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Original Article

Internal Medicine Section

# Minimal Unified Wilson's Disease Rating Scale (M-UWDRS) Score Compared to UWDRS Neurological Subscore in Wilson's Disease: A Cross-sectional Study

S MISHRA[1], SD NAYAK[2], AK MALLICK[3], BD MORE[4], G MOHANTY[5], M SAMANTA[6], AK SAHU[7]




## ABSTRACT

**Introduction:** Wilson's Disease (WD) is a copper metabolic disorder that affects the nervous system and liver. The Unified Wilson's Disease Rating Scale (UWDRS) is used for diagnosing WD, but it is time-consuming. Therefore, a less exhaustive scale is needed as a screening tool, such as the minimal Unified Wilson's Disease Rating Scale (M-UWDRS).

**Aim:** To evaluate the utility of M-UWDRS in assessing signs and symptoms associated with WD and compare it with the UWDRS (Neurological) subscore.

**Materials and Methods:** This prospective, observational, non interventional, cross-sectional study was conducted in the Department of Neurology, Srirama Chandra Bhanja Medical College and Hospital, Cuttack, Odisha, India from November 2017 to October 2020. A total of 42 patients with WD, based on the European Association for the Study of the Liver (EASL) guidelines, were enrolled. They were assessed using both M-UWDRS and UWDRS (Neurological) scoring before treatment and at a three-month follow-up.

**Results:** A total of 42 cases were enrolled, of which 28 were males and 14 were females. The mean age of presentation was 15.4±5.1 years. Both the neurological subscore of UWDRS and M-UWDRS were used pre and post-treatment, revealing a significant improvement in the majority of subjects. Both scores fared similarly in predicting disease severity, treatment outcome, and follow-up. The score of the "minimal UWDRS" correlated with the scores of the UWDRS for neurological subscores (r value: 0.6, p-value <0.001).

**Conclusion:** M-UWDRS is a user-friendly, quick, and practical prescreening scoring scale for evaluating disorder severity and quantification of the outcomes in comparison to the UWDRS score, especially in resource-constrained and busy neurology departments. Scoring in WD will help in better prognostication of the disease.


**Keywords:** Copper, Hepatic symptoms, Progressive lenticular degeneration, Psychiatric symptoms

## INTRODUCTION

The WD is an inherited autosomal recessive condition associated with mutations in the ATP7B gene, which encodes a transmembrane copper-transporting ATPase, leading to derangement in copper metabolism. The prevalence of WD is 1:30,000-1:50,000 in the Americas, European countries, and the Asian region. Population-based data demonstrate that the genetic prevalence is 3-4 times higher than clinically based estimates [1]. According to the World Health Organisation, the worldwide prevalence of WD is 1/10,000 to 1/30,000. The prevalence in Asian countries other than India varies between 33 and 68 per 100,000. There is no Indian community-based prevalence data available, but WD is more common where consanguinity is prevalent (South India) [2].

Mutations in the ATP7B gene and inactivation of the ATP7B transporter result in failure of biliary copper excretion, resulting in copper deposition in body organs, predominantly in the liver and brain [3]. Patients with WD present differently, and it remains unclear why some of them present with hepatic symptoms while others present with neurological, psychiatric, or combined symptoms [4]. Hepatic disease can be the clinical manifestation (40-60%) of WD, ranging from asymptomatic subjects with slightly elevated hepatic enzymes to cirrhosis or acute liver failure [5]. The presentation can vary with age, gender, and duration of untreated copper overload.

Neurological symptoms include several motor dysfunctions associated with abnormalities of the basal ganglia and the cerebellum abnormities. They present as tremor, rigidity, dyskinesia, dystonia, ataxia, chorea, swallowing difficulties, dysarthria, or sialorrhoea. Various psychiatric symptoms have been found, such as attention problems, decreased concentration span, and behavioural issues, along with changes in personality, sadness, and neurosis [3]. The intensity of these symptoms has an adverse impact on Activities of Daily Living (ADL).

The aetiology of WD may be multifactorial, involving a combination of genetic, epigenetic, hormonal, and environmental factors. Timely identification of the disease and individualised therapy are critical to prevent the development of illness and resultant cirrhosis or hepatic failure [6,7]. The available laboratory tests are not perfect or specific for WD, as characteristic medical symptoms may not be present in a significant proportion of individuals. Therefore, a comprehensive, standardised, and practical clinical rating scale is essential for monitoring individual treatment responses in routine clinical settings and for utility as a valid endpoint in clinical trials evaluating different interventions [8].

