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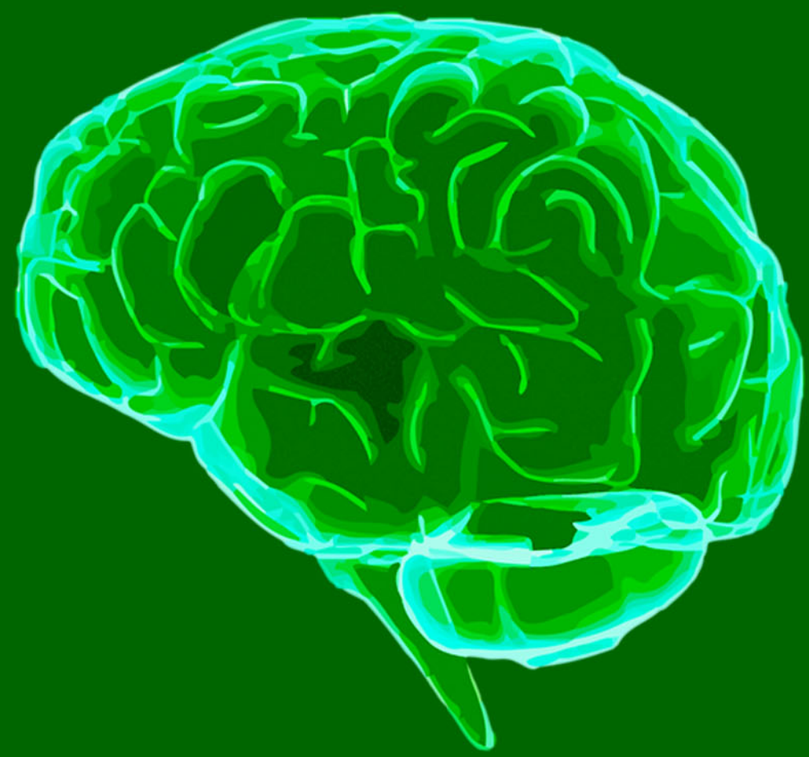

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Iranian Journal of Neurology

INFORMATION FOR AUTHORS

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The Iranian Journal of Neurology is dedicated to the Iranian Neurological Association. The journal is a peer-reviewed journal published quarterly and publishes neurological experiences in basic or clinical fields in *English Language*. *The Iranian Journal of Neurology* aims to publish manuscripts of a high scientific quality representing original clinical, diagnostic or experimental works or observations in neurological sciences. Papers in *English* are welcomed, particularly those which bring novel information and researches in clinical or basic fields from the neurological disorders. All received manuscripts coving the scope of the journal will be evaluated by properly competent referees.

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Submissions should be accompanied by a cover letter including a declaration by the first author on behalf of the others to the effect that

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(2) The paper has not been accepted for publication elsewhere.

(3) All persons listed as the authors have read it and approved it for publication. The cover letters should be submitted in section "Comments for the Editor".

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- Where available, URLs for the references have been provided.
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The journal publishes:

- Original Article
- Review Article
- Case Report
- Short Communication
- Clinical Notes
- Editorial
- Letters to Editor
- Neurological Images
- Neurological Videos
- Iranian Neurological Events
- Clinical Quiz

Details

Original and review papers: The maximum length of original and review papers (including tables and figures materials) is 3000 words.

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Neurological images or videos: Interesting cases as **neurological images** or **videos** are welcome. They should be maximally 400 words with legends without abstract and unstructured. The videos should be uploaded as supplementary files.

Letter to the Editor: May concern short scientific reports and comments. The maximum number of words should be below 800 words with maximum 5 references, no abstract, no table or figure, and unstructured.

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Iranian neurological events: Include the brief description of major regional events (congresses or seminar) implemented in Iran.

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- Manuscripts should be submitted in 12 points, Arial font, with double line spacing and sufficient margins of 2.5 cm.
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- Each section of the paper should begin on a new page

The manuscript must include:

- Page 1: Title Page
- Page 2: Abstract and Key Words
- Page 3 and subsequent pages: manuscript body including Introduction, Materials and Methods, Results, Discussion, Conclusion, References, Tables, Figures

1. Title page:

Title page should contain paper title, full names of authors, authors' place of work, full name and address of the corresponding author (including e-mail address and telephone number), given in that order.

2. Abstract page:

- The length of the abstract should be at least 200 and not more than 250 words for original papers and not more than 150 words for review papers and case reports. Abstracts of original papers should be structured to include the background, methods, results and conclusion.
- Below the abstract authors should provide between three and six keywords conforming to Medical Subject Headings (Index Medicus).

3. Page three and subsequent pages of the original paper and short communication should include the text arranged in the following order (for other mansucript type, see above):

1. **Introduction:** The introduction should be as concise as possible and introduce the context of the paper to the reader; the paper should clearly state the research hypothesis and the objective of the study.
2. **Materials and Methods:** Description of the studied population or material should be detailed and include all information necessary to assess the reliability of results obtained in the study and/or allow the experiment to be repeated by other researchers; the section related to statistical analysis should have information on applied statistical tests and programs.
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In the paper references should be given in **superscripts** with no space between the comma and the consecutive number.

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Abbreviations should be always clarified when used for the first time in the text (including the abstract). Abbreviations should not be used in paper titles, unless in exceptional circumstances.

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Original Paper

Iran J Neurol 2015; 14(2): 59-66

Effects of hydroalcoholic extract of Coriandrum sativum on oxidative damage in pentylenetetrazole-induced seizures in rats

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Keywords
Coriandrum sativum, Pentylenetetrazole, Seizures, Rat, Oxidative Stress, Brain

Abstract

Background: An important role for oxidative stress, as a consequence of epileptic seizures, has been suggested**.** Coriandrum sativum has been shown that have antioxidant effects**.** Central nervous system depressant effects of C. sativum have also been reported. In this study, the effects of hydroalcoholic extract of aerial parts of the plants on brain tissues oxidative damages following seizures induced by pentylenetetrazole (PTZ) was investigated in rats.

Methods: The rats were divided into five groups and treated: (1) Control (saline), (2) PTZ (90 mg/kg, i.p.), (3-5) three doses (100, 500 and 1000 mg/kg of C. sativum extract (CSE) before PTZ. Latencies to the first minimal clonic seizures (MCS) and the first generalized tonic-clonic seizures (GTCS) were recorded. The cortical and hippocampal tissues were then removed for biochemical measurements.

Results: The extract significantly increased the MCS and GTCS latencies ($P < 0.01$, $P < 0.001$) following PTZ-induced seizures**.** The malondialdehyde (MDA) levels in both cortical and hippocampal tissues of PTZ group were significantly higher than those of the control animals ($P < 0.001$). Pretreatment with the extract prevented elevation of the MDA levels ($P < 0.010$–$P < 0.001$). Following PTZ administration, a significant reduction in total thiol groups was observed in both cortical and hippocampal tissues ($P < 0.050$). Pre-treatment with the 500 mg/kg of the extract caused a significant prevention of decreased in total thiol concentration in the cortical tissues ($P < 0.010$).

Conclusion: The present study showed that the hydroalcoholic extract of the aerial parts of C. sativum possess significant antioxidant and anticonvulsant activities.

Introduction

Epilepsy is a common neurological disease, which affects approximately 1% of the population.[1] It is characterized by abnormal episodic bursts of electrical activity in neurons, which is followed by a significant impact on the behavior of the affected patients.[2] An important role for oxidative stress both as a consequence and as a cause of epileptic seizures has been suggested.[3] It has been reported that production

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of free radicals increases during seizures, which is lead to oxidative damage to lipids, DNA and susceptible proteins.[4]

Due to high levels of membrane lipid constituents, the central nervous system (CNS) is very susceptible to oxidative injury.[5] In addition, oxidative damage plays a significant role in the pathogenesis of various CNS disorders and neurobehavioral impairments.[5] The functional impairments of CNS, which occur during seizures have also been suggested to be at least in part, related to the brain tissues oxidative damages.[6] Furthermore, the anticonvulsant activities of several agents with antioxidant effects such as melatonin, vineatrol, trans-resveratrol and alpha lipoic acid have been documented.[7,8] There are also some reports that reactive oxygen species (ROS) may underlie the convulsant and neurotoxic effects of pentylenetetrazole (PTZ).[9] The results of human and animal studies imply that epilepsy and seizures are lead to the brain tissues oxidative damages, especially in the cortical and hippocampal regions, which are accompanied with cognitive, learning and memory deficits.[4,6,8,10]

Medicinal plants are good sources to find new therapeutic agents for human diseases. Coriandrum sativum, an annual herb belonging to the Apiaceae family, has been reported to have a wide range of biological activities including sedative-hypnotic, antidiabetic, hypolipidemic, and hepatoprotective effects.[11-15] Experimental studies have also revealed a strong antioxidant activity for C. sativum that is superior to the well-known antioxidant agents like ascorbic acid.[15-20] In our previous work, we found that the hydroalcoholic extract of aerial parts of this plant bearing some compounds with the hypnotic effects.[21] Regarding the antioxidant and CNS depressant effects of C. sativum, we aimed to evaluate the possible protective effects of aerial parts of the plant on PTZ-seizures and the brain tissues oxidative damages in rats.

Materials and Methods

PTZ was purchased from Sigma-Aldrich Company (St. Louis, USA). Other chemical compounds such as thiobarbituric acid (TBA), trichloroacetic acid (TCA), hydrochloric acid (HCL), ethylenediaminetetraacetic acid (EDTA) and 2, 2'-dinitro-5, 5'-dithiodibenzoic acid (DTNB) were bought from Merck Company.

In this study, 40 virgin male Wistar rats, 250 ± 20 g in weight were used. The animals were maintained at the animal house under controlled conditions including 12 h light and dark cycle, 22-24 °C temperature and appropriate humidity with laboratory chow and water provided ad libitum.

The animals were randomly divided into five groups and treated (n = 8 in each group) as follows: (1) Control (saline), (2) PTZ, (3) C. sativum extract (CSE) 100 mg/kg (CSE 100) + PTZ, (4) CSE 500 mg/kg (CSE 500) + PTZ and (5) CSE 1000 mg/kg (CSE 1000) + PTZ. The doses were chosen regarding our previous study.[21]The number of animals was also based on our previous studies.[9,21-24]

The animals in groups 2-5 were treated intraperitoneally (i.p.) with saline or the extract 30 min before i.p. injection of a single dose (90 mg/kg) of PTZ. In our previous works, we showed that PTZ in this dose induces generalized tonic-clonic seizures (GTCS) in rats.[9,22,24,25] The time interval between injection of the extract and PTZ was chosen regarding our previous work in which injection of the extract 30 min before injection of pentobarbital increased the sleeping time.[21]

The cortical and hippocampal regions were then removed for biochemical measurements. In the control group, saline was injected instead of both PTZ and CSE and the brain tissues were removed without inducing the seizures. All efforts were made to maintain the animals in good general health, in accordance with the European Communities Council Directive (2010/63/UE). All behavioral tests were conducted between 10:00 and 14:00 O'clock. Animal handling and all related procedures were confirmed by the Mashhad University of Medical Sciences, Iran, Ethical Committee.

The aerial parts (leaves, stems, twigs) of C. sativum were collected from Neyshabur, Iran. The identity of the plant was confirmed and for future reference a voucher specimen (10068) was deposited at the herbarium of School of Pharmacy (Mashhad University of Medical Sciences). To prepare the hydroalcoholic extract, the plant materials (50 g) were dried and extracted with 300 ml ethanol-water (70/30, v/v) using a Soxhalet apparatus. The extract reduced to dryness with a rotary vacuum evaporator (Stuart RE300, UK).[26]

In order to observe ictal behavior, PTZ was injected and the animals were placed in a Plexiglas arena (30 cm × 30 cm × 30 cm) on the day of the experiment. The animals were observed during 60 min after PTZ (90 mg/ kg) administration.[9,22,24,25,27] The behavioral responses of the animals to PTZ administration were evaluated using these criteria: latency to the first minimal clonic seizure (MCS), incidence of MCS, latency to the first GTCS, incidence of GTCS, protection percentage against GTCS and protection percentage against mortality.[23-25]

After behavioral study, the rats were quickly decapitated under deep sodium pentobarbital anesthesia, their brains were removed and the cortical and hippocampal regions were separated and conserved for biochemical measurements. The animals were killed by a competent person with a

minimum pain, suffering, and distress. The method was performed as set out in that Annex IV of the guidelines from Directive EU/2010/63 of the European Parliament.

For total thiol (SH) content measurement, the cortical and hippocampal regions were dissected on an ice-cold surface and homogenized in iced-cold phosphate-buffered saline to give 10% homogeny. Total SH groups were measured using DTNB as the reagent. This reagent reacts with the thiol groups to produce a yellow colored complex, which has a peak absorbance at 412 nm. Briefly, 1 ml Tris-EDTA buffer (pH = 8.6) was added to 50 µl of the brain homogenates, and the sample absorbance was read at 412 nm against Tris-EDTA buffer alone (A_1). Then, 20 µl DTNB reagents (10 mm in methanol) were added to the mixture and after 15 min (stored in laboratory temperature), the sample absorbance was read again (A_2). The absorbance of DTNB reagent was also read as a blank (B). Total thiol concentration (mm) was calculated from the following equation.[9,28-30]

Total thiol concentration (mM) = $(A_2-A_1-B) \times 1.07/0.05 \times 13.6$

Malondialdehyde (MDA) levels, as an index of lipid peroxidation, were also measured. MDA reacts with TBA as a TBA reactive substance to produce a red colored complex, which has a peak absorbance at 535 nm. The TBA/TCA/HCL reagent was added to the homogenates, and the solution was heated in a water bath for 40 min. After cooling, the whole solutions were centrifuged within 1000 g for 10 min. The absorbance was measured at 535 nm.[9,28-30] The MDA concentration was calculated as follows: $C (M) = Absorbance/(1.56 \times 10^5)$

All data were expressed as mean ± standard error of the mean and analyzed by using ANOVA, followed by Tukey's post-hoc comparison test. $P < 0.0500$ were considered to be statistically significant.

