ABSTRACT
In the present study, one model that has already been proposed for understanding the etiology of Alzheimer’s disease, i.e., ‘Latent Early-Life Associated Regulation’ (LEARn) model is studied for the Parkinson’s disease (PD). LEARn model postulates latent expressions of specific genes triggered at the developmental stage. According to this model, environmental agents (e.g. heavy metals ions, pesticides, temperature and pH) disturb gene (primarily PARK 1) regulation in a long-term fashion, beginning at early developmental stages. Pathologically, α-synuclein is identified as the main culprit; oxidative stress and mitochondrial dysfunction play important role in onset of disease followed by degeneration of dopamine-producing brain cells. The clinical symptoms of PD has been studied with the help of an expert clinician and identified as it is expressed under four major classes of clinical symptoms: (i) Communication problems, (ii) Personality changes, (iii) Loss of voluntary control and (iv) Health problems. All these symptoms appear very late and it get worsen over time. In this work, an artificial neural network (ANN) has been used to identify the PD conditions with the help of clinical symptoms with an accuracy of 98%. The used symptomatic inputs to the ANN have provided very effective identification rate for PD conditions. Based on this study, it can be suggested that the outputs of biochemical network models can be combined with smart computational tools to get effective diagnostic system for neurodegenerative disorders.

Key Words: Artificial Neural Network, Environmental Factors, Learn Model, Parkinson’s Disease

INTRODUCTION
Neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expression affecting specific subsets of neurons in definite functional anatomic systems: they arise for unknown reasons and progress in a relentless manner (Przedborski et al., 2003). Parkinson’s disease (PD) is the second most common neurodegenerative disease among elderly people (Takahashi & Imai, 2003). It is a chronic, progressive neurodegenerative disorder that affects at least 1% of the population by age 70 (Savitt et al., 2006), regarded as the loss of dopamine-containing neurons in the substantia nigra pars compacta (SNPC) (Brochard et al., 2009) and clinically described by the symptoms of bradykinesia, resting tremor, rigidity, postural instability, autonomic, cognitive, and psychiatric disturbances (Moore et al., 2005). Basically two main theories are considered for pathogenesis of PD (Dauer and Przedborski, 2003). One hypothesizes that misfolding and aggregation of proteins are influential in the loss of SNPC dopaminergic neurons, while the other is based on the idea that irregular mitochondrial structure and function contributes to increased oxidative stress and toxic dopaminergic species. PD pathogenesis also includes abnormalities in cellular protein transport, interaction between proteins, mitochondrial dysfunction, oxidative stress as well as the genetic mutation. These processes are considered to form a complex cascade of unified events that lead to neuronal death by the manner of apoptosis. In humans, appearances of PD usually start in latter half of life. It is characterized by progressive loss of muscle control, stiffness, slowness, and impaired balance (Fahn, 2003). All these symptoms appear very late and it get worsen over time and as symptoms appear, 60-70% of the striatal dopaminergic terminals have been already lost (Drechsel and Patel, 2008). It is still not clear when this disease actually starts and
how long it will take to be visible symptomatically. Thus, development and progression of PD with the help of biochemical models is difficult. Considering this limitation, the established model for understanding the etiology of Alzheimers disease, the ‘Latent Early-Life Associated Regulation’ (LEARn) model (Lahiri et al., 2007; 2008; Lahiri and Maloney, 2010) has been considered for the explanation of PD. This model suggests a latent expression of specific genes triggered at the developmental stage. According to this model, environmental agents disturb gene regulation in a long-term fashion, beginning at early developmental stages.

It is revealed that multiple symptoms arise progressively that may be indicative of PD. Thus, its automated differentiation with normal subjects is important as the manual screening is a tedious and error frame task. The proposed artificial neural network (ANN) model is based on a set of multilayered interconnected equations, which uses non-linear statistical analysis to reveal previously unrecognized relations between given input variables (assigned according to the severity of expressed symptoms) along with an output variable. Several studies have shown that ANN is accurate and reliable in diagnosis and outcome prediction in diverse clinical setting (Sinha, 2008). ANNs also appear to be promising for classification of neurodegenerative disorders (Litvan et al., 1996; Ene, 2008). In near past, its application is also reported in identification of the metabolic marker for the detection of PD from plasma and to validate the variations by spotting out through gene responsibility (Ahmed et al., 2009).