At present, two clinical rating scales are used for the assessment of WD, namely the UWDRS and the Global Assessment Scale for WD (GAS for WD). In 2007, Czlonkowska A et al., reported the UWDRS scale, which reflects the extent of neurological impairment [9]. A year later, Leinweber B et al., extended the UWDRS scale by adding hepatic and psychiatric subscales. Currently, the UWDRS consists of three subscales: neurological, hepatic, and psychiatric [10]. In 2009, Aggarwal A et al., proposed the GAS for WD, which significantly takes less time compared to the UWDRS. It is composed of two tiers: scoring global disability (Tier 1) and neurological dysfunction (Tier 2) [11]. Both rating scales require a relatively long duration to complete the clinical assessment, making it difficult in daily practice. Moreover, they require two to three different medical

specialists i.e., a neurologist, gastroenterologist, and psychiatrist for assessment [4].

To reduce the time required, a modified "minimal UWDRS" was proposed as a prescreening tool for use outside scientific trials. The initial nine items of the UWDRS neurological subscale were used to develop a minimal neurological subscale, considered as the "minimal UWDRS." This abridged scoring scale serves as a questionnaire, with items reported by the patient or their family, allowing the score to be evaluated before the consultation with the treating neurologist (which typically takes 2 to 4 weeks) [12]. The utility of this scale has not been previously studied in an Indian set-up like our institution. Therefore, this cross-sectional study was carried out with the primary objective of determining the utility of M-UWDRS in assessment of clinical radiological features in WD and compare it with the UWDRS (Neurological) subscore. The other objectives include estimating the hospital-based incidence of neurological manifestations of WD.

## MATERIALS AND METHODS

A hospital-based, non international, observational, prospective, cross-sectional study was carried out at Department of Neurology, SCB, Medical College and Hospital in Cuttack, Odisha, India from November 2017 to October 2020, over a period of three years. The study was carried out after obtaining protocol approval from the Institutional Ethics Committee (IEC) (898/14.08.2017).

**Inclusion criteria:** Patients aged >8 years who were admitted with clinical features of neurological manifestations of WD in the neurology department at SCB Medical College were further evaluated for WD based on the EASL criteria [Table/Fig-1] [8]. Those who were diagnosed with WD and provided written consent were enrolled in the study. In the case of children and adolescent patients, consent was obtained from their parents or legal guardians in writing.

**Exclusion criteria:** Patients treated on an outpatient basis were excluded from the study. Patients with suspected neuro-WD who fell into the probable category of the EASL criteria, as well as those with any chronic liver disease, history of birth asphyxia, global developmental delay, and substance abuse, were also excluded from the study.

**Sample size:** As a pilot study, a sample size of 42 patients was selected.

**Parameters studied:** All epidemiological and clinical parameters, along with patient history, were recorded in a prestructured case record form. Patient demographic details, age at assessment, and treatment at assessment were collected.

The penicillamine challenge test, which involves copper estimation after a penicillamine challenge, was performed on patients as needed. This test has significant value in the identification of WD [12]. The penicillamine challenge involved administering a 500 mg dose of penicillamine (irrespective of body weight) at the start of a 24-hour urine collection, which was repeated at 12 hours. Copper excretion in urine of >1600 µg per 24 hours (>25 micromol) is commonly observed in WD compared to other types of liver disease.

Neurological UWDRS and minimal UWDRS were performed before treatment. The full UWDRS, with a maximum score of 320 points, comprises of three subscales representing the major characteristics of clinical expression in WD [Table/Fig-2].