Results

Effect of C. sativum on PTZ-induced seizures

All the animals in different groups (except the control group, which did not receive PTZ) showed MCS and GTCS following administration of a high dose of PTZ. Data analysis using one-way ANOVA showed that there was a significant difference between the groups in MCS latencies ($F_{3,28} = 19.65$, $P < 0.0001$). MCS latencies in the extract pre-treated groups were significantly higher than that of PTZ group. When compared with PTZ group (61.66 ± 4.76 s), 100, 500 and 1000 mg/kg of the extract significantly ($P < 0.0100$ to $P < 0.0010$) increased the MCS latencies to 77.3 ± 2.07, 93.5 ± 4.35 and 339.3 ± 58.96 s, respectively (Figure 1).

Data analysis using one-way ANOVA also showed that there was a significant difference between the groups in GTCS latencies ($F_{3,28} = 24.13$, $P < 0.0001$). The GTCS latencies in the animals, which had received 100, 500 and 1000 mg/kg of CSE before PTZ, were 183 ± 4.69, 341.88 ± 44.16, and 710.3 ± 98.84 c, respectively. All 3 doses of the extract significantly increased the GTCS latencies ($P < 0.0100$ to $P < 0.0010$) compared with PTZ group (114 ± 1.8 c) (Figure 2). There were no significant differences in mortality rate following PTZ administration between groups.

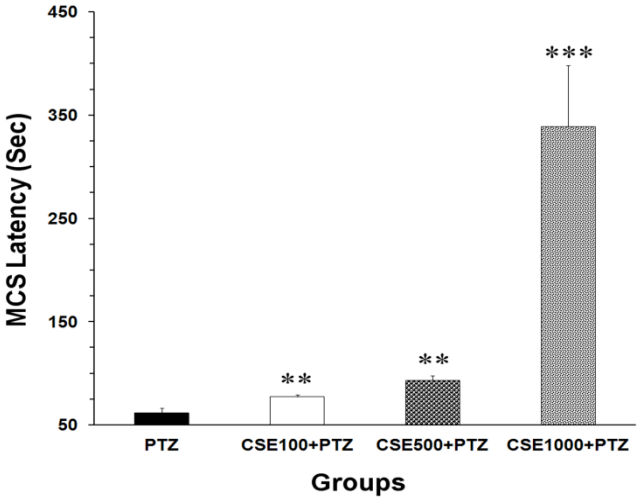

Figure 1. Latencies to minimal clonic seizures (MCS) onsets in pentylenetetrazole (PTZ), C. sativum extract (CSE) 100 mg/kg (CSE 100)-PTZ, CSE 500 mg/kg (CSE 500)-PTZ, CSE 1000 mg/kg (CSE 1000)-PTZ groups. The animals were treated with saline or CSE (100, 500 or 1000 mg/kg) before a single injection (90 mg/kg) of PTZ; ** $P < 0.010$; *** $P < 0.001$ as compared to PTZ group

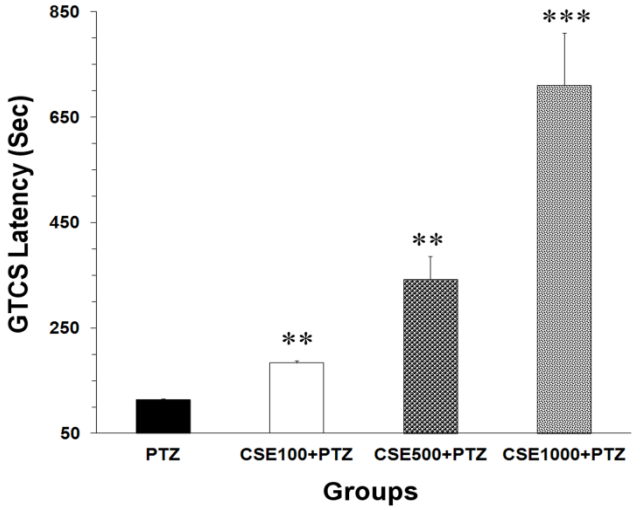

Figure 2. Latencies to generalized tonic-clonic seizures (GTCS) onsets in pentylenetetrazole (PTZ), C. sativum extract (CSE) 100 mg/kg (CSE 100)-PTZ, CSE 500 mg/kg (CSE 500)-PTZ, CSE 1000 mg/kg (CSE 1000)-PTZ groups. The animals were treated with saline or CSE (100, 500 or 1000 mg/kg) before a single injection (90 mg/kg) of PTZ; ** $P < 0.010$; *** $P < 0.001$ as compared to PTZ group

Effect of C. sativum on brain tissues oxidative damage

Data analysis using one-way ANOVA showed that there was a significant difference between the groups in MDA concentrations of cortical tissues ($F_{4,35}$ = 6.93, P < 0.001). The MDA levels in cortical regions of PTZ group were significantly higher than those of control animals (P < 0.001) (Figure 3). As shown in figure 3, pretreatment with both 100 and 1000 mg/kg of the extract resulted in a significant reduction in the free radical-mediated lipid peroxidation as indicated by a decrease in the MDA levels (P < 0.001 and P < 0.010, respectively).

Data analysis using one-way ANOVA also showed that there was a significant difference between the groups in total thiol contents of cortical tissues ($F_{4,35}$ = 6.78, P < 0.001). Following PTZ administration, a significant reduction in total SH groups in cortical samples was observed (P < 0.050, Figure 4). Pretreatment with 500 mg/kg of the extract prevented of decreased total thiol concentration in cortical tissues, as compared with PTZ group (P < 0.010).

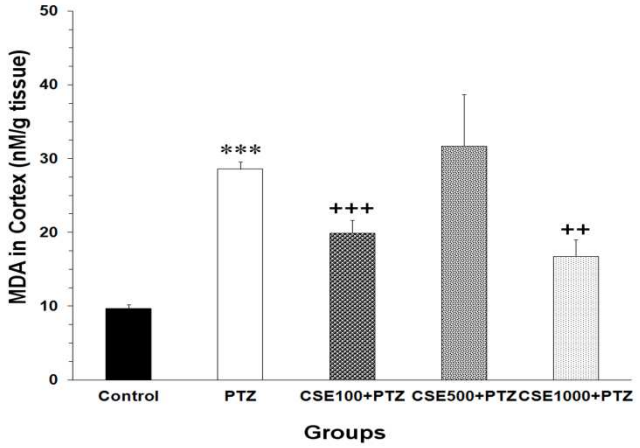

Figure 3. Comparison of the malondialdehyde (MDA) levels in cortical tissues of control, pentylenetetrazole (PTZ), C. sativum extract (CSE) 100 mg/kg (CSE 100)-PTZ, CSE 500 mg/kg (CSE 500)-PTZ, CSE 1000 mg/kg (CSE 1000)-PTZ groups. The animals were treated with saline or CSE (100, 500 or 1000 mg/kg) before a single injection (90 mg/kg) of PTZ; The animals in control group received saline instead of PTZ; *** P < 0.001 as compared to control group; ++ P < 0.010; +++ P < 0.001 as compared to PTZ group

Data analysis using one-way ANOVA showed that there was a significant difference between the groups in MDA concentrations of hippocampal tissues ($F_{4,35}$ = 24.53, P < 0.0001). The MDA levels in the hippocampal regions of PTZ group were significantly higher than those of control animals (P < 0.001) (Figure 5). The results also showed that all three doses of CSE prevented the elevation of MDA concentration in hippocampal tissues (P < 0.001 for all, Figure 5).

Data analysis using one-way ANOVA also showed that there was a significant difference between the groups in total thiol contents of hippocampal tissues ($F_{4,35}$ = 3.19, P < 0.050). Following PTZ administration, a significant reduction in total SH groups in the hippocampal samples was observed (P < 0.050, Figure 6). There were no significant differences between CSE treated rats and PTZ group when total thiol content in hippocampal tissues was compared (Figure 6).

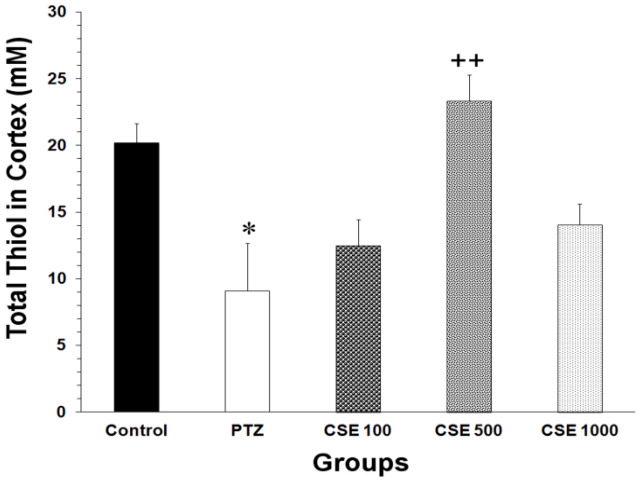

Figure 4. Comparison of the total SH groups in cortical tissues of control, pentylenetetrazole (PTZ), C. sativum extract (CSE) 100 mg/kg (CSE 100)-PTZ, CSE 500 mg/kg (CSE 500)-PTZ, CSE 1000 mg/kg (CSE 1000)-PTZ groups. The animals were treated with saline or CSE (100, 500 or 1000 mg/kg) before a single injection (90 mg/kg) of PTZ. The animals in the control group received saline instead of PTZ; * P < 0.0500 as compared to Control group; ++ P < 0.0100 as compared to PTZ group

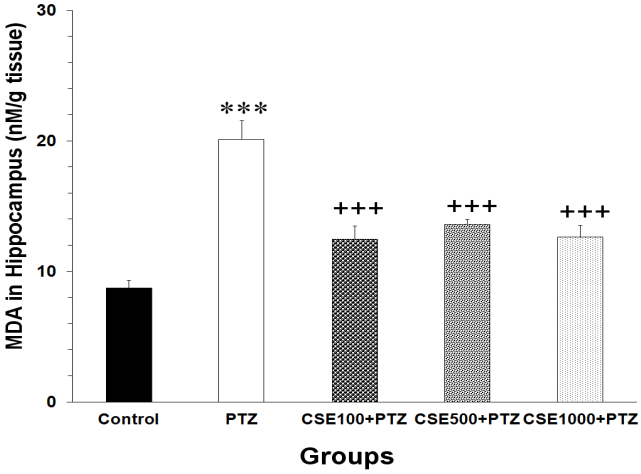

Figure 5. Comparison of the malondialdehyde (MDA) levels in hippocampal tissues of control, pentylenetetrazole (PTZ), C. sativum extract (CSE) 100 mg/kg (CSE 100)-PTZ, CSE 500 mg/kg (CSE 500)-PTZ, CSE 1000 mg/kg (CSE 1000)-PTZ groups. The animals were treated with saline or CSE (100, 500 or 1000 mg/kg) before a single injection (90 mg/kg) of PTZ. The animals in the control group received saline instead of PTZ; *** P < 0.0010 as compared to control group; +++ P < 0.001 as compared to PTZ group

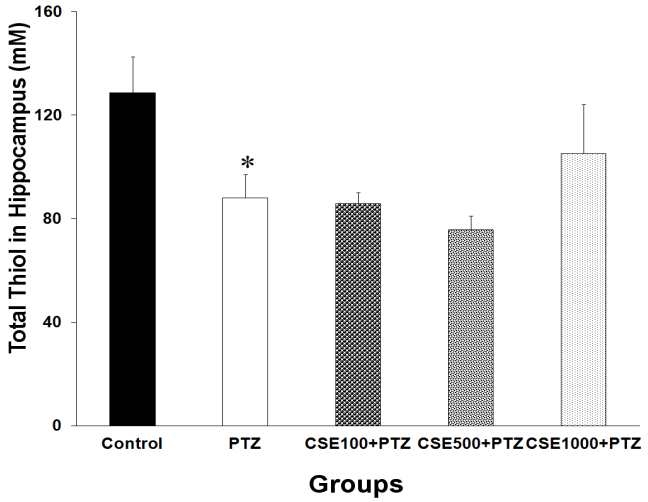

Figure 6. Comparison of the total SH groups in hippocampal tissues of control, pentylenetetrazole (PTZ), C. sativum extract (CSE) 100 mg/kg (CSE 100)-PTZ, CSE 500 mg/kg (CSE 500)-PTZ, CSE 1000 mg/kg (CSE 1000)-PTZ groups. The animals were treated with saline or CSE (100, 500 or 1000 mg/kg) before a single injection (90 mg/kg) of PTZ; The animals in control group received saline instead of PTZ; * $P < 0.050$ as compared to control group.