In this paper, the biochemical pathway of PD has been studied by using the LEARn model. The proposed LEARn model for PD is based on environmentally induced hypomethylation or oxidative damage as the physical mechanism that perturbs gene expression and considers the effects of environmental factors (heavy metals ions, pesticides, temperature and pH) on both oxidative stress and genetic mutation (PARK 1) associated with this disease. Further, apart from LEARn model, the present work is aimed to develop an ANN model to predict the appearance of PD by use of the symptoms routinely available to the clinicians.

ETIOLOGY OF PARKINSON’S DISEASE

PD arises from genetic and possibly neurotoxic causes that produce massive cell death of the neuromelanin-containing dopaminergic neurons of the substantia nigra (Sulzer, 2011). Substantia nigra degeneration is one of the major features of PD because symptoms only get visible when most of the cells are dead in this region. There was a decline in axonal transport motor proteins in sporadic PD that preceded other well known nigral cell-related pathology such as phenotypic down regulation of dopamine (Chu et al., 2012). Reduced axonal transport contributes to the degeneration of neuronal processes in PD. Mitochondria supply the ATP needed to support axonal transport and contribute to many other cellular functions essential for the survival of neuronal cells. Oxidative stress causes mitochondrial dysfunction and can impair proteasomal function. Impairment of proteasomal function induces oxidative and nitrative stress and inhibits mitochondrial function (Jenner, 2003) that impairs protein clearance as ATP production is required for normal proteolytic activity. Along with all pathological pathways, age cannot be denied as a contributing factor for PD and loss of dopaminergic neurons seen in PD can be distinguished from normal changes associated with aging. In those with PD, neuronal cell death occurs mainly in ventrolateral and caudal portions of the SNPC. In normal aging, these changes are seen in the dorsomedial aspect of the SNPC (Dauer & Przedborski, 2003).

Peptide Aggregation

Protein aggregation is a common feature of many neurodegenerative diseases, and it is assumed that the aggregation process plays a central role in pathogenesis. In this process, the monomer of a soluble protein interacts with other monomers of the same protein to form dimers, oligomers, and polymers. As the size of the aggregates increases, they may precipitate as insoluble amyloid fibrils (Irvine et al., 2008). One of the pathological hallmarks of PD, Lewy bodies (LB) are spherically-shaped eosinophillic cytoplasmic protein aggregates found in all affected brain regions that are made up of several proteins, including α-synuclein, parkin, ubiquitin, and neurofilaments. In PD, LBs contain α-synuclein that has been altered by
oxidative activity. The α-synuclein was identified as the major component of amyloid fibrils found in LB body and Lewy neurites, the characteristic proteinaceous deposits that are the diagnostic hallmarks of PD. In vitro studies have shown to this form of the protein demonstrates a greater tendency to aggregate than unmodified α-synuclein, which supports the theory that oxidative stress plays a key role in PD pathogenesis. It is an intrinsically unfolded protein that can adopt a partially helical structure when it interacts with different lipid membranes. The amino-terminal sequence of α-synuclein is almost entirely composed of variants of an imperfect 11 amino acid repeat (XKTKEGVXXXX) (Bisaglia et al., 2009).