Among the 55 items in the scale, the patient responds to 26 questions, while the physician scores 29 items. Each item is scored on a rising 5-point scale, with a score of 0 indicating no symptoms and a score of 4 indicating the worst possible characteristic [9,10].

| Typical clinical characteristics (signs and symptoms) | Score |
|---|---|
| **KF rings** | |
| Present | 2 |
| Absent | 0 |
| **Neurological symptoms**** (dystonia, neuropsychiatric manifestations etc., or typical abnormalities at brain magnetic resonance imaging) | |
| Severe | 2 |
| Mild | 1 |
| Absent | 0 |
| **Serum ceruloplasmin** | |
| Normal (>0.2 g/L) | 0 |
| 0.1-0.2 g/L | 1 |
| <0.1 g/L | 2 |
| **Coombs-negative haemolytic anaemia** | |
| Present | 1 |
| Absent | 0 |
| **Liver copper (in the absence of cholestasis)** | |
| >5x ULN (>4 µmol/g) | 2 |
| 0.8-4 µmol/g | 1 |
| **Rhodanine-positive granules*** | 1 |
| Normal (<0.8 µmol/g) | -1 |
| **Urinary copper (in the absence of acute hepatitis)** | |
| Normal | 0 |
| 1-2x ULN | 1 |
| >2x ULN | 2 |
| Normal, but >5x ULN after D-penicillamine | 2 |
| **Mutation analysis** | |
| On both chromosomes detected | 4 |
| On 1 chromosome detected | 1 |
| No mutations detected | 0 |
| **Total score** | **Inference** |
| 4 or more | Diagnosis established |
| 3 | Diagnosis possible, more tests needed |
| 2 or less | Diagnosis very unlikely |

**[Table/Fig-1]:** Diagnostic criteria: (EASL Diagnostic criteria) [8].
*If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging. KF: Kayser-Fleischer; ULN: Upper limit of normal

| Subscale | Items | Points |
|---|---|---|
| Neurological | 27 | 208 |
| Hepatic | 9 | 36 |
| Psychiatric | 19 | 76 |
| Total | 55 | 320 |

**[Table/Fig-2]:** The full UWDRS (maximum score 320 points).

### The "minimal UWDRS":

The initial 9 items of the UWDRS neurological subscale were used to construct the minimal neurological subscale, which is referred to as the "minimal UWDRS" [4]. Since this reduced rating scale consists solely of a questionnaire where the items are reported by the patient or their family (usually referring to the previous two to four weeks), the resulting score can be assessed before the consultation with the treating physician. The items used in the minimal UWDRS are as follows:

- Mobility
- Falling
- Salivation
- Swallowing

- Feeding
- Dressing
- Taking a bath or shower
- Grooming
- Toilet use

Except for items 3 and 4, all other items evaluate the degree of independence for Activities of Daily Living (ADL) [4].

Treatment was done according to the recent WD: Clinical Practice Guidelines of the Indian National Association for Study of the Liver, the Indian Society of Paediatric Gastroenterology, Hepatology and Nutrition, and the Movement Disorders Society of India [13]. Rescoring was done on follow-up after three months.

The study cohort was classified into three severity groups by the authors based on the scores. Patients with scores of 0-12 were classified as mild, those with scores of 13-24 were classified as moderate, and those with scores of 25-36 were classified as severe. The post-treatment outcome was categorised as good improvement or mild improvement. Good improvement was defined as a decrease in score of nine points or reaching a minimal (0) score after treatment. As there are nine categories, it was postulated by the authors after discussion with experts that a decrease in score of nine would reflect an improvement in ADL. A decrease in score of less than nine was considered a mild improvement. These cut-offs were considered for the present study only by the authors after discussion with experts.

## STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Software version 21.0 with the help of a departmental statistician. The score of the "minimal UWDRS" was correlated with the scores of the UWDRS for neurological subscores. A correlation coefficient (r) of less than 0.5 and a p-value <0.05 were considered statistically significant.

## RESULTS

A total of 42 cases were included in the study, with 28 being males and 14 being females. The mean age of presentation was 15.4±5.1 years (mean±SD). The maximum age observed was 32 years, while the minimum age was 9 years. The mean duration of disease was nine months, and the average length of hospitalisation was 14 days. All patients received treatment with Zinc. Among the patients, 30 (71.43%) were treated with penicillamine, 34 (80.95%) received trihexyphenidyl, 25 (59.53%)were given dopamine, and 23 (54.76%) received antipsychotics. Additionally, 7 (16.7%) of patients were given antiepileptics, and 50% (N=21) received tetrabenazine for symptomatic benefit.