Discussion

Oxidative stress is a basis etiology for many neurological and neurodegenerative disorders. Previous studies demonstrated that oxidative stress plays an important role in the pathogenesis of epileptic seizures.[3,4,31] Elevation of free radical levels during seizures[7,31] has been well documented therefore, it is suggested that oxidative stress has an important role in the brain damages due to epilepsy.[9,32] Furthermore, the brain tissues oxidative damage contributes to the complications of seizures and epilepsy including cognitive, learning and memory impairments.[2,10] In the present study the possible protective effects of C. sativum aerial parts on PTZ-induced seizures and the brain tissues oxidative damages was investigated. PTZ, is a selective inhibitor of the chloride channel which is coupled to the gamma-aminobutyric acid receptor.[33] It is a well-known chemoconvulsant which is frequently used for evaluation of antiepileptic drugs.[34,35] A high dose of PTZ induces a continued seizure activity which progress from mild myoclonic jerks to face and forelimbs clonus without loss of righting reflex (which is known as MCS), to clonic seizures of limbs with loss of righting reflex which is followed by full tonic extension of both forelimbs and hindlimbs (GTCS).[36] PTZ has been repeatedly used in 90-100 mg/ kg to induce MCS and GTCS seizures.[9,22-25,27,28] We also previously showed that PTZ-induced seizures are accompanied with brain tissues oxidative damage.[9] The contribution of ROS to the neurotoxic effects of PTZ has also been suggested.[37,38] Similarly, in the present study, we observed an increase in MDA levels and a reduction in total SH groups in the brains of the animals subjected to PTZ-induced seizure. Increase in ROS production, including superoxide anions, hydroxyl radicals, and hydrogen peroxide, in the brains subjected to seizures, have been well documented.[39,40] It has been suggested that oxidative damages of brain tissues by free radicals may lead to psychiatric or cognitive problems such as depression, anxiety and memory loss.[31,41] The decreasing in the life span, which has been reported in the epileptic persons may also be at least in part, due to oxidative damages.[42] Oxidative stress has also been suggested as a link between aging and seizure.[43] In the present study, we assessed the effect of the extract by studying its effect on lipid peroxidation, which was measured in terms of MDA concentrations. Studies with animal models using the MDA assay have generally reported an increased lipid peroxidation in the brain tissues in seizures and epilepsy.[37,44] In our experiments, we observed a significant increase of lipid peroxidation in the both hippocampal and cortical tissues which was prevented by 100 and 1000 mg/kg of the extract however, 500 mg/kg of the extract prevented MDA elevation in hippocampal but not cortical tissues. These results are in consistent with the recently reported protective effects of the plant against hippocampal tissues oxidative damage.[45-47] It has been previously suggested the brain regions are differently vulnerable to increased lipid peroxidation. For example Shila et al. showed that lipid peroxidation was increased to the highest level in hippocampus among the brain regions, followed by cortex in arsenic intoxicated rats which was attributed to the different levels of iron contents.[48] Regarding the results of the present study, it seems that the plant extract was more effective to prevent of increased lipid peroxidation due to PTZ-induced seizures in hippocampal tissues compared to cortical tissues. In consistent with these results, Velaga et al. also reported that the hydroalcoholic extract of C. sativum seeds was more effective to decrease lipid peroxidation in hippocampus of lead intoxicated rats, compared to the cortical, cerebellum and brain stem tissues.[45] It has also been reported that training exercise and vitamin E were more effective to reduce lipid peroxidation in the hippocampal tissues of aged rats compared with the cortical tissues.[49] SH groups are also known to be sensitive to oxidative damage and depleted following an oxidative insult[50] therefore, we studied the effect of the extract on total thiol concentrations in the brain tissues after seizures. Similar to other studies, thiol groups were decreased in the brain following seizures injury. As mentioned

earlier, CSE prevented PTZ-induced thiol depletion only in the cortex and not hippocampus. One possible explanation for this observation might be due to brain regional-dependent glutathione (GSH) metabolism, as a major source of thiol group.[51] It has been observed that brain GSH concentrations varied in the range of 0.2-10 mM.[52] It was reported that GSH levels are highest in cortex, followed by hippocampus and brain stem.[53,54] Consistent with this finding, some studies reported a strong antioxidant activity for C. sativum.[15-20] Furthermore, we showed that this activity of C. sativum was accompanied by an anticonvulsant effect as it increased both MCS and GTCS latencies. In keeping with these observations, the anticonvulsant activity of several agents with antioxidant effect such as melatonin, vineatrol, trans-resveratrol and alpha lipoic acid have also been shown.[7,8] Using pentobarbital-induced hypnosis animal model, we previously found that the injection of 50, 100, 200 and 400 mg/kg of hydroalcoholic extract of C. sativum before pentobarbital increased the sleep time of the rats.[12] Even a higher dose of the extract has also been previously used in the rats without observation of any toxic effect.[55] In the current study, therefore we used comparable doses of CSE 30 min before PTZ injection to test its anticonvulsive effect. Previously, Hosseinzadeh and Madanifard reported an anticonvulsant effect for the aqueous and ethanolic extracts of C. sativum seeds.[56] The same effect was found by Emamghoreishi and Heidari-Hamedani for aqueous and hydroalcoholic extracts and essential oil of the seeds.[57] Regarding the results of present study the beneficial effects of aerial parts of the plant on seizures and its complications such as brain tissues oxidative is suggested however, further studies using other animal models are needed to be done in the future. The electrophysiological studies are also suggested for future.

However, no pharmacological studies have been yet evaluated the anticonvulsant activity of aerial parts of this plant. These parts of C. sativum are widely consumed as a vegetable all over the world. With the present study, we showed that aerial parts of C. sativum are effective in protection against seizures and oxidative stress induced by PTZ.

In the present study, the chemical compound(s) responsible for these effects of C. sativum were not identified and needs to be more investigated in future studies. The presence of the flavonoids such as quercitin has been reported in CSE.[58] On the other hand, it has been shown that the flavonoids have considerable anticonvulsant effects.[59,60] Regarding sedative and CNS depressant effects of falvonoids such as quercetin, these effects could be attributed to the affinity of the compounds for the central benzodiazepine receptors.[61-65] The beneficial effect of linalool in PTZ as well glutamate-related seizure models has been suggested.[66,67] It might be suggested the beneficial effects of the extract which was observed in the present study, might be at least in part, due to linalool which is one the main constituents of coriander and has considerable antioxidant effects.[68]

Conclusion

The present data demonstrate that the hydroalcoholic extract of C. sativum aerial parts possesses anticonvulsant activity. This activity is accompanied by an antioxidant effect in brain tissues. Isolation of the active compound(s) from the extract needs to be done in the future.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Efficacy of high-dose vitamin D3 supplementation in vitamin D deficient pregnant women with multiple sclerosis: Preliminary findings of a randomized-controlled trial

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Vitamin D, Multiple Sclerosis, Pregnancy, Iran

Abstract

Background: The aim of this preliminary study was to assess the safety and efficacy of high-dose oral vitamin D3 supplementation during pregnancy in women with multiple sclerosis (MS) in Isfahan, Iran.

Methods: In a single center open-label randomized, controlled clinical Phase I/II pilot study, 15 pregnant women with confirmed MS with low serum 25-hydroxyvitamin D (25(OH)D) levels were randomly allocated to receive either 50,000 IU/week vitamin D3 or routine care from 12 to 16 weeks of gestation till delivery. The main outcome measures were mean change in serum 25(OH)D levels, expanded disability status scale (EDSS) score, and number of relapse events during pregnancy and within 6 months after delivery.

Results: Average serum 25(OH)D level at the end of trial in vitamin D3 supplemented group was higher than routine care group (33.7 ng/mL vs. 14.6 ng/ml, P < 0.050). In vitamin D3 group, the mean EDSS did not changed 6 months after delivery (P > 0.050), whereas in routine care group, the mean EDSS increased from 1.3 (0.4) to 1.7 (0.6) (P < 0.070). Women in vitamin D3 group appeared to have fewer relapse events during pregnancy and within 6 months after delivery. No significant adverse events occurred.

Conclusion: Adding high dose vitamin D3 supplementation during pregnancy to routine care of women with MS had significant effect on the serum 25(OH)D levels, EDSS and number of relapse events during pregnancy and within 6 months after delivery.

Introduction

Multiple sclerosis (MS), a demyelinating disease of unknown cause, is the most common in women of childbearing age, and these women are most affected by low vitamin D levels.[1,2] The increased physiological needs in pregnancy and more indoor activity are also important risk factors increasing the vulnerability to vitamin D deficiency in these women. Low serum level of 25-hydroxyvitamin D (25(OH)D) which is the biologically inactive storage form of vitamin D3 appears to be a risk factor for both MS development and the MS course.[3-6] Some studies provide a direct correlation between vitamin D3 intake and serum 25(OH)D levels in non-pregnant MS patients.[5,7-9] No well-designed clinical trial is available adding high dose vitamin D3 supplementation to routine care in pregnant women with MS.

Vitamin D3 plays an important role in bone

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formation and mineral homeostasis. Some in-vitro and animal studies have also suggested that vitamin D3 has anti-inflammatory actions, including enhanced Th2 and decreased Th1 cytokines production, dendritic cell effects and enhanced macrophage phagocytosis.[10-12] There is accumulating evidence for a possible protective role of vitamin D3 in the development and disease course of MS.[7,13-16] Several studies have reported that low serum 25(OH)D levels may increase the risk of relapses in non-pregnant patients with MS.[3,8,17] Whether high dose vitamin D3 is also effective in treating pregnant women with MS and low serum 25(OH)D level is not known. We hypothesize that high dose vitamin D3 supplementation during pregnancy are safe, increases the serum 25(OH)D level, changed expanded disability status scale (EDSS) and number of relapse events in pregnant women with MS.

Materials and Methods

This was a single center open-label exploratory Phase I/II randomized parallel-group clinical trial to evaluate the effect of oral high-dose vitamin D3 on the serum 25(OH)D levels, EDSS, and number of relapse events in pregnant women with MS.

The original study sample comprised of 52 consecutive clinically definite MS patients who intended to be pregnant and sought treatment at our MS outpatient clinics of Isfahan University of Medical Sciences, Iran, between July 2011 and December 2012: of these 15 became pregnant and returned for follow-up. Entry criteria were women age between 20 and 40 years with a magnetic resonance imaging, clinical or laboratory-supported diagnosis of definite MS,[18] stable neurological functioning for at least 1-month prior to study entry, and an EDSS[19] score ≤ 6, serum 25(OH)D level < 20 ng/ml[20] and a willingness to continue current medications for the duration of the study. Assessments of serum 25(OH)D levels was carried out routinely as part of the clinical management of MS and used to detect vitamin D3 insufficiency. Serum 25(OH)D was measured using a commercially available radioimmunoassay kit (DiaSorin, Stillwater, MN, USA). Exclusion criteria were evidence of substantial abnormalities in psychiatric, cardiac, endocrinological, hematologic, hepatic, renal or metabolic functions, vitamin D3 supplement, and any condition predisposing to hypercalcemia, nephrolithiasis, and renal insufficiency as determined by history, physical examination, and screening blood tests. Patients who demonstrated poor compliance with instructions to take vitamin D3, or who failed to attend for follow-up visits, abortion, not become pregnant and 25(OH)D measurements during the study were also excluded. Tenets of the current version of the Declaration of Helsinki and the guidelines of the International Conference on Harmonization of Good Clinical Practice were followed, the study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences and the nature of the trial was explained to all participants. After a detailed discussion with the neurologist, patients made a final decision, and each participant provided written informed consent.

A total of 52 consecutive patients were eligible for the study. Thirty-seven patients were excluded because, they refused entry, or they did not meet the inclusion criteria, or failed to become pregnant, or did not attend for a follow-up visit. Fifteen pregnant patients completed the study without interruption. Patients were randomized according to a preexisting list produced by a computer program. The first treatment group received a single dose of 50,000 IU vitamin D3 (trade name Vitamin D3, Zahravi Pharm. Co. Tabriz, Iran) per week in the form of oral pearls from 12 to 16 weeks of gestation and continued during pregnancy. The second group received routine care. Compliance with the study treatment was verified by asking the patients about missed doses and by counting unused pearls. All patients underwent pretreatment evaluation to record demographic data, complete neurologic and medical history, the finding of physical and neurologic examination, and previous treatment. Figure 1 illustrates the patient allocation algorithm. In the final sample of participants, mean (standard deviation) age was 29.1 (3.5) years (range 22 to 36 years).

The trial was open-label in that both patients and investigators were aware of the type of treatment each patient received. Participants were evaluated by a qualified neurologist (ME) at baseline and every 8 weeks after the start of the therapy till delivery and 6 months after delivery to evaluate the development of side effects of the medications, compliance, and disease activity. The number of relapses, the proportion of patients free from relapses, the EDSS, and other medical events were recorded at baseline and each visit. Acute relapse was defined as the appearance of a new neurological symptom or severe deterioration in a pre-existing symptom that lasted for at least 24 h in the absence of fever/infection and caused an increase of at least 1 point in EDSS[21] and confirmed by the treating physician. Patients experiencing relapses received steroids (IV methylprednisolone or oral prednisone) as deemed appropriate by treating physician.

The primary outcome measure was mean changes in serum level of 25(OH)D from baseline to 6 months after delivery. Mean changes in the EDSS and number of relapses were also measured for both groups. Safety and tolerability were assessed by vital signs, safety lab, ECG, and adverse reporting.

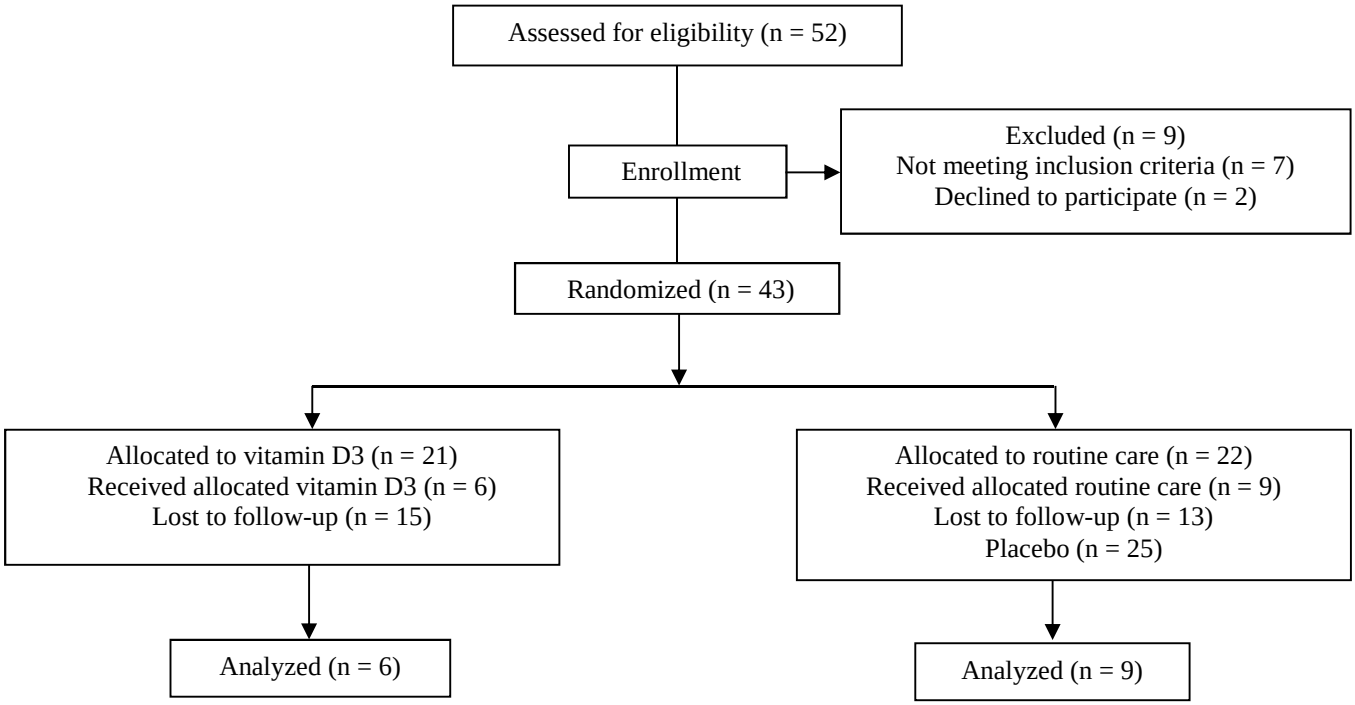

Figure 1. Design of the trial to compare oral vitamin D3 (50,000 IU/week) versus routine care in pregnant patients with multiple sclerosis

Since available data on the beneficial therapeutic effects of high dose vitamin D3 supplementation on pregnant women with MS are not sufficient for an exact statistical sample size calculation the study was designed as pilot study with a priori determined sample size of 7 patients per intervention arm.