**Genetic Causes**

Most cases of PD arise sporadically, but newer etiological research is discovering a smaller number of cases caused by genetic mutations (de Lau & Breteler, 2006). PD was thought, until recently, to have little or no genetic component. This notion has changed with the identification of three genes, and the mapping of five others, that are linked to rare familial forms of PD (FPD). Recent evidences suggest the involvement of single gene mutations including α-synuclein (PARK 1), Parkin (PARK 2), and ubiquitin-C-hydrolase-L1 (PARK 5); LRRK 2, DJ-1, PARK 3, PINK 1, and HTRA 2 are the underlying mechanism of FPD pathogenesis. There is evidence that mutation of the gene and over expression of α-synuclein is associated with decreased mitochondrial function, abnormal mitochondria, damaged mitochondrial DNA, increased cytochrome c release, and increased free radical production (Henchcliffe & Beal, 2008). PINK 1 gene encodes a putative serine/threonine protein kinase with a mitochondrial import sequence located at its N-terminus (Yao et al., 2011). PINK 1 interacts with Parkin to regulate mitochondrial dynamics, including fission/fusion. PINK 1 initiates mitophagy via phosphorylation of Parkin. Its stabilization on the outer mitochondrial membrane is necessary for Parkin ligase, which is normally localized to the cytosol, to translocate to damaged mitochondria. PINK 1 mutation that is related to PD pathology impairs mitochondrial autophagy by compromising initial Parkin translocation to mitochondria. In normal circumstances, PINK 1 recruits Parkin following a loss of mitochondrial membrane potential (Geisler et al., 2010). DJ-1 is normally localized in the cytosol, but its expression is noticed in the mitochondria under conditions of oxidative stress and has been found to play a significant part in the defensive cellular response to oxidative stress. It is also suggested that this could work upstream of the PINK 1/Parkin activation or it could work within an independent, but parallel, pathway in conjunction with PINK 1/Parkin. DJ-1 deficient cells also have lower mitochondrial fusion, an increased tendency to fragment, and impaired mitochondrial dynamics leading to an increase in autophagy. This also suggests that DJ-1 function in normal cells could regulate autophagy or attenuate the downstream negative effects of reactive oxygen species (Thomas et al., 2011). LRRK 2 is associated with idiopathic PD. It is typically late-onset PD LRRK 2, also called leucine-rich repeat serine/threonine-protein kinase 2, is localized in the cytoplasm. Mutations of LRRK 2 cause PARK 8 (FPD, type 8) and augment MAPK activity. It causes an increase in phosphorylation intra and inter-cellularly (Farrer & Ross, 2006). The pathology of LRRK 2 includes deposits of aggregated protein (Smith et al., 2005). It is rare to find mutations of the HTRA 2 gene in individuals with PD. Mutations of the gene result in increased mitochondrial volume, electrochemical changes in the mitochondrial membrane, and increased risk of cell death related to the activity of staurosporine, an ATP kinase inhibitor. It is also thought that mutations to the PINK 1 gene negatively influence HTRA 2 function (Henchcliffe & Beal, 2008).

**Environmental Risk Factors**

Several studies have demonstrated that environmental factors implicated in PD, including heavy metals and pesticides, accelerate *in vitro* fibril formation. Epidemiological studies have demonstrated that the following environmental factors are positively correlated with the risk of developing PD: pesticide use for example rotenone and paraquat (Tansey et al., 2007), contact with certain industrial chemicals (trichloroethylene, manganese, carbon disulfide, carbon monoxide, cyanide, methanol), exposure to wood preservatives, drinking well water (Priyadarshi et al., 2001), and exposure to MPTP (Ballard et al., 1985). There are thoughts that some of these environmental factors contribute to the mitochondrial dysfunction seen in primary PD (Dick, 2006). One of the strongest relationships reported in the literature is the
negative correlation between cigarette smoking (Baron, 1986) and caffeine intake and risk of PD development (Hernán et al., 2002; Checkoway et al., 2002).

**LEARn Model and Its Implications**

A ‘Latent Early-life Associated Regulation’ (LEARn) model, postulates a latent expression of specific genes triggered at the developmental stage. It is already proposed that the majority of Alzheimer’s disease cases would, instead, follow an etiology based on ‘LEARn’ (Lahiri et al., 2007; 2008; Lahiri and Maloney, 2010). According to that, LEARn posits that early-life influences, such as exposure to metals, nutritional variation, variation in maternal care, and other stressors modify potential expression levels of disorder-associated genes in a latent fashion. Such latent changes are maintained by epigenetic markers in the promoter sequences of such genes. Based on this hypothesis, in the present work, we integrated both the reasons of PD; the neuropathological features (e.g., α-synuclein and LB) as well as the oxidative stress effected by environmental factors such as Pesticides, metal ions exposure (Uversky et al., 2001; Willis et al., 2010), pH and temperature (Mcnulty et al., 2006). Environmental agents perturb gene regulation in a long-term fashion, beginning at early developmental stages, but these perturbations do not have pathological results until significantly later in life.