All patients were evaluated using both the M-UWDRS and UWDRS (neurological subscore) before treatment and after three months of follow-up. In the MIN-UWDRS, the mean prescore was 20.29, and the mean post-score was 12.95, with a mean difference of 7.34. This indicates a 36% decrease in the mean score. In the UWDRS (neurological subscore), the mean prescore was 98.29, and the mean post-score was 64.71, with a mean difference of 33.57. This corresponds to a 34% decrease in the mean score [Table/Fig-3]. The score of the "minimal UWDRS" was found to be correlated with the scores of the UWDRS for neurological subscores (r=0.6), and a p-value of 0.001 was considered statistically significant.

The comparison percentage of decrease in mean scores between UWDRS (Neurological subscore) and M-UWDRS is summarised in [Table/Fig-4]. An easy severity-based classification was performed using the M-UWDRS score. Good improvement was observed in the low-score cohort, with 16 (38.1%) of patients showing significant improvement. Patients in the moderate severity group accounted for 12 (28.6%), and those in the severe severity group accounted for 14 (33.3%). These groups had limitations in disability and a poorer prognosis based on the severity classification using the M-UWDRS score [Table/Fig-5].

| Scores | Pretreatment mean (N=42) | Post-treatment mean (N=42) | Mean difference |
|---|---|---|---|
| **UWDRS (Neurological subscore)** | | | |
| Mean | 98.29 | 64.71 | 33.57 (34%) |
| SD | 11.01 | 22.68 | |
| SE | 1.7 | 3.5 | |
| The 95% confidence interval of the difference between pretest and post-test score is 25.83 to 41.32. By conventional criteria, the difference was considered statistically significant p=0.001 | | | |
| **M-UWDRS** | | | |
| Mean | 20.29 | 12.95 | 7.34 (36%) |
| SD | 9.07 | 7.77 | |
| SEM | 1.4 | 1.2 | |
| The 95% confidence interval of the difference between pretest and post-test score is 3.36 to 11.00. By conventional criteria, the difference was considered statistically significant p=0.001 | | | |

**[Table/Fig-3]:** Pre- and post-treatment scores with UWDRS (Neurological subscore) and M-UWDRS.

| Scores | UWDRS (Neurological subscore) (N=42) | M-UWDRS (N=42) | Mean difference |
|---|---|---|---|
| Mean | 36.00 | 34.00 | 2 |
| SD | 6.48 | 3.88 | |
| SE | 1.00 | 0.6 | |
| The 95% confidence interval of the difference between two groups is -0.32 to 4.30. By conventional criteria, the difference is considered not statistically significant p=0.09 | | | |

**[Table/Fig-4]:** Comparison percentage of decrease in mean scores between UWDRS (Neurological subscore) and M-UWDRS.

| Class of severity | Scores | Numbers of patients (%) | Outcome | | |
|---|---|---|---|---|---|
| | | | Good improvement | Mild improvement | Death |
| Mild | 0-12 | 16 (38.1%) | 16 | 0 | 0 |
| Moderate | 13-24 | 12 (28.6%) | 10 | 2 | 0 |
| Severe | 25-36 | 14 (33.3%) | 6 | 6 | 2 |
| Total | | 42 | 32 | 8 | 2 |

**[Table/Fig-5]:** Severity classification using M-UWDRS score.

## DISCUSSION

Epidemiological data on the community-based incidence and prevalence of WD in India is lacking. Most of the available data comes from hospital-based reports. The exact incidence of WD has not been previously documented in any Indian study [14]. The NIMHANS WD registry mentions a yearly incidence of 15-20 new cases [2]. At SCB Medical College, Cuttack, India, the annual incidence is approximately 10-15 cases. In a study by Yachha SK et al., it was reported that among 235 patients with hepatobiliary spectrum disorders studied over a three-year period, eight patients (7.6%) had WD [15].

The onset of WD symptoms varies widely, but it mostly manifests between the ages of 5 and 35 years [3]. In this study, the ages of patients ranged from 9 to 32 years. The reasons for the early age of onset of WD in this series in Eastern India cannot be explained. However, it is possible that certain environmental factors or cooking food in copper vessels may be responsible for triggering WD symptoms. Adult patients with WD are more likely to have liver cirrhosis compared to children [3].

This study found a higher prevalence of WD, with a male to female ratio of 2.1:1, which was similar to the findings of the study by Litwin T et al., [16]. Gender appears to have a modifying effect, as females are more likely to present more often with acute liver failure than males. Litwin T et al., reported that liver involvement in WD occurs more frequently in women, and they tend to express neuropsychiatric symptoms almost two years later compared to men. The neuropsychiatric type of WD is expressed at diagnosis in both men and women [16]. These differences could be because of due to the protective effect of estrogens and differences in iron metabolism.