Between-group comparison of changes was made using Mann–Whitney U-tests. Within group comparisons were undertaken using Wilcoxon sign-rank test, to determine differences between baseline and 6 months after delivery assessment of serum level of 25(OH)D, EDSS, and relapse events. Comparisons between proportions were undertaken using Fisher's exact test. Results are expressed as mean [standard deviation (SD)] and $P < 0.050$ was considered statistically significant. All statistical tests were two-sided. The analyses were undertaken using SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA).

Results

Fifteen patients who met the entry criteria were enrolled in the study. All 15 patients who completed treatment were available for follow-up at 6 months after delivery. The two treatment groups were generally well-matched at baseline with regard to age, age at pregnancy, onset of MS to pregnancy, EDSS before pregnancy, number of relapses/year prior to the trial and other characteristics. With respect to serum 25(OH)D level, women in the vitamin D3 supplemented group had slightly but significantly lower serum 25(OH)D level ($P < 0.050$). Mean ± SD serum 25(OH)D level at the start of treatment was 15.3 ± 2.9 ng/ml in the vitamin D3 group and 18.3 ± 1.9 ng/ml in the routine care group. Mean ± SD age in the vitamin D3 and routine care groups were 27.7 ± 2.4 and 30.0 ± 3.9 years, respectively. Five women in routine care group relapsed within 6 months after delivery and 4 women relapsed during pregnancy. In vitamin D3 group, no women relapsed within 6 months after delivery (Table 1).

High dose vitamin D3 supplementation was tolerated well, and no adverse events with the use of vitamin D3 were reported. There were no instances of urinary dysfunction or a symptomatic nephrolithiasis. No disturbances of cardiac rhythm were seen. In both arms of the study, patients received similar therapies before/during trial.

Changes in mean serum 25(OH)D level, EDSS, and relapse events before and after receiving vitamin D3 supplementation or routine care are shown in table 2. As expected, in vitamin D3 group, the average serum 25(OH) level increased significantly. Of the six patients treated with vitamin D3, the mean ± SD serum 25(OH)D level increased from 15.3 ± 2.9 ng/ml at baseline to 33.7 ± 15.2 ng/ml at the end of study period ($P < 0.050$). Whereas in routine care group, the average serum 25(OH)D level decreased significantly. In the nine patients treated with routine care, the mean ± SD serum 25(OH)D level decreased from 18.3 ± 1.9 ng/ml at baseline to 14.6 ± 1.3 at the end of study period ($P < 0.001$). Six months after delivery, average increase in serum 25(OH)D level between vitamin D3 and routine

care groups was 19.1 [95% confidence interval (CI), 8.3, 29.9 ng/ml (around 57%)], indicating there is evidence of an effect on the serum 25(OH)D level in patients who received high-dose vitamin D3 supplementation compared to those who received the routine care.

In vitamin D3 group, the mean EDSS did not change (P > 0.050). Whereas in routine care group, the mean EDSS increased from 1.3 ± 0.4 to 1.7 ± 0.6 (P < 0.070). There was a significant difference in the EDSS at the end of the study period between the vitamin D3 and routine care groups (mean difference, −0.6; 95% CI −1.2, −0.1). The mean EDSS was lower in vitamin D3 supplemented group than in the routine care group (1.1 vs. 1.7, P < 0.050) (Table 2).

In both vitamin D3 and routine care groups, the mean number of relapses within 6 months after delivery significantly decreased. Mean number of relapses in vitamin D3 group decreased from 1.3 to 0.0, while in routine care group, it also decreased, from 1.1 to 0.4. There was a significant difference in the average number of relapses within 6 months after delivery between the vitamin D3 and routine care groups (mean difference, −0.4; (95% CI −0.9, 0.2; P < 0.060) (Table 2). In routine care group, relapses during pregnancy were observed in five cases and relapses after delivery were observed in four cases.

Table 1. Characteristics of pregnant women with multiple sclerosis who received high-dose vitamin D3 or routine care at baseline.

Characteristics	Treatment group at baseline				P*
	Vitamin D3 (n = 6)		Routine care (n = 9)		
	Mean ± SD	n (%)	Mean ± SD	n (%)	
Age (year)	27.7 ± 2.4		30.0 ± 3.9		NS
Age at pregnancy (year)	25.3 ± 2.4		27.9 ± 3.9		NS
Onset of MS to pregnancy (year)	3.3 ± 2.2		5.0 ± 3.9		NS
Relapse rate/year before pregnancy	1.3 ± 0.5		1.1 ± 0.4		NS
EDSS before pregnancy	1.2 ± 0.3		1.3 ± 0.4		NS
Serum 25(OH)D level (ng/ml)	15.3 ± 2.9		18.3 ±1.9		< 0.050
Relapse during pregnancy		0.0 (0.0)		5.0 (55.6)	< 0.050
6-7 months		-		2.0 (22.2)	NS
7-8 months		-		3.0 (33.3)	NS
Relapse up to 6 months after delivery		0.0 (0.0)		4.0 (44.4)	NS
0-1 month		-		1.0 (11.1)	NS
2-3 months		-		1.0 (11.1)	NS
3-4 months		-		2.0 (22.2)	NS

* Differences in mean (Mann–Whitney U-test) or percentage (Fisher exact test) values of variables between vitamin D3 and routine care; NS: Non-significance; MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale; 25(OH)D: 25-hydroxyvitamin D; SD: Standard deviation

Table 2. Comparison of serum 25(OH)D level, expanded disability status scale (EDSS), and relapses in 15 pregnant women with multiple sclerosis before and 6 months after delivery with vitamin D3 supplementation and routine care

Treatment group	N	Baseline (mean ± SD)	6 months after delivery (mean ± SD)	P*
Serum 25(OH)D level				
Vitamin D3	6	15.3 ± 2.9	33.7 ± 15.2	< 0.050
Routine care	9	18.3 ±1.9	14.6 ± 1.3	< 0.001
P**	-	< 0.05	< 0.01	-
EDSS				
Vitamin D3	6	1.2 ±0.3	1.1 ± 0.2	NS
Routine care	9	1.3 ± 0.4	1.7 ± 0.6	NS
P**	-	NS	< 0.05	-
Relapses				
Vitamin D3	6	1.3 ± 0.5	0.0 ± 0.0	< 0.010
Routine care	9	1.1 ± 0.4	0.4 ± 0.5	< 0.010
P**	-	NS	NS	-

* Differences in mean values of variables between baseline and 6 months after delivery (Wilcoxon sign-rank test); ** Differences in mean values of variables between vitamin D3 and routine care (Mann–Whitney U-test); EDSS: Expanded disability status scale; NS: Non-significance; 25(OH)D: 25-hydroxyvitamin D; SD: Standard deviation

Discussion

In this exploratory study we found that adding high dose vitamin D3 supplementation during pregnancy to routine care of women with MS had significant effect on the serum 25(OH)D levels, EDSS, and number of relapse events during pregnancy and within 6 months after delivery. The serum 25(OH)D levels before supplementation were about 17 ng/ml in our pregnant women with MS. Therefore, the primary aim of our study was to bring the serum 25(OH)D levels of the women in vitamin D3 supplemented group to > 40 ng/ml zone, which is often considered the critical physiological lower limit for protect patients with MS.[9,22-24] After high-dose vitamin D3 supplementation, an average serum level of 33.7 ng/ml reached. While serum level of routine care group decreased. No unusual or unexpected safety risks were found with high-dose vitamin D3 supplementation in our pregnant women with MS 6 months after delivery. Previous studies have shown that high dose vitamin D3 is fairly safe in non-pregnant MS patients.[13,25]

We paid particular attention to the EDSS and number of relapses since the anti-inflammatory, and immunomodulatory effects of vitamin D3 could particularly influence these variables. Our findings showed a significant decreased EDSS and mean number of relapses during pregnancy in vitamin D3 supplemented group.

While the efficacy of vitamin D3 supplementation for treatment of MS in non-pregnant adults has been examined in a few small non-controlled trials with variable results,[14-16,26] only one open-label randomized controlled trial conducted over 52 weeks, which treated 25 patients with escalating doses of vitamin D compared with control.[13] This trail provided some evidence of the potential benefit of the high dose vitamin D3 on several outcomes i.e. the annualized relapse rate, EDSS score, suppression of T-cell proliferation and illustrated a measure of comparative safety in the relative absence of any adverse events or of high serum calcium level over the study period. Our findings in pregnant women with MS are consistent with this study in non-pregnant MS adult patients that found high-dose vitamin D3 (~10,000 IU/day) is safe, with evidence of immunomodulatory effects.[13] To the best of our knowledge, no study is available adding high dose vitamin D3 to routine care in pregnant women with MS.

The mechanisms whereby vitamin D3 supplementation exerts positive effects on MS course in pregnant women are not clear because there is not enough research in this area. Similar to non-pregnant MS patients, anti-inflammatory and immunomodulatory effects are probably most important. However, low serum 25(OH)D appears to be an important modifiable external risk factor for MS course in pregnant women with MS. Relative low serum 25(OH)D levels during pregnancy may worsen the course of MS by influencing metabolic pathways in the myelinating central nervous system that we do not understand at present. Furthermore, prevention of demyelination has also been demonstrated in a model of toxic demyelination.[27]

Albeit, this study is only controlled trials to date of effect of high-dose oral vitamin D3 on the serum 25(OH)D level, EDSS, and number of relapses in pregnant women with MS the sample sizes was small, and was limited by the loss to follow-up of 37/52 of the original baseline cohort. Hence, selection and volunteer bias cannot be ruled out. The efficacy should, therefore, be tested in a larger sample. The present results clearly need to be replicated and extended across multiple centers and investigators.

Serum levels of 25(OH)D are often quite low in MS patients.[5] Thus, we expect that low serum levels of 25(OH)D will be detected in pregnant women with MS. From an ethical point of view and bearing in mind the importance of vitamin D3 for bone metabolism, anti-inflammatory, and immunomodulatory effect, it would be difficult not to supplement these women with vitamin D3. On the other hand, we do not know, at which doses or serum levels vitamin D3 start to have anti-inflammatory and immunomodulatory effects. Thus, we choose the maximum dose for which sufficient safety data are available, which currently corresponds to 10,000 IU/day.[28] Thus, it appears wise to supplement all pregnant women with MS currently in a state of vitamin D3 deficiency or insufficiency in order to bring their serum 25(OH)D to >40 ng/ml level which might be neurologically beneficial for the course of the disease.

Although vitamin D deficiency or insufficiency is thought to be common among pregnant women, and substantial evidence supports the safety of even large dose of vitamin D3 in non-pregnant individuals, such evidence is based on studies of limited size and duration and there is no evidence of its usefulness and safety in pregnant women. A recent Cochrane review on vitamin D supplementation for women during pregnancy conclude that the clinical significance of vitamin D supplementation in pregnancy and the potential use of this intervention as a part of routine antenatal care are yet to be determined as the number of high-quality trials and outcomes reported is too limited to draw conclusions on its usefulness and safety. There is no evidence that vitamin D supplementation prevents pre-eclampsia, gestational diabetes, impaired glucose tolerance, caesarean

section, gestational hypertension, or death in the mothers; or preterm birth, stillbirth, neonatal death, neonatal admission to intensive care unit, newborns with low Apgar score or neonatal infection. The number of trials and outcomes reported are too limited, and, in general, are of low quality, to draw conclusions on the usefulness and safety of this intervention as a part of routine antenatal care. Further rigorous randomized trials are required to evaluate the role of vitamin D supplementation in pregnancy.[29] In addition, it is well-established that pregnant women with MS have a low risk of relapse and that lactation does not increase the risk of relapses. There is also no evidence that hormonal effects of pregnancy or lactation are different in women with MS compared with healthy women.[30,31]

The best level of 25(OH)D for health is uncertain.[22] Many experts believe that blood levels of 25(OH)D > 40 ng/ml are adequate.[9,22-24] Some investigators also suggested that levels higher than 40 ng/ml may further help protect patients with MS.[9,17,23,24,32,33] The US Institute of Medicine has determined that concentrations greater than 50 nmol/l or 20 ng/ml are adequate based on the current studies available.[34] However, there is controversy regarding the 25(OH)D levels that are considered adequate or optimal for overall health. It has been suggested that a supplemental dose of vitamin D of 1000 to 1600 IU (25-40 µg/d) might be necessary to achieve the optimal level of this vitamin in the body.[33] This dose is expected to raise serum 25(OH)D by 1.2 nmol/l for every µg (40 IU) of vitamin D_3 given orally to individuals with low 25(OH)D levels; those with higher baseline concentrations would have smaller increments with the same dose.[33] However, the dose of vitamin D needed to have an effect during pregnancy or to prevent or treat vitamin D deficiency is not clear. Some researchers have suggested that doses around 1000 IU/d may be needed in order for pregnant women to maintain a blood concentration of vitamin D of more than 50 nmol/l (20 ng/ml).[35] Others have suggested providing vitamin D as weekly doses of 5000 IU (125 µg/week)[36] or a single dose of 200,000 IU (5 mg) or greater (9).[37]

Weekly high-doses of up to 280,000 IU vitamin D3 and long-term treatment with a mean weekly dose of at least 70,000 IU for 36 weeks have been well-tolerated in non-pregnant adults.[6,13] Furthermore, non-pregnant patients with MS tolerated a pilot dose-escalation trial up to 40,000 IU/day.[13] A daily supplement of 10,000 IU of vitamin D3 is considered advisable for all adults with normal renal function[22,28] and this dose should be routinely recommended to all women, particularly women with insufficient serum 25(OH)D levels, during pregnancy and lactation. Therefore, our study suggests that the dose of 50,000 IU/week vitamin D3 in patients with insufficient serum 25(OH)D levels, which is well above current recommendation for pregnant and lactating women, may be considered relatively safe. Although this trial was not powered nor blinded to properly address clinical outcomes, we observed that clinical outcomes appeared to favor the treatment group.