![Figure 1: Block diagram of Latent Early-life Associated Regulation (LEARn) model](image-url)
Like all other Neurodegenerative diseases PD apparent very late in adult life, it is still not clearly understood that when the disease actually starts and how long the biochemical events and neuropathological processes take to develop the disease. So the major unresolved question is related to the time and aging. There are multiple pathways contributing to PD, and there are several indications that environmental factors affecting these pathways in various manners (Uversky et al., 2001; Meigal & Lupandin, 2005; Coon et al., 2006). Therefore, to explain the etiology of PD with the help of LEARn model, we considered effect of various environmental factors associated with PD. As the LEARn model is based on environmentally induced hypomethylation or oxidative damage that effect the gene expression (Bolin et al., 2006), these perturbations are latent. They are not immediately apparent in the same manner found in conventional toxic responses.

Peptide aggregation is major cause of PD. In the present model, both the causes are considered genetic mutation and result of oxidative stress due to environmental insult such as temperature, heavy metals, pH and pesticides. Genetic mutation initiated by environmental insult causes six imperfect repeats in PARK 1 gene this is immediate effect on gene but the symptoms only get visible after a long time or aging when due to this mutation peptide aggregation starts here that can be noticed in the LEARn response. Simultaneously, it is also shown that oxidative stress caused by environmental factors leads to mitochondrial dysfunction as an immediate response but after LEARn response it also results in peptide aggregation, which ultimately leads to cell death and neurodegeneration. The LEARn model proposes that the initial triggering mechanism activates early in life, but the development of disease occurs very late. Figure-1 explains the pathways of LEARn response.

**CLINICAL SYMPTOMS BASED ANN IDENTIFIER FOR PARKINSON’S DISEASE**

As discussed in LEARn response (figure-1), with peptide aggregation that leads to neuronal cell death, the clinical symptoms of PD appear very late, usually in the latter half of the life. The clinical symptoms of PD has been studied with the help of an expert clinician and identified as it is expressed under four major classes: (i) Communication problems, (ii) Personality changes, (iii) Loss of voluntary control and (iv) Health problems. The characteristics of the PD under each of the mentioned major classes are further focused on the specific symptoms and explained in table-1. Appearance of majority of these clinical symptoms, if not all, is used as confirmatory parameters in clinical domain.

Based on clinical symptoms, the present paper has used three layered feed-forward back propagation ANN to differentiate PD from the normal condition. The ANN network was coded using C++ programming language (Rao and Rao, 1996). The backpropagation ANN has advantage of available effective training and better-understanding of system behavior. Neurons or nodes in each layer are interconnected in a feed-forward fashion. The connections between different layers of nodes have associated weights, which act upon outputs of the first layer of nodes before they are processed next. In the present network, the nodes of hidden and output layers have a sigmoid transfer function (Aggarwal et al., 2007). The weights were adjusted as follows:

$$W_j(t+1) = W_j(t) + \eta \delta_j X_i + \alpha(W_j(t) - W_j(t-1))$$

Where $W_j(t)$ is the connection weight from a node $i$ in one layer at time $t$, $X_i$ is either an input or the output of the hidden node $i$, $\delta_j$ is an error term for node $j$, $\eta$ is a learning rate factor and $\alpha$ is a momentum factor ($0 < \alpha < 1$). If $j$ is an output node, then

$$\delta_j = y_j(1- y_j)(d_j - y_j)$$

Where, $d_j$ is the desired output of node $j$ and $y_j$ is the actual output. If node $j$ is hidden node, however, the computation of error terms becomes

$$\delta_j = X_j(1- X_j) \sum_k \delta_k W_{jk}$$
Where \( k \) is summed over all nodes in the layer above node \( j \). Hidden node thresholds were adjusted in a similar way by assuming they are connection weights on links from auxiliary constant valued inputs.