Most current WD treatment guidelines recommend the use of chelators to manage symptoms [5,8,13]. The maintenance treatment typically includes zinc, especially at the start of therapy for asymptomatic or presymptomatic individuals. Zinc has been found to be effective and well-tolerated in neurological WD patients. However, caution should be exercised in patients with liver WD because of the due to the potential worsening of liver condition. In this study, all patients received zinc as maintenance therapy. Other medications used included penicillamine, trihexyphenidyl, dopamine, antipsychotics, antiepileptics and tetrabenazine based on individual presenting symptoms. However, the management of neurological WD is faced by therapeutic challenges, especially in individuals with tremors, parkinsonism, and involuntary muscle contractions, which significantly contribute to the UWDRS score [10]. It is recommended that initial drug therapy for WD should comprise chelating agents such which D-penicillamine, as was also followed in this study [10].

The UWDRS scale was developed to assess neurological deficits and functional impairment due to the wide heterogeneity and combined neurological symptoms observed in WD. In this study, no significant difference was found in monitoring therapy between the minimal UWDRS score and the UWDRS neurological subscore, which was in concurrence with trends observed in earlier studies [4,15]. Oder W et al., demonstrated a definite correlation between the intensity of neurological dysfunction and restricted functional activity [17]. Volpert HM et al., also demonstrated a significant correlation between the "minimal UWDRS" (UWDRS Part II without one item) and total as well as neurological UWDRS scores [4]. In clinical practice, the "minimal UWDRS" is a convenient and time-saving screening tool to identify neurological dysfunction in WD patients [4].

The presentation of WD can vary widely in terms of type and severity. The minimal UWDRS can aid in the classification of disease severity. In this study, an easy severity-based classification was conducted using the M-UWDRS score. It was found that patients in the mild group had a good outcome with improvement, while those in the moderate and severe groups had limitations in disability and a poorer prognosis. The typical presentation of WD is observed in adolescents and young adults, but it can manifest at any age. There is significant variations in the neurological abnormalities of WD, both in terms of presentation and severity. These abnormalities are classified into syndrome types based on the predominant symptoms, which include tremor and ataxia, bradykinesia (parkinsonism-like symptoms), and dystonia. However, in many cases, it is difficult to classify the neurological characteristics as patients may have multiple signs and abnormalities, each with varying degrees of intensity [18]. The M-UWDRS score can also be used to classify the neurological cohort of WD and serve as a severity scale. Primary care physicians, pediatricians, and nurses can use this score to classify the disease and determine if referral to a higher centre is necessary.

One advantage of the minimal UWDRS scale is that the neurological questionnaire can be filled out by the patient or their caregiver prior to the medical appointment, even in the absence of a neurologist. Additionally, a brief questionnaire can be administered more frequently compared to an extensive neurological evaluation. This can help in self-reflection on disease symptoms, resulting in adherence to the treatment and better outcomes. The physician can quickly assess whether the patient's ADL are limited by neurological symptoms, as seven out of the nine items in the minimal UWDRS evaluate the level of independence in ADL.

### Limitation(s)

There were a few limitations associated with the present study. Firstly, the analysis was based on a relatively small group of 42 patients, which may not allow for meaningful analyses of all subgroups. WD is a rare inherited disorder, so obtaining a large sample size can be challenging. Another limitation was that the neurological subscores of the M-UWDRS were compared with the UWDRS, Therefore, the assessment of hepatic and psychiatric involvement may have been missed.

## CONCLUSION(S)

The "Minimal UWDRS" is a pragmatic, non exhaustive, and cost-effective tool for evaluating the neurological status of WD patients with neurological symptoms. It allows for quantification of outcomes and can be used for prognostication and severity classification. It can be administered by all health professionals and aids in improved follow-up and prognostication. However, further investigations in larger samples of patients are needed to confirm the validity of the Minimal UWDRS and its classification of severity.