Conclusion

This exploratory Phase I/II comparative trial of vitamin D3 supplementation and routine care showed that adding vitamin D3 to routine therapy had significant effect on the serum 25(OH)D levels, EDSS and number of relapse events within 6 months after delivery. Further studies with larger sample and longer follow-up are needed to be able to recommend routine high-dose vitamin D3 supplementation in pregnant women with MS.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Effects of pyridoxine supplementation on severity, frequency and duration of migraine attacks in migraine patients with aura: A double-blind randomized clinical trial study in Iran

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Keywords
Migraine with Aura, Pyridoxine, Headache, Iran

Abstract

Background: Migraine is a chronic disease that affects nearly 6% of men and 18% of women worldwide. There are various drugs, which can successfully decrease migraine symptoms and frequency of migraine attacks, but these drugs usually are expensive. Hence, this study aimed to assess the effects of pyridoxine supplementation on severity, frequency and duration of migraine attacks as well as headache diary results (HDR).

Methods: This double-blind randomized clinical trial study was conducted on 66 patients with migraine with aura (MA) in Khorshid and Emam Mosa Sadr clinics of Isfahan University of Medical Sciences, Iran, in 2013. Patients were randomly allocated to receive either pyridoxine supplements (80 mg pyridoxine per day) or placebo. Severity, frequency and duration of migraine attacks and HDR were measured at baseline and at the end of the study.

Results: Mean age of patients was 34.24 ± 9.44 years old. Pyridoxine supplementation led to a significant decrease in headache severity (−2.20 ± 1.70 compared with −1 ± 1.50; P = 0.007), attacks duration (−8.30 ± 12.60 compared with −1.70 ± 9.60; P = 0.030) and HDR (−89.70 ± 134.60 compared with −6.10 ± 155.50; P = 0.040) compared with placebo, but was not effective on the frequency of migraine attacks (−2.30 ± 4 compared with −1.20 ± 7.80; P = 0.510).

Conclusion: Pyridoxine supplementation in patients with MA was effective on headache severity, attacks duration and HDR, but did not affect the frequency of migraine attacks.

Introduction

Migraine is a debilitating and chronic disorder that affects 10-20% of the general population worldwide.[1,2] This disorder is characterized by severe recurrent headache, nausea, vomiting, sensitivity to light and sound, neck pain and muscle tension.[3-5] Migraine headaches are one-sided and throbbing that usually last between 4 and 72 h.[3,5] This disease is more prevalent in women than men and often occurs in middle-aged individuals.[6,7] Based on International Headache Society (IHS) criteria; there are two major classes of migraine: migraine with aura (MA) and migraine without aura.[3] These two subtypes have the

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same symptoms, but 25% of patients with migraine perceive an aura, which is a transient disturbance in visual, sensory, language, or motor function and it can be defined as a signal of headache occurrence.[3,8]

Pathophysiology of migraine is influenced by genetic factors and environmental triggers.[9-11] Lowering cerebral blood flow in the brain can induce depolarization waves in MA attacks. These waves spread across the brain cortex and stimulate trigeminovascular system (TVS). Activation of TVS can initiate attacks of head pain.[12,13] Furthermore, vascular diseases, such as ischemic stroke, are considered as risk factors for MA.[14-16] One of other factor that recent studies have shown its important in etiology of migraine is nutritional factors.[17] It has been shown that high levels of serum homocysteine, obesity and nutritional intakes including caffeine, chocolate and tyramine as well as starvation can increase the incidence of MA.[17,18] In addition, it's suggested that pyridoxine, folate and cobalamin supplementations can play a role in severity and frequency of migraine attacks.[19,20]

Pyridoxine is a kind of vitamin B that is involved in several metabolism reactions. Previous studies have shown that pyridoxine administration improve vascular functions that are link to migraine attacks.[21,22] However, there is no studies that assess the effects of pyridoxine supplementation on migraine profiles directly. Earlier studies have mostly focused on pyridoxine, folate and cobalamin combination.[19,20] Furthermore; findings of these studies are inconsistent. One study reported that vitamin supplementation can decrease the severity and frequency of migraine attacks,[19] while others reported no impact of vitamin intake on frequency of migraine attacks.[20] Hence, due to scarce studies and conflicting results in this regard, the present study aimed to assess the effects of pyridoxine supplementation on characteristics of migraine attacks including severity, frequency, duration and headache diary results (HDR) in patients with MA.

Materials and Methods

This double-blind randomized clinical trial study (IRCT2013060411763N9) was conducted on 66 patients with MA (12 men and 54 women) in Khorshid and Emam Mosa Sadr clinics of Isfahan University of Medical Sciences, Iran, from February 1st through April 22th, 2013.

Age of 30-65 years old, Having history of migraine for a long time (> 5 years), 1 year history of severe, recurrent and long-lasting migraine attacks (at least one attack per month lasting 4 h) and current diagnosis of MA according to IHS criteria.[3] Hence that studies have shown that homocysteine level in MA patients is positively associated with severity and frequency of migraine, and combine intake of pyridoxine, folate and cobalamin can reduce the mentioned symptoms in MA patients,[19,20] we perform the study only on migraine patients who had aura. In this study, every patient having visual disturbance before head pain was considered as MA.

Current taking vitamin supplementation, clinical cardiovascular diseases, pregnancy occurrence and changing the supplement intake during the study.

Because of the lack of a similar study as a model, we estimated sample size based on the number of parameters of the regression model as 66 subjects. The study power was considered to be 80%.

Detailed information about age, medical history, taking medications and supplements were collected with a researcher-made checklist. Height was measured in a standing position without shoes by a tape measure with the nearest 0.5 cm. Weight was determined with minimal clothing and without shoes by analog scale with a precision of 100 g. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Waist circumference (WC) was measured by inelastic tape in the middle of bottom ribs and pelvic bones after a normal exhale.

Characteristics of migraine attacks including severity, frequency, duration (hour) and HDR were determined at baseline and at the end of the study. To measure the severity of MA attacks, we used visual analogue scale ranking the severity of a headache attack between 1 and 10.[23] Number of migraine attacks in a month was considered as the frequency of attacks. To determine HDR index, we used the formula of frequency of attacks × duration of headache.[23]

Dietary intakes were assessed by means of 3 days food record at the 1st, 2nd and the last week of study based on estimated values in household measurements. Nutrient intakes of participants were obtained using Nutritionist IV software (First Databank) modified for Iranian foods.

The incidence of adverse events was evaluated by recording all observed or volunteered adverse events. For this purpose, any study related adverse events during treatment were monitored by daily evaluation. For patients who withdrew or patients lost to follow-up, adverse events were acquired by telephone.

To carry out this study, after taking approve by Ethics Committee of Isfahan University of Medical Sciences, researcher referred to the clinics and selected patients, who had inclusion criteria, and after obtaining an informed consent from all the participants and providing verbal explanation about the research and assurance of confidentiality and anonymity, patients were randomly assigned to

consume pyridoxine supplement (n = 33) or placebo (n = 33) for 12 weeks using envelopes containing numbers from a table of random numbers. Match of patients was done for age, gender, WC, BMI and characteristics of migraine attacks. Patients and investigators were not aware of allocated groups. Patients in pyridoxine group should consume 2 capsules containing 40 mg pyridoxine 2 times/day (80 mg pyridoxine/day) and patients in placebo group should consume 2 capsules of placebo containing lactose 2 times/day. Placebo capsules were similar in shape, color, and taste to pyridoxine capsule, which was produced in the School of Pharmacy, Isfahan University of Medical Sciences. We gave supplements to the participants in two stages (at the first and 6th weeks) by someone except the researcher in the recruitment centers. All patients received pyridoxine supplementation or placebo in addition to routine treatment of migraine (pain killers or other anti-migraine drugs). Subjects' compliance was measured through the remaining capsules at the end of the study using the following formula as: number of used capsules/ all given capsules × 100.

All statistical analyses were done by means of SPSS software (version 18, SPSS, Inc. Chicago, IL, USA). We applied Kolmogrov–Smirnov test to ensure the normal distribution of variables. To determine the differences in general characteristics and dietary intakes between pyridoxine and placebo groups, we used Independent-samples t-test. We used paired-samples t-test to determine the effects of pyridoxine and placebo on characteristics of migraine attacks including severity, frequency, duration and HDR. We applied Independent-samples t-test to compare the changes between pyridoxine and placebo groups. To assess the effects of age, gender and BMI on variables changes, we adjusted confounding variables by using analysis of covariance. P < 0.050 was considered as a significant level.

Results

Follow-up

In total, 10 patients in pyridoxine group were excluded due to change of medications (changing the routine treatment of migraine or vitamin supplementation) (n = 5), gastrointestinal disorders (heartburn) (n = 3) and personal reason (n = 2). Because of the change of medications (changing the routine treatment of migraine or vitamin supplementation), two patients were excluded from the placebo group. A total of 54 patients (23 in the pyridoxine group and 31 in the placebo group) completed the study, and they were considered for final analysis (Figure 1).

Primary outcomes

Mean of patients' age, BMI and WC was almost 34.24 ± 9.44 years, 25.28 ± 4.28 kg/m^2 and 82.80 ± 9.17, respectively. No significant difference was found in terms of age, BMI and WC between pyridoxine and placebo groups at the beginning of the study. In addition, baseline characteristics of migraine attacks including severity, frequency, duration and HDR between two groups were not different, significantly (Table 1). On the basis of 3 day's food record, mean dietary intakes were not different between those receiving pyridoxine and those receiving placebo (Table 2).

Secondary outcomes

Severity of migraine attacks decreased in both pyridoxine and placebo groups, significantly, but the reduction in the pyridoxine group was significantly more than a placebo group (-2.20 ± 1.70 compared with -1 ± 1.50; P = 0.007). Pyridoxine supplementation reduced frequency of migraine attacks, but as compared with a placebo group, this reduction was not significant (-2.30 ± 4 compared with -1.20 ± 7.80; P = 0.510). Intake of pyridoxine supplements led to a significant decrease in attacks duration (-8.30 ± 12.60 compared with -1.70 ± 9.60; P = 0.030) and HDR (-89.70 ± 134.60 compared with -6.10 ± 155.50; P = 0.040) compared with placebo group (Table 3).

Table 1. General characteristics of patients with migraine with aura (MA) who received either pyridoxine supplement or placebo[*]

Variables	Pyridoxine group[**]	Placebo group[***]	P[£]
Age (year)	35.39 ± 9.50	33.38 ± 9.45	0.440
BMI (kg/m^2)	25.00 ± 3.85	26.24 ± 4.89	0.350
WC (cm)	80.55 ± 6.84	84.70 ± 10.51	0.110
Severity[€]	7.30 ± 0.87	7.00 ± 0.89	0.210
Frequency (per month)	10.30 ± 8.63	13.16 ± 12.02	0.310
Duration (h)	23.56 ± 16.86	17.35 ± 16.35	0.170
HDR[§]	222.60 ± 227.50	175.30 ± 167.40	0.380
Female (%)	19 (82.6)	24 (77.4)	0.450

BMI: Body mass index; WC: Waist circumference; HDR: Headache diary result; [*]All values are expressed as mean ± standard deviation (SD) and number (percent); [**] Received 80 mg vitamin B_6 (2 capsules containing 40 mg vitamin B_6) per day for 12 weeks; [***] Received 2 capsules of placebo per day for 12 weeks; [£] Obtained from independent sample t-test; [€] Measured by visual analogue scale that ranked headache severity from 1 to 10; [§] Determined by formula: frequency × duration

