move’ (100%) achieved the highest normalized importance, followed by ‘relief by moving’ (85.7%), ‘sleep disturbance’ (62%), ‘impact on mood’ (51.3%), ‘age’ (23%), ‘tiredness” (21%) and ‘impact on activities (23%).

DISCUSSION

We built a successful artificial intelligence (AI) based model multiplayer perceptron (MLP), with good prediction efficiency and reduced errors. This model will help physicians and neurologists to predict outcome for the restless leg syndrome (RLS) in patients with DM type-2. Our DM-type 2 patients reported around 28% of restless leg syndrome (RLS). The clinical assessment of RLS is usually poor and difficult. Therefore, there is a need to use an efficient methods, such as, trained ANN models, which can help the neurologist to diagnose the RLS before complications occur (Martinot *et al.,* 2020). Back-propagation neural networks have been tested and validated in neurological issues such as obstructive sleep apnea (OSA). El-Solh *et al.* (1999) had successfully developed ANN. Questionnaire-based prediction models have long been used to identify to find various features and symptoms in clinical disorders. Stretch *et al* (2019) used logistic regression in ML methods to help physicians to better leverage in existing neurological conditions related to sleep diagnostic modalities. A US patent is also available, in which artificial intelligence (AI) based unit was utilized by Nazari (2016) to describe a platform for diagnosing movement disorder together with inertia-sensing units. Artificial intelligence has been applied in exploring depression, sleep disorders, anxiety disorders, phobias, etc. (Lueken *et al.,* 2015). Nichols *et al.,* (2003) reported a high prevalence of RLS in primary care, adult population, through a questionnaire analysis. RLS was significantly associated with older age, smoking, high BMI, sedentary lifestyle, diabetes and low socioeconomic status (Phillips *et al.,* 2000). In the present study, a significant correlation was found between restless leg syndrome (RLS) with smoking, hypertension and chronic renal failure (CRF). Walters and Rye (2009) had reviewed and mentioned that RLS is well associated co-morbidities such as insomnia, stroke, renal failure, diabetes, peripheral vascular, heart disease and low hemoglobin levels. The majority of our patients were having hypertension (63%) and with peripheral neuropathy (69%). RLS as a movement disorder is significantly associated with mood swings and alike disorders (Bayard *et al.,* 2013). In mild forms of RLS, the patient usually feels relief in rubbing or stretching legs, but in its severe form, the patient can leave the bed and start walking. A strong circadian pattern can exists in RLS disorder, with usually a high intensity occurs during the earlier night time (Cotter and O’Keeffe, 2006). RLS often leads to sleep disturbances, leading to insomnia, daytime sleepiness, tiredness, (Modarresnia *et al.,* 2018) anxiety, depression, and overall reduction in the physical and mental aspects of quality of life (Stevens, 2015). Primary RLS is often familial or idiopathic, while secondary RLS occurs with pregnancy, iron deficiency (Ekbom and Ulfberg, 2009) and comorbidities such as heart disease, diabetes, hypertension, (Trenkwalder *et al.,* 2018) and chronic renal failure (Lin 2019). RLS association with chronic renal failure both in dialysis and nondialysis patients is also well known (Rohani *et al.,* 2015).

CONCLUSION

There is a scarcity of data in identifying/predicting RLS in DM-type 2 patients from AI based computational methods. We built a successful artificial intelligence (AI) based model multiplayer perceptron (MLP), which will help physicians to predict outcome for the restless leg syndrome in patients with DM type-2. There is a need to ascertain the incidence of RLS in diabetes patients to save them from comorbidities through more advanced tools of artificial based models. Most of the time, RLS is considered a trivial diagnosis, but it has a devastating effect on the quality of life. A primary care physician should be aware of it so that overall morbidity associated with RLS could be reduced. These models can help physicians to identify RLS existence, so that active measures can be taken in time to avoid further complications.

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