## REFERENCES


[1] Sandahl TD, Laursen TL, Munk DE, Vilstrup H, Weiss KH, Ott P. The prevalence of Wilson's Disease: An update. Hepatology. 2020;71(2):722-32.
[2] Taly AB, Prashanth LK, Sinha S. Wilson's disease: An Indian perspective. Neurol India. 2009;57(5):528-40.
[3] Członkowska A, Litwin T, Dusek P, Ferenci P, Lutsenko S, Medici V, et al. Wilson disease. Nat Rev Dis Primers. 2018;4(1):21.
[4] Volpert HM, Pfeiffenberger J, Gröner JB, Stremmel W, Gotthardt DN, Schäfer M, et al. Comparative assessment of clinical rating scales in Wilson's disease. BMC Neurol. 2017;17(1):140.
[5] Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: An update. Hepatology. 2008;47(6):2089-111.
[6] Członkowska A, Tarnacka B, Litwin T, Gajda J, Rodo M. Wilson's disease-cause of mortality in 164 patients during 1992-2003 observation period. J Neurol. 2005;252(6):698-703.
[7] Ferenci P. Diagnosis of Wilson disease. Handbook of Clin Neurol. 2017;142:171-80.
[8] European Association for the Study of the L. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-85.
[9] Czlonkowska A, Tarnacka B, Moller JC, Leinweber B, Bandmann O, Woimant F, et al. Unified Wilson's disease rating scale-A proposal for the neurological scoring of Wilson's disease patients. Neurologia I Neurochirurgia Polska. 2007;41(1):1.
[10] Leinweber B, Möller JC, Scherag A, Reuner U, Günther P, Lang CJ, Evaluation of the Unified Wilson's Disease Rating Scale (UWDRS) in German patients with treated Wilson's disease. Movement Disorders. 2008;23(1):54-62.
[11] Aggarwal A, Aggarwal N, Nagral A, Jankharia G, Bhatt M. A novel global assessment scale for Wilson's disease (GAS for WD). Movement Disorders. 2009;24(4):509-18.
[12] Mazumder MW, Karim MB, Rukunuzzaman M. Penicillamine challenge test in the diagnosis of Wilson's disease. Mymensingh Med J. 2014;23(3):489-95.
[13] Nagral A, Sarma MS, Matthai J, Kukkle PL, Devarbhavi H, Sinha S, et al. Wilson's Disease: Clinical Practice Guidelines of the Indian National Association for Study of the Liver, the Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition, and the Movement Disorders Society of India. J Clin Exp Hepatol. 2019;9(1):74-98.
[14] Pediatric Liver Study Group of India. Metabolic liver diseases in childhood: Indian scenario. Indian J Pediatr. 1999;66(1 Suppl):S97-103.
[15] Yachha SK, Sharma BC, Khanduri A, Srivastava A. Current spectrum of hepatobiliary disorders in northern India. Indian Pediatr. 1997;34(10):885-90.
[16] Litwin T, Gromadzka G, Członkowska A. Gender differences in Wilson's disease. J Neurol Sci. 2012;312(1-2):31-35.

[17] Oder W, Grimm G, Kollegger H, Ferenci P, Schneider B, Deecke L. Neurological and neuropsychiatric spectrum of Wilson's disease: A prospective study of 45 cases. J Neurol. 1991;238(5):281-87.

[18] Liver EAFTSOT. EASL clinical practice guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-85.

**PARTICULARS OF CONTRIBUTORS:**
1. Senior Resident, Department of Neurology, Srirama Chandra Bhanja Medical College, Cuttack, Odisha, India.
2. Associate Professor, Department of Neurology, MKCG Medical College, Berhampur, Odisha, India.
3. Professor, Department of Neurology, Srirama Chandra Bhanja Medical College, Cuttack, Odisha, India.
4. Associate Professor, Department of Pharmacology, Mahatma Gandhi Medical College and Research Institute, Puducherry, India.
5. Professor, Department of Neurology, Srirama Chandra Bhanja Medical College, Cuttack, Odisha, India.
6. Assistant Professor, Department of Neurology, Srirama Chandra Bhanja Medical College, Cuttack, Odisha, India.
7. Assistant Professor, Department of Neurology, Srirama Chandra Bhanja Medical College, Cuttack, Odisha, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. BD More,
Associate Professor, Department of Pharmacology, Mahatma Gandhi Medical College and Research Institute, Puducherry-607402, India.
E-mail: drbdmore@gmail.com

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