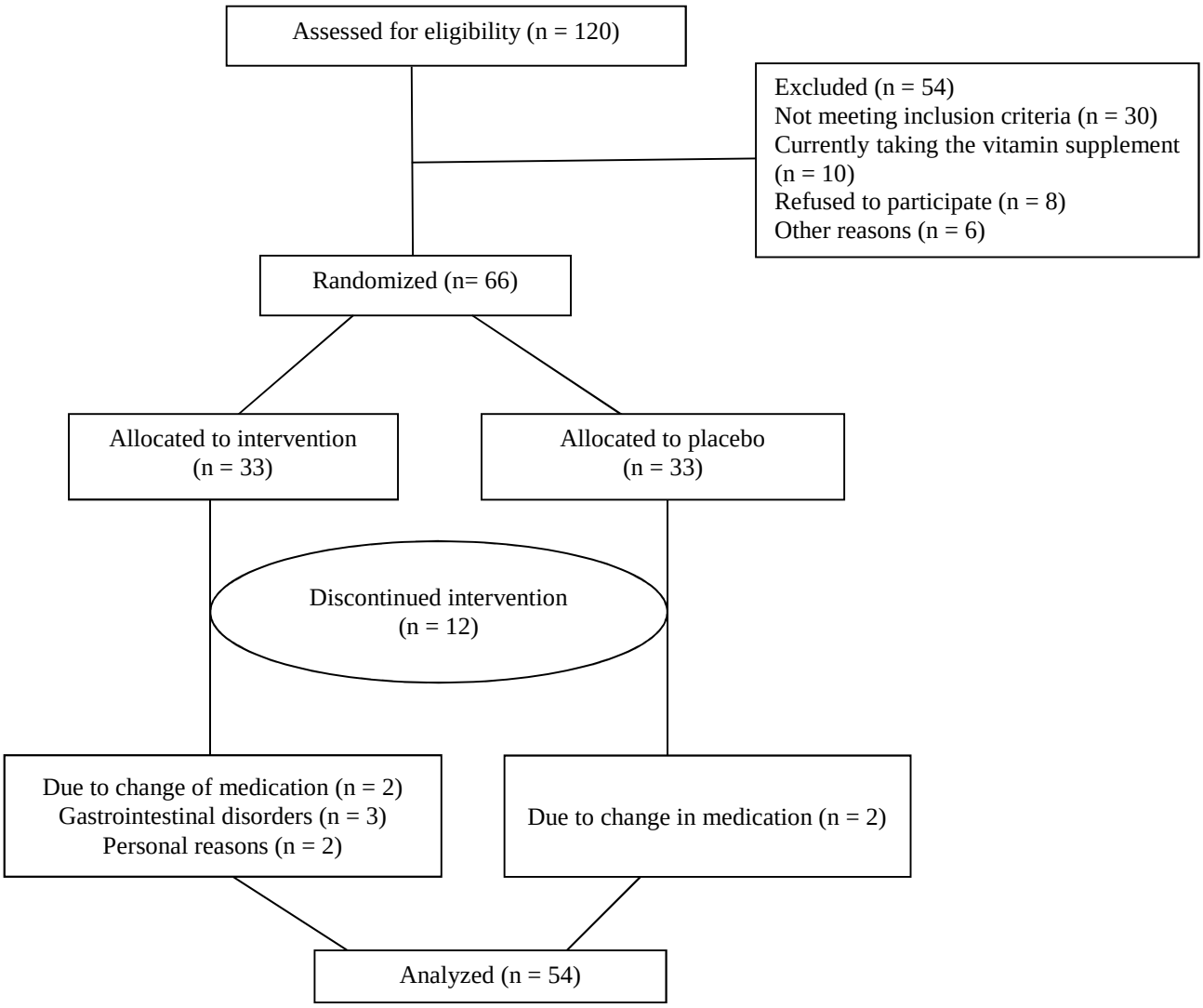

Figure 1: Flowchart showing allocation and exclusion of patients

Table 2. Dietary intake of migraine with aura (MA) patients who received either pyridoxine supplement or placebo*

Nutrients	Pyridoxine group**	Placebo group***	P§
Energy (kcal/d)	1957.70 ± 515.80	2191.00 ± 316.20	0.100
Protein (g/d)	68.70 ± 9.80	69.30 ± 8.80	0.840
CHO (g/d)	340.70 ± 33.40	364.90 ± 55.30	0.080
Fat (g/d)	72.20 ± 17.10	61.40 ± 25.90	0.110
Thiamine (mg/d)	2.01 ± 0.20	2.10 ± 0.30	0.370
Riboflavin (mg/d)	1.50 ± 0.30	1.40 ± 0.30	0.830
Niacin (mg/d)	22.80 ± 3.05	23.30 ± 4.50	0.650
Pyridoxine (mg/d)	1.30 ± 0.30	1.30 ± 0.40	0.90
Folate (µg/d)	244.30 ± 88.80	248.50 ± 99.90	0.880
Cobalamin (µg/d)	2.70 ± 1.10	2.60 ± 0.90	0.740
Magnesium (mg/d)	245.20 ± 46.90	244.20 ± 115.80	0.970
Calcium (mg/d)	865.00 ± 257.06	845.40 ± 212.40	0.780
Potassium (mg/d)	2885.30 ± 723.40	2901.50 ± 878.30	0.940
Tryptophan (mg/d)	568.80 ± 136.50	502.30 ± 173.01	0.160
EPA (mg/d)	9.40 ± 8.20	6.40 ± 5.30	0.160
DHA (mg/d)	28.20 ± 27.10	24.50 ± 12.70	0.560

CHO: Carbohydrate; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; * All values are expressed as mean ± standard deviation (SD) and number (percent); ** Received 80 mg vitamin B6 (2 capsules containing 40 mg vitamin B6) per day for 12 weeks; *** Received 2 capsules of placebo per day for 12 weeks; § Obtained from independent sample t-test

Table 3. Characteristics of migraine attacks including severity, frequency, duration and headache diary result (HDR) at baseline and week 12 of migraine with aura (MA) patients who received either pyridoxine supplement or placebo*

Group	Migraine characteristics			
	Severity**	Frequency	Duration	HDR***
Pyridoxine group§				
Before	7.30 ± 0.80	10.30 ± 8.60	23.50 ± 16.80	222.60 ± 227.50
After	5.04 ± 1.90	7.90 ± 7.05	15.20 ± 8.50	132.80 ± 169.30
Change€	-2.20 ± 1.70	-2.30 ± 4	-8.30 ± 12.60	-89.70 ± 134.60
P£	< 0.001	0.009	0.004	0.004
Placebo group¥				
Before	7.00 ± 0.80	13.10 ± 12.02	17.30 ± 16.30	175.30 ± 167.40
After	6.00 ± 1.40	11.90 ± 10.70	15.60 ± 11.50	169.20 ± 188.70
Change	-1.00 ± 1.50	-1.20 ± 7.80	-1.70 ± 9.60	-6.10 ± 155.50
P£	0.001	0.390	0.320	0.820
P∫	0.007	0.510	0.030	0.040

HDR: Headache diary result; * All values are expressed as mean ± standard deviation (SD) and number (percent); ** Measured by visual analogue scale that ranked the headache severity from 1 to 10; *** Determined by formula: frequency × duration; § Received 80 mg vitamin B6 (2 capsules containing 40 mg vitamin B6) per day for 12 weeks; € Changes in each group are obtained by subtracting the week 12 value from the baseline value of each variable; £ Obtained from paired t-test; ¥ Received 2 capsules of placebo per day for 12 weeks; ∫ Obtained from independent sample t-test

Table 4. Adjusted changes of characteristics of migraine attacks in migraine with aura (MA) patients who received either pyridoxine supplement or placebo*

Variables	Vitamin B6 group**	Placebo group***	P£
Severity€	-2.28 ± 0.39	-1.04 ± 0.34	0.011
Frequency	-2.41 ± 1.58	-1.10 ± 1.35	0.480
Duration	-6.82 ± 2.63	-0.18 ± 2.25	0.037
HDR§	-82.44 ± 35.36	4.99 ± 30.17	0.040

HDR: Headache diary result; ANCOVA: Analysis of covariance; * All values are means ± standard error (SEs) adjusted for age, gender and body mass index; ** Received 80 mg vitamin B6 (2 capsules containing 40 mg vitamin B6) per day for 12 weeks; *** Received 2 capsules of placebo per day for 12 weeks; £ Obtained from ANCOVA; € Measured by visual analogue scale that ranked the headache severity from 1 to 10; § Determined by formula: frequency × duration

When the analyses were adjusted for age, gender and baseline BMI, no significant changes were observed in our findings (Table 4).

Adverse effects

In this study, no side-effects of vitamin intake were reported at the end of the trial except the heartburn in 3 participants who stop the consumption of vitamin and excluded from the trial.

Discussion

In this study, pyridoxine supplementation in MA patients resulted in a decrease in headache severity, attacks duration and HDR compared with placebo intake, but did not affect the frequency of migraine attacks, significantly. To the best of our knowledge, this study is the first study to examine the effects of pyridoxine supplementation on migraine attacks profiles including severity, frequency, duration and HDR.

Migraine is a chronic disease that affects nearly 6% of men and 18% of women worldwide. Migraine headache results in a substantial reduction in quality of life and it lead to heavy costs for migraine patients.[24] There are various drugs, which can successfully decrease migraine symptoms and frequency of migraine attacks, but these drugs are often expensive and have many side-effects, and they are not always an effective treatment.[25,26] It has been shown that some non-pharmacologic therapies such as relaxation, training, butterbur, riboflavin, magnesium, and coenzyme Q10 supplementation are effective to improve migraine symptoms.[25-27] These methods often have a low risk of serious side-effects and they are less expensive than pharmacologic therapies. One of other kinds of supplementation, which its effectiveness was proven in combination with other vitamins in symptoms of MA patients is pyridoxine;[19,20] however, data on the effects of single vitamin B_6 supplementation are scarce.

In this study, we observed that pyridoxine supplementation lead to a reduction on severity and duration of migraine attacks as well as HDR, and it has no effects on attacks frequency. Our finding are supported by recent randomized, double-blinded placebo-controlled clinical trial by Menon et al., who done a 6 months trial of daily pyridoxine (25 mg), folic acid (2 mg) and cobalamin (400 µg) on 206 female patients diagnosed with MA. In this trial, a significant decrease was reported in headache

severity and high migraine disability, after taking a 6 months vitamin supplementation compared with placebo intake while frequency of migraine attacks did not reduce significantly.[20] In another similar clinical trial conducted by Lea et al., intake of pyridoxine, folate and cobalamin decreased severity and frequency of migraine attacks in addition to migraine disability significantly.[19] Villegas-Salas et al., conducted a randomized, triple-blinded controlled trial to evaluate the effects of taking 150 mg pyridoxine supplements on severity of headache for 30 days. They found a significant reduction of headache severity in the pyridoxine group compared with a placebo group while no evidence on the effects of pyridoxine or vitamin Bs supplementation on attacks duration and HDR was observed.[28]

The exact mechanism explaining the beneficial effects of pyridoxine intake on MA symptoms is not clear. Earlier studies have shown that a point mutation in methylenetetrahydrofolate reductase (MTHFR) gene is more prevalent in MA patients.[29] This mutation (MTHFR C677T) results a 50% reduction in MTHFR activity, which can induce serum hyperhomocysteinemia.[30] It has been shown that reduced level of homocysteine can diminish headache severity, attacks frequency and migraine disability, too.[19] Therefore, pyridoxine supplementation may improve MA symptoms, through reduction of serum homocysteine concentration.

Some limitations of our study need to be taken account. First, we did not measure the plasma pyridoxine and homocysteine levels because of limited financial resources, so it was not possible to diagnosis the patients who had vitamin B_6 deficiency and it was not clear that vitamin supplementation could reduce the homocysteine levels. Therefore, it was not clear that pyridoxine supplementation decreased the migraine symptoms by lowering the homocysteine levels or by other possible mechanism. Second, we could not examine the effects of pyridoxine supplementation on other MA symptoms including nausea, vomiting, sensitivity to light and sound and especially aura symptom. Third, because of small sample size of the participants, we were unable to examine the favorable effects of pyridoxine supplementation is genders, separately. Hence, additional studies are required to provide more insight into our aims. In addition, the appropriate dosage of pyridoxine supplementation in patients with MA cannot be inferred from this study, and further studies are required.

Conclusion

Pyridoxine supplementation in patients with MA was effective on headache severity, attacks duration and HDR, but did not affect the frequency of migraine attacks.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Comparison of serum vitamin D level in multiple sclerosis patients, their siblings, and healthy controls

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Keywords
Multiple Sclerosis, Vitamin D, Population Control, Siblings

Abstract

Background: Multiple sclerosis (MS) is an autoimmune, neuro-inflammatory disease of central nervous system affecting physical, emotional, and cognitive aspects of patients. Association of vitamin D deficiency and MS has been shown in previous studies. The aim of this study was to evaluate serum vitamin D level in MS cases and their sex-matched healthy siblings (who are genetically near similar) and non-relative sex-matched healthy controls.

Methods: A total of 135 subjects enrolled in this case-control study. Group one (n = 45) consisted of patients with established MS. Group two (n = 45) included sex-matched healthy siblings of the group one and group three participants (n = 45) were non-relative sex-matched healthy controls. Demographic data (age, sex), level of education, daily sun exposure duration, and month of birth gathered for all. Serum sample of all participants was collected for 25-hydroxy vitamin D measurement.

Results: There was no significant difference between vitamin D level, sun exposure duration, education level, and season of birth in three evaluated groups. Mean vitamin D level was 8.2 ± 10.1 (nmol/l) in women and 13.3 ± 7 (nmol/l) in men (P = 0.001). There was a significant positive correlation between daily sun exposure duration and vitamin D level in whole participants (r = 0.28, P < 0.001) as well as in MS patients (r = 0.32, P = 0.030). Mean vitamin D level was significantly lower in participants who have born in spring and summer.

Conclusion: Vitamin D deficiency is high among Iranian population as well as MS patients.

Introduction

Multiple sclerosis (MS) is an autoimmune, neuro-inflammatory disease of central nervous system affecting physical, emotional, and cognitive aspects of patients.[1] It has been reported that more than two million individuals are affected all over the world, and annual incidence of the disease is increasing during the time in different geographical regions.[2-8] In addition to strong genetic component, environmental factors such as vitamin D deficiency, Epstein-Barr virus infection, and smoking have been considered as influential factors in MS development.[9]

As MS prevalence is low in tropical areas and its incidence increases with distancing from the equator, it is hypothesized that latitude and sunlight have impacts on MS pathogenesis.[10-12] In this regard, some previous studies reported that duration and intensity of sunlight as well as serum vitamin D level are

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negatively correlated with the incidence of MS.[13-15] Pathophysiologically, vitamin D has a strong effect on cytokine profiles and plays a major role in modifying the inflammation in immune cells.[16] In vitro studies support that vitamin D prevents interleukin (IL) 12, IL2 and interferon-gamma production along with B cells production inhibition.[16-18] In addition, it has a preventive and therapeutic impact on TH17-mediated autoimmune diseases like MS.[19]

MS incidence is reported to increase rapidly in Tehran, Iran, in comparison with other cities all over the world.[8] We hypothesized that vitamin D deficiency could be one of the underlying causes of increased MS incidence in our population.