In ANN, digital values of the PD symptoms (table 1) were used as the input vector to the ANN. The inputs have been manually prepared in digital form in the scale between 0 and 1. The severity of any symptom has an assigned value > 0.5 and for the normal conditions, it is assigned < 0.5. Similarly, the PD condition was predicted with the firing intensity of the output node. The output value > 0.5 of output node confirms the PD and the increasing intensity of firing of output node provides the severity of PD condition in digital form. In the present study, 160 data sets (80 normal and 80 PD) have been prepared with the help of expert clinician to test the ANN. The 13:20:1 architecture of ANN was obtained with the optimization both for training and testing purpose. During training, a training file ‘TRAINING.DAT’ with the digital values of all thirteen symptoms along with an output was presented to the input. For training of network 60 datasets (30 each for normal and PD) were randomly arranged. Remaining 100 data sets (50 each for normal and PD) were used for testing purposes. The error tolerance, number of iterations and learning rate parameter were assigned as 0.01, one million and 0.1, respectively. Once the simulator reaches the error tolerance specified or achieved the maximum number of iterations, assigned for training, the simulator save the state of network by saving all its weights in ‘WEIGHT.DAT’ file. The output values have been compared to the desired outputs and if the outputs have found same as desired outputs, no further training is required. Otherwise weights have to adapt further by training with least mean square rule. Obtaining the error in minimum possible value, results in absolute correction. During testing, the testing file ‘TEST.DAT’ with digital values of clinical symptoms is presented to the input nodes of ANN, which read the input and finds the output of the network.

Table 1: Clinical variable of Parkinson’s disease used to build the predictive model.

<table>
<thead>
<tr>
<th>Major Variables</th>
<th>Clinical Stages</th>
<th>Primary Symptoms</th>
<th>Secondary Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversation</td>
<td></td>
<td>Soft whispery voice</td>
<td></td>
</tr>
<tr>
<td>Comprehension</td>
<td></td>
<td>Small cramped handwriting</td>
<td></td>
</tr>
<tr>
<td>Slow response</td>
<td></td>
<td>Slow response to questions</td>
<td>Depression</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td>Anxiety, Isolation</td>
</tr>
<tr>
<td>Mental disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality Changes</td>
<td></td>
<td>Slowness in voluntary movements such as standing up, walking and sitting down,</td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td></td>
<td>freezing episodes</td>
<td></td>
</tr>
<tr>
<td>Loss of voluntary control</td>
<td>Tremors</td>
<td>Often occur in the hands, fingers, forearms, foot, mouth or chin</td>
<td>Depression</td>
</tr>
<tr>
<td>Rigidity</td>
<td></td>
<td>Stiff muscles, muscles pain during movement</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Poor balance</td>
<td></td>
<td>Unsteady balance, which oftentimes leads to fall, loss of reflexes that help posture</td>
<td></td>
</tr>
<tr>
<td>Health problems</td>
<td>Loss of bowel and bladder control</td>
<td>Constipation, loss of bowel and bladder control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Throat, mouth and esophagus complications</td>
<td>Difficulties in swallowing, choking, coughing or drooling, excessive salivation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dermatological effects</td>
<td>Excessive sweating, scaling, dry skin on the face or scalp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dependence</td>
<td>At advanced stage needs complete assistance</td>
<td></td>
</tr>
</tbody>
</table>
Before applying the ANN for the identification of PD, the network was optimized to get optimum performance. Different learning rates were investigated in the range of 0.01-0.5. The best performance was when the learning rate was chosen as 0.1 with which the accuracy of 100% was obtained for training set. The effects of number of hidden nodes in the range of 5-50 with a fixed number of iterations (1 million) are tested. 20 hidden nodes resulted in the best performance compared with other combinations of hidden nodes. With the 13:20:1 structure and optimized learning rate value (0.1), the ANN classified 50 normal and 50 diseased test sets with the accuracy of 98%.

DISCUSSION
Like other neurologic diseases, PD is related to aging, may be determined by chronic exposure of adverse environmental factors early during the life span or even during pregnancy (Logroscino, 2005). Earlier the etiologic model for PD has explored mainly risk factors associated with adult life or in many cases after the age of 65 (Kuh & Ben-Shlomo, 1997). The data for PD and AD suggest that a number of environmental insults occurring early in life may lead or contribute to these diseases (Landrigan et al., 2005). PD also fits in two-hit disorder, similarly to those found in currently accepted models of cancer etiology (Knudson, 1971) and Alzheimer’s disease (Lahiri and Maloney, 2010).