In this regard, this study is designed to evaluate serum vitamin D level in MS cases and their sex-matched healthy siblings (who are genetically near similar) and non-relative sex-matched healthy controls to determine vitamin D levels in MS patients, their families, and healthy ones.

Materials and Methods

This case-control study was approved by ethics committee of Tehran University of Medical Sciences and was conducted in the MS clinic of Sina Hospital (affiliated hospital of Tehran University of Medical Sciences). After filling informed consent forms, 135 participants were enrolled in three groups. Group one (n = 45) consisted of patients with established MS according to 2010 McDonald criteria.[20] Group two (n = 45) included sex-matched healthy siblings of the group one, and group three participants (n = 45) were non-relative sex-matched healthy controls.

Inclusion criteria for group one were relapsing-remitting form of the disease, expanded disability status scale (EDSS) (EDSS which was assessed by an expert neurologist) score < 6, having a sex-matched healthy sibling with age range of maximum 10 years less or more and no other systemic diseases. Exclusion criteria were relapsing phase of the disease for MS patients and application of vitamin D supplement during last year for all participants.

Demographic data (age, sex), level of education, daily sun exposure duration (asked from each participant as a self-report question), and a month of birth gathered for all. Disease duration, medication, and Kurtzke EDSS score (after neurological examination by an expert neurologist) were recorded for each patient.

A volume of 2 ml blood sample between 20th of March and 20th of June was taken from all participants and then, 25-hydroxy vitamin D level was measured with chemiluminescent immunoassay method by using the DiaSorin LIAISON 25-OH Vitamin D Total assay in Masoud laboratory.

According to endocrinology guideline,[21] vitamin D level < 20 nmol/l considered as deficient and levels between 20-30 and 30-100 nmol/l considered as insufficient and sufficient, respectively. Subjects with lower than normal vitamin D levels were also subdivided into three subgroups with vitamin D level < 12.5 nmol/l, between 12.5 and 25 and the third group 25-30 nmol/l[22] and the level of vitamin D deficiency was compared between MS group, siblings, and healthy controls.

All data were analyzed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA). Continuous variables compared by means of independent sample t-test, Mann Whitney-U or ANOVA tests, and Fisher's exact test was used to compare categorical variables. Correlation coefficient (Pearson or Spearman) calculated to assess the relationship between variables. Multiple regression analysis was used for the predictive value of age, education, and sun exposure duration for the vitamin D level. P < 0.050 was considered as significant.

Results

One hundred and thirty-five participants enrolled in this study. Mean disease duration of patients was 2.5 ± 3.2 years and mean EDSS score was 1.3 ± 1.4. EDSS scores of male and female patients were not significantly different (male: 2.3 ± 1.2, female: 1.2 ± 1.4, P = 0.080).

There was no significant difference between vitamin D level, sun exposure duration, education level, and season of birth in three evaluated groups (Table 1).

The severity of vitamin D deficiency was not significantly different between MS group versus siblings and healthy controls (Table 2).

Mean vitamin D level was 8.2 ± 10.1 (nmol/l) in women and 13.3 ± 7 (nmol/l) in men (P = 0.001). This mean value was significantly different between male and female ones in MS group (women = 8.7 ± 7.7, male = 15.9 ± 6.9, P = 0.040) while no significant differences was detected between male and female participants in two other groups. We did not find any significant difference in mean serum vitamin D levels between three study groups (P = 0.500).

The rate of vitamin D deficiency was 86.6% in MS group and in sibling and healthy subject groups were, respectively, 84.4 and 93%. No significant difference found in vitamin D distribution in study groups by univariate analysis (P = 0.200).

There was no significant correlation between EDSS and vitamin D level and disease duration in patients (r = 0.09, P = 0.500 and r = 0.1, P = 0.500) whereas EDSS score was significantly correlated with age (r = 0.33, P = 0.020).

Table 1. Age, sun exposure duration, season of birth, and vitamin D level in three groups of participants

Demographic characteristics	MS group	Siblings	Controls	P
Age (mean ± SD)	30.3 ± 7.5	31.2 ± 8.7	31.1 ± 8.2	0.8
Education level (year) (mean ± SD)	13.8 ± 2.6	13.4 ± 3.1	14.5 ± 3.1	0.2
Daily sun exposure duration (min)	52.5 ± 41.4	60.0 ± 48.4	59.5 ± 36.5	0.6
Serum vitamin D level (nmol/l) (mean)	9.7 ± 7.9	9.4 ± 9.9	7.5 ± 11.6	0.5
Season of birth				
Spring	19.0	11.0	11.0	
Summer	15.0	15.0	15.0	0.3
Autumn	6.0	8.0	11.0	
Winter	5.0	11.0	8.0	
Median	6.5	6.0	4.2	
Vitamin D status				
Deficient	39.0	38.0	42.0	0.2
Insufficient	6.0	6.0	1.0	
Sufficient	0.0	1.0	2.0	

MS: Multiple sclerosis; SD: Standard deviation

Table 2. Level of vitamin D deficiency in three groups

Vitamin D level	MS group	Siblings	Controls	P
< 12.5 (nmol/l)	2	2		
12.5-25(nmol/l)	14	8	5	0.09
25-30 (nmol/l)	29	34	38	

MS: Multiple sclerosis

Table 3. Season of the birth and vitamin D level in participants

Groups	Spring Number (mean ± SD)	Summer Number (mean ± SD)	Autumn Number (mean ± SD)	Winter Number (mean ± SD)	P
MS	19 (8.9 ± 8.3)	15 (8.0 ± 7.3)	6 (15.3 ± 8.5)	5 (11.7 ± 6.1)	0.200
Siblings	11 (8.0 ± 8.5)	15 (8.3 ± 7.9)	8 (9.6 ± 9.1)	11 (12.3 ± 14.2)	0.700
Controls	11 (5.5 ± 5.6)	15 (4.8 ± 4.0)	11 (6.1 ± 6.6)	8 (17.4 ± 23.8)	0.060
Total	41 (7.7 ± 7.7)	45 (7.0 ± 6.7)	25 (9.4±8.4)	24 (13.9 ± 16.5)	0.030

MS: Multiple sclerosis; SD: Standard deviation

In MS group, 16 patients were under treatment by Avonex followed by Betaferon (6 cases) and Rebif (4 patients). Mean vitamin D levels were not significantly different in these treatment subgroups (13.4 ± 7, 6.8 ± 6.7, 11.2 ± 9, P = 0.300).

Although the season of the birth was not significantly different between case and controls (P = 0.300), mean vitamin D level was significantly lower in participants who have born in spring and summer (Table 3).

There was a significant positive correlation between daily sun exposure duration and vitamin D level in whole participants (r = 0.28, P < 0.001) as well as in MS patients (r = 0.32, P = 0.030) (Table 4).

Table 4. Linear regression considering vitamin D level as dependent variable and Sun exposure duration, education level, and age as independent variables

Independent variables	B	P
Sun exposure duration	0.29	0.010
Education level	0.01	0.800
Age	0.10	0.200

Discussion

In this study, we evaluated the serum vitamin D levels in MS patients in comparison to their siblings as well as healthy controls. In addition to similar underlying genetics, patients and their siblings have grown up in similar environmental and socioeconomic states. It might help to limit the confounders that have affect in developing MS.

Our results did not show any difference in vitamin D level between MS patients and their siblings as well as healthy controls. It is in contrast to most previous studies that reported lower serum level of vitamin D in MS patients than healthy controls.[23-25] However, in studies which conducted in Switzerland and Finland, the prevalence of vitamin D deficiency in MS patients was not lower than healthy ones in such countries.[26,27]

It is proposed that insignificant difference between serum vitamin D levels might be related to the fact that Tehran citizens generally have lower levels of serum vitamin D; a fact which makes it difficult to assess the significance of serum metabolite levels

differences among different groups.[9,23,28] To support this hypothesis, in a previous study, evaluating 1210 people in Tehran, 81.3% had vitamin D deficiency and prevalence of severe, moderate, and mild vitamin D deficiency was 9.5, 57.6, and 14.2 percent, respectively.[22]

Thus, in the presence of general vitamin D deficiency in our patients and controls, there is a possibility that other interacting factors including polymorphism in vitamin D receptor genes might play a key role in developing MS. However, existing epidemiological studies have insufficient power to address this hypothesis.[29,30]

Different factors such as insufficient sun exposure, clothing habits, air pollution, and insufficient intake of vitamin D are considered as effective factors in vitamin D deficiency.[31] Although, Tehran, is located in 36° 21"N and has a mean sun exposure of 8 h per day, the high rate of air pollution in this city which prevents enough UV exposure to skin, could consider as a leading factor for vitamin D deficiency in people living in this city. In addition, significant higher level of vitamin D in men than women in this study could be indicative of clothing effect on vitamin D level. The mean sun exposure duration in participants of all three groups was near 1 h daily, and we found positive significant correlation between duration of sun exposure and vitamin D level in our population.

Although vitamin D has been known as calcium homeostasis modulator, its role as an environmental factor affecting MS prevalence becomes focus of interest in recent years.

Sunlight exposure, use of Vitamin D supplements, and higher levels of vitamin D in serum were associated with reduced risk of MS onset.[15,23,32] On the other hand, literature show that higher vitamin D level was associated with lower relapse rate in MS cases along with findings which show that serum 25(OH) vitamin D was lower during relapse time in comparison with remission period in MS patients.[33-36] These findings support immunomodulatory effects of vitamin D in autoimmune diseases. Although we found no statistically significant difference between vitamin D level and duration of sun exposure between three groups, sun exposure was positively correlated with vitamin D level and it considered as an independent predictor of serum vitamin D level.

Season of birth, according to exposure to ultraviolet radiation in early life, is important for developing diseases that affect central nervous system such as MS. In current study, we observed that most MS patients were born in spring in comparison with other two groups although the difference was not significant. In addition, vitamin D levels of participant who were born in spring and summer were significantly lower than other two groups. Willer et al. conducted a large population study, evaluating population of Canada, Great Britain, Denmark, and Sweden. They reported that people who born in May are at increased risk of MS in comparison with people born in the rest of the year especially in November.[37]

Our study had some limitations. First, our sample size was limited due to our inclusion criteria and time period of the study. Second, the study was single center study which was conducted in Tehran. In addition, the overall dietary vitamin D intake has not been evaluated in this study that might make a confounding bias in our findings. It is necessary to develop a large, multi-center study to evaluate vitamin D levels in MS patients.

Conclusion

There are no significant differences in vitamin D levels between MS patients and their siblings as well as healthy controls. The prevalence of Vitamin D deficiency is very high in Iranian population.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Comparison of frequencies of non motor symptoms in Indian Parkinson's disease patients on medical management versus deep brain stimulation: A case-control study

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Parkinson Disease, Deep Brain Stimulation, Subthalamic Nucleus, Dopamine Agents, Comprehensive Health Care

Abstract

Background: Non motor symptoms (NMS) of idiopathic Parkinson's disease (PD) are a major cause of disability and recognition of these symptoms and treatment is important for comprehensive health care. Deep brain stimulation of bilateral subthalamic nucleus deep brain stimulation (STN DBS) has been shown to improve motor symptoms in PD and effects on NMS are unknown. To investigate the NMS among PD patients who underwent STN DBS.

Methods: We recruited prospectively 56 patients with PD, who had undergone bilateral STN DBS and 53 age and duration of illness matched PD patients on dopaminergic therapy (controls). NMS were assessed using 30 item questionnaire NMS Quest. These questions evaluated 9 domains, gastrointestinal, urinary, cardiovascular, sexual, cognition (apathy/attention/memory), anxiety/depression, hallucinations/delusions, sleep and miscellaneous. Comparison was done on individual symptoms as well as in various domains. This study was carried at Nizam's Institution of Medical Sciences and study period was from January 2011 to December 2012.

Results: Patients who underwent STN DBS had a significantly lower mean total score on NMS quest (6.7 ± 3.8) compared to controls (8.4 ± 3.7) ($P < 0.00100$). Symptoms in the domains of cardiovascular, gastrointestinal, sleep were significantly less frequent while sexual disturbances were significantly more frequent among patients compared to controls. On individual symptom analysis, nocturia ($P < 0.00010$), unexplained pains ($P < 0.00010$), nausea and vomiting, constipation, lightheadedness, depression, and insomnia were less prevalent, while sexual disturbances were significantly more common in STN DBS group compared to controls.

Conclusion: Bilateral STN DBS not only improves the motor symptoms but also improves many NMS in PD patients.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative worldwide,[1] with a prevalence of 52.85/100,00 in India.[2] The emphasis in most of the last decade has been on the motor symptoms of PD,

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concentrating mainly on tremor, rigidity, postural instability, and bradykinesia. It is now increasingly recognized that the disease is more pervasive with various non motor manifestations. Non motor symptoms (NMS) of PD are common in all stages of the disease, are very often under recognized[3] and are a major cause of disability.[4] Recognizing and treating these symptoms are essential for improving functional outcome. Deep brain stimulation (DBS) of the bilateral subthalamic nucleus (STN) or globus pallidus has been established to be superior to oral dopaminergic medications for control of motor symptoms.[5] However, there are very few studies which estimated the effect of DBS on NMS.[6,7] The objective of the present study was to investigate the NMS in PD patients who have undergone bilateral STN DBS. Limited data are available from the Indian subcontinent.

Materials and Methods

We recruited prospectively 56 cases and 53 controls from movement disorder clinic at Nizam's Institution of Medical Sciences (NIMS) Hyderabad India. NIMS is one of the referral university teaching hospitals in South India. We used United Kingdom PD society brain bank criteria[8] for diagnosis of PD in both cases and controls. This study was approved by the Institutional ethical committee and study period from January 2011 to December 2012.

Cases are defined patients who underwent bilateral STN DBS with ≥ 1 year follow-up were considered as cases. Similar age and duration of illness matched 53 PD patients on oral dopaminergic therapy was defined as controls.

Inclusion criteria were PD disease duration of ≥6 years, good response to levodopa (improvement in Unified PD Rating Scale [UPDRS] part III by more than 30%), able to walk independently in drug "on" state (Hoehn and Yahr stage < 4 in "on" state), normal cognition (Montreal cognitive assessment > 25). Both case and control patients who were wheelchair or bed bound had dementia, or severe psychiatric disturbances were excluded.

Detailed neurological examination was done in case controls by movement disorder specialist and neurologist. Both cases and control's present and past medical records were reviewed by a trained neurology resident. All patients were on appropriate pharmacological and non-pharmacological therapies (e.g., physical, occupational, and speech therapies) titrated to achieve optimal functioning.

Assessment of motor deficits was done in both "off" (dopaminergic drugs stopped for a period of 12 h) and "on" states (after the patient has the maximum improvement with medication), using UPDRS part III which evaluates the motor functions. Among cases, the neurostimulator was kept "on" and thus the "off" state was in "medication off, stimulator on" state while "on" state was in "medication on stimulator on" state.[9]

NMS were assessed using NMS Quest, a 30 item comprehensive questionnaire which assesses all NMS. All items detect the presence or absence of symptoms based on yes-no answers.[10] The questionnaire was taken from the patient in the "on" state (stimulator "on" and medication "on" in cases and medication "on" in controls) by a movement disorder specialist. We further classified the 30 questions in 9 domains: gastrointestinal, urinary, cardiovascular, sexual, cognition (apathy/attention/memory), anxiety/depression, hallucinations/delusions, sleep and miscellaneous.[4] Seven questions i.e., dribbling of saliva, reduced taste or smell, dysphagia, nausea, constipation, bowel incontinence and incomplete bowel emptying were included in gastrointestinal domain. Cardiovascular domain included 2 questions–feeling light-headed and falling (syncope) while urinary domain included questions on urgency and frequency of micturition. Memory problems, loss of interest and difficulty in concentration were classified under memory domain while feeling sad and feeling anxious/frightened were questions in anxiety/depression domain. Presence of hallucinations and delusions were the two questions in hallucinations/depression domain while reduced interest and difficulty in performing sex were included in a sexual domain. Sleep domain included 5 questions on insomnia, increased drowsiness with difficulty in staying awake, vivid dreams, talking or moving in sleep (rem sleep behavioral disorders), unpleasant sensations in leg (restless leg syndrome) whereas the last 5 questions on unexplained pains, changes in weight, swelling of feet, excessive sweating, and double vision were included in miscellaneous domain.[4]

The frequency of involvement in each domain was further analyzed and compared among the two groups.

The detailed medication history was noted from both cases and controls. This included the dosage of various dopaminergic drugs levodopa-carbidopa combination, dopaminergic agonists (pramipexole, ropinirole), amantadine, trihexyphenidyl (anticholinergics) and monoamine oxidase B inhibitors (rasagiline and selegiline).

Levodopa equivalent daily dosage (LEDD) was calculated for each patient to finally calculate the total dose.[11]

Continuous variables were presented in titer of mean and ± standard deviation. Student t-test was used to study the difference between the two groups.

Categorical variables were expressed as proportions, and chi-square test was used to study the difference between two groups. The medication in each group was analyzed based on the percentage of patients on each drug as well as the mean LEDD. Odds ratio was used to assess the impact of DBS on NMS. All tests were two-sided and P < 0.05000 was considered statistically significant.

Results

Mean age of the cases and controls were 57.1 ± 9.4 and 56.6 ± 8.2 years respectively. Men in DBS group and controls constituted 67.8% (38/56) and 81.1% (43/53), respectively. Mean disease duration was 9.39 ± 2.3 and 9.17 ± 2.9 among cases and controls, respectively. The mean duration after surgery in DBS patients was 1.9 ± 2.4 years. On evaluation of UPDRS-III in off state, significantly lower scores among DBS group (UPDRS III in off state 28.8 ± 8.4) compared to controls (UPDRS III in off state 43.2 ± 7.9, P < 0.01000) were detected (Table 1).

The medication in both the groups varied. The levodopa equivalent dose was significantly lower in cases compared to patients on medical management. There was also significantly lesser usage of amantadine in cases. Compared to controls, mean levodopa dosage was lower while the mean dose of pramipexole was significantly higher in cases. This is because of the policy in our institute to manage most patients on dopaminergic agonists predominantly after DBS surgery. Very few patients in both groups were on anticholinergic medication (Table 2).

Overall, 99% of all 109 PD patients reported one or more NMS. The average NMS Quest total score was 7.6 ± 4.1 and ranged from 0 to a maximum of 22. The mean total score on NMS quest was significantly lower among patients who had undergone DBS (6.7 ± 3.8) compared to controls (8.4 ± 3.7, P = 0.02000).

On the comparison of both groups, symptoms in the domains of cardiovascular, gastrointestinal, sleep and miscellaneous were significantly less frequent, while sexual disturbances were significantly more frequent among cases (Table 3).

Table 1. Baseline characteristics

Parameters	Cases (n = 56)	Controls (n = 53)	P
Men	38	43	0.11000
Age range	34-77	39-75	
Duration of disease range	6-15	6-15	
Mean age	57.80 ± 9.60	56.64 ± 8.22	0.77000
Mean disease duration	9.62 ± 2.48	9.16 ± 2.94	0.39000
Mean UPDRS III score in “off” state	32.90 ± 11.40	43.20 ± 7.90	< 0.00010
Mean UPDRS III score in “on” state	8.80 ± 3.70	9.80 ± 5.50	0.27000

UPDRS: Unified PD Rating Scale

Table 2. Percentage and mean dose of various dopaminergic drugs used by cases and controls

Parameters	Cases (n = 56)	Controls (n = 53)	P
Number of patients on levodopa [n (%)]	53 (95.0)	50 (94.00)	0.94000
Number of patients on dopamine agonists [n (%)]	51 (91.0)	33 (62.00)	0.00035
Number of patients on anticholinergics [n (%)]	6 (10.0)	12 (22.60)	0.09000
Number of patients on amantadine [n (%)]	8 (14.20)	16 (28.57)	0.04500
Number of patients on MAO-inhibitors [n (%)]	4 (7.10)	4 (7.50)	0.93000
Mean levodopa dose (mg/day) (mean ± SD)	353.50 ± 228.00	447.20 ± 241.10	0.03900
Mean pramipexole dose (mg/24hours) (mean ± SD)	4.19 ± 1.53	3.45 ± 1.94	0.00800
Mean Ropinirole dose (mg/24 hours) (mean ± SD)	4.11 ± 0.86	3.88 ± 1.10	0.93000
Mean levodopa equivalent dose (mg/24 h) (mean ± SD)	672.50 ± 302.4	815.80 ± 414.60	0.04000

MAO: Monoamine oxidase; SD: Standard deviation

Table 3. Frequency of involvement of various non motor domains in cases and controls

NMS domains	Cases (n = 56) [n (%)]	Controls (n = 53) [n (%)]	P
Gastrointestinal complaints	38 (67.86)	50 (94.3)	< 0.00010
Urinary disturbances	41 (73.2)	46 (86.7)	0.08000
Cardiovascular problems	18 (32.14)	33 (62.2)	< 0.01000
Sexual disturbances	29 (51.7)	15 (28.3)	0.01000
Cognitive impairment/apathy	26 (46.4)	17 (32.0)	0.13000
Anxiety/depression	16 (28.5)	37 (69.8)	< 0.01000
Hallucinations/delusions	12 (21.4)	8 (15.0)	0.39000
Sleep disturbance	25 (44.6)	37 (69.8)	0.01000
Miscellaneous	21 (37.5)	44 (83.0)	< 0.01000

NMS: Non motor symptoms

Table 4. Frequency of each non motor symptom in cases and controls

Individual symptoms [n (%)]	Cases (n = 56)	Controls (n = 53)	Odds	P
Gastrointestinal complaints				
Dribbling of saliva during the daytime	17 (30.4)	25 (47.2)	0.49	0.07000
Loss or change in ability to taste or smell	4 (7.1)	4 (7.5)	0.94	0.94000
Difficulty swallowing food or drink	8 (14.3)	11 (20.7)	0.64	0.37000
Feeling of nausea/vomiting	1 (1.8)	6 (11.3)	0.14	0.04000
Constipation	29 (51.7)	38 (71.7)	0.42	0.03000
Bowel incontinence	3 (5.4)	6 (11.32)	0.44	0.26000
Incomplete bowel emptying	11 (19.6)	15 (28.30)	0.62	0.29000
Cardiovascular abnormalities				
Feeling light headed dizzy	7 (12.5)	28 (52.8)	0.13	< 0.00010
Falling	14 (25)	12 (22.6)	1.14	0.77000
Urinary problems				
Urgency of micturition	27 (48.2)	20 (37.7)	1.54	0.80000
Getting up regularly for urine	35 (62.5)	44 (83.0)	0.34	0.02000
Cognitive impairment/apathy				
Memory problems	14 (25.0)	11 (20.7)	1.27	0.60000
Loss of interest	10 (17.8)	8 (15.1)	1.22	0.70000
Difficulty concentration	7 (12.5)	8 (15.1)	0.80	0.69000
Anxiety/depression				
Feeling sad	16 (28.5)	34 (64.1)	0.22	0.00040
Feeling anxious, frightened	17 (30.3)	14 (26.4)	1.21	0.65000
Hallucinations/delusions				
Seeing things-hallucinations	10 (17.8)	5 (9.4)	2.08	0.30000
Believing things-delusions	3 (5.3)	3 (5.6)	0.94	0.70000
Sexual disturbances				
Feeling less interested in sex	25 (41.1)	14 (26.42)	1.94	0.11000
Finding it difficult to perform sex	26 (42.9)	11 (20.75)	2.86	0.01000
Sleep				
Finding it difficult to stay awake	6 (10.7)	7 (13.2)	0.75	0.90000
Difficulty getting to sleep at night	15 (26.7)	29 (54.7)	0.30	0.00500
Vivid dreams	12 (21.4)	19 (35.8)	0.49	0.100000
Talking or moving in sleep	11 (19.6)	4 (7.5)	2.99	0.07000
Unpleasant sensation in legs	5 (8.9)	8 (15.1)	0.55	0.32000
Miscellaneous/ others				
Unexplained pains	18 (32.1)	41 (77.3)	0.13	< 0.00010
Change in weight	9 (16.1)	7 (13.2)	1.25	0.67000
Swelling of legs	9 (16.1)	3 (5.6)	3.19	0.08000
Excessive sweating	9 (16.1)	9 (17)	0.94	0.90000
Double vision	4 (7.1)	1 (1.9)	4.00	0.19000

Individual symptom analysis showed significantly lower frequency of nocturia, unexplained pains, nausea and vomiting, constipation, lightheadedness, depression, and insomnia while sexual disturbances were significantly more common post DBS (Table 4).

Discussion

This is a comparative study of NMS in PD patients who have undergone bilateral STN DBS versus controls. All controls and 98% of cases in our study had one or more non motor symptom and similar findings were reported by Krishnan et al.[12] We noted significantly lower mean total score on NMS Quest in cases compared to controls. Our findings were advocated by other studies.[6,7,13]

Individual non motor domains

The effects of bilateral STN DBS on individual NMS are varied and still unclear. In our study on comparison of both groups, symptoms in the domains of cardiovascular, gastrointestinal, sleep and miscellaneous were significantly less frequent in controls, while sexual disturbances were significantly more frequent among cases with an odds ratio of 2.72. Witjas et al. in his study noted evaluated fluctuations in NMS and found significant improvement in sensory-painful fluctuations, dysautonomia and cognitive functions in 40 patients after bilateral STN DBS,[14] while Zibetti et al. found improvement only in constipation and sleep in 36 patients, after bilateral STN DBS when compared to presurgery state.[15]

Gastrointestinal symptoms

Among PD patients, gastrointestinal system is a common non motor domain to be involved, and constipation followed by dribbling of saliva are the major symptoms.[16-19] In our study, gastrointestinal symptoms were significantly lower in cases (67.8%) compared controls (94.3%), and similar finding have been noted by others.[20] Among the gastrointestinal symptoms, sialorrhea, constipation, and nausea and vomiting were significantly lower among cases compared to controls. Similar findings have been noted in previous studies. While Zibetti et al. found improvement in constipation[15] and Ciucci et al. found improved deglutition after DBS surgery.[21] This effect may be secondary to change in medications. Anticholinergics used may worsen constipation and nausea, but, on the other hand, should improve sialorrhea. As all gastrointestinal NMS have improved, a central cause may also be responsible. The proposed central mechanism is that subthalamic nucleus stimulation possibly modulates the brain stem structures involved in controlling gut motility and secretion.[21]

Cardiovascular

We established in our study that significantly reduced cardiovascular symptoms were reported by cases 18 (32.14%) compared to controls 33 (62.2%). Postural hypotension can be disabling and in an epidemiologic study, 9.1% of PD patients required such medications to treat orthostatic hypotension.[22] Symptomatic postural hypotension evaluated by the presence of lightheadedness was significantly lower in the STN DBS group.

This positive effect may be because of the direct effect of neurostimulation or maybe secondary to levodopa dose reduction. However, there has been conflicting reports regarding the impact of bilateral STN DBS on cardiovascular autonomic functions.[23] Contrary to our findings, Holmberg et al. in a cohort of 11 patients did not find any change in cardiovascular autonomic functions after STN DBS.[24] Ludwig et al. in their study demonstrated that STN DBS improved cardiovascular autonomic function by levodopa dose reduction but had no direct effect on cardiovascular autonomic functions.[25]

Sleep disorder

Sleep disturbances are a general problem in PD patients.[18,26] Varanese et al. noted in his study, sleep disturbance in 98% of patients with PD.[18] In our study we noted symptoms of insomnia were significantly lower in cases compared to controls. These are similar to previous studies which have shown significant improvement in sleep symptoms with