LEARn mechanism reveals the interaction between oxidative stress, gene and environmental factors in early developmental etiology for PD. The promoter regions of gene PARK 1 provide the substrate for LEARn activity. Environmental factors such as exposure to temperature, heavy metal and pH result in six imperfect repeats in PARK 1 gene and also the effect of environmental factors (temperature, heavy metals and pesticides) on oxidative stress that alter the function of mitochondria, which ultimately results in peptide aggregation and cell death, both the pathways contribute to neurodegeneration. In LEARn systems, alterations are latent and effects are primarily notable later in life. In both immediate and LEARn systems, epigenetic changes in gene regulation result in disorders. However, the LEARn model has its limitations as it does not provide any predictive output to analyze the severity of the disorder. PD is age-associated progressive neurodegenerative disease that gradually affects human brain. It is already known that the disease starts early in the life but the symptoms appear very late. LEARn model is only to explain that what the factors are affecting in our early life which later results in to the disease and to explain that there is the latent period between immediate effect and symptoms to be get visible. This model does not explain that when during the life course that a given exposure has its greatest effect and how exposures may accumulate over the life span. More elaborative and ultimate knowledge of risk factors involved will be needed to implement intervention and preventative strategies early in life to reduce or prevent any adverse late-life outcomes. However, the LEARn model will help to efficiently detect these changes and early-life remediation methods to eliminate PD before it occurs. We extended the Lahiri’s LEARn model (Lahiri et al., 2007; 2008; Lahiri & Maloney, 2010) by adding symptomatic classification of Parkinson’s after onset of disease with the help of ANN.

In this study, we used ANN based technique is an attempt to envisage the severity of PD. For any predictive technique to be useful in making a diagnostic decision, an important feature is that only data that are readily available to the clinician at the time of diagnosis are used. Our model used only data derived from clinical history and physical examination. We accentuate that our model is not meant to replace or substitute for an experienced clinician; on the contrary, we suggests that the model should be viewed as a decision aid for the busy clinicians. The result of this study are promising, suggesting that a system based on this approach will be accurate and user friendly, while simple enough to be implemented at low cost.

The review of literature revealed that the ANN is being applied in broad areas of prediction and classification. In the field of health and medicine it is used by many researchers for diagnosis and prediction of diseases. Neural networks are powerful computational methods that have resulted from work in the area of neurophysiology and are being applied to an increasing range of medical problems (Paliwal & Kumar, 2009). In the field of neurodegenerative diseases ANN is applied for classification of...
cognitively normal, demented, AD and vascular dementia from single photon emission with computed tomography image data from brain (deFigueiredo et al., 1995), to distinguish AD patients from controls in the nun study (Grossi et al., 2007), also for the classification of essential tremor, PD tremor, and physiological tremor (Ai et al., 2008). In 1996, Litvan and co-workers applied supervised and unsupervised ANN for differentiating the subtypes of progressive supranuclear palsy (PSP), and in differentiating PSP from postencephalitic Parkinsonism (PEP) and corticobasal degeneration, or Pick's disease from corticobasal degeneration. The supervised learning ANN achieved excellent accuracy in classifying PSP but had difficulty in classifying the other disorders. There have been no reports on the application of ANN methods for symptomatic diagnostic classifications of PD with the help of symptoms regularly available to the clinicians. Further, there are no clinically useful predictive techniques available to aid the physician in the diagnosis of patients. Therefore, it can be suggested that the prediction of severity with the help of ANN following the understanding of LEARn response of PD may provide a useful tool in clinical domain.

**Conclusion**

PD is a progressive neurodegenerative disorder manifested by a broad spectrum of motor and non-motor features. Occurrence of PD has been reported to be associated with environmental factors by many researchers. LEARn model along with the ANN classifier is not only useful for diagnosing the disease in affected persons, it will be useful for identifying family members or populations at risk, thus providing an opportunity to initiate neuroprotective therapy at an asymptomatic stage.

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**Conflict of Interest**

Authors of the manuscript certify that there is no ethical issue or conflict of interest involved in this work. Further, they have no financial interests related to the material in the manuscript.

**REFERENCES**


Research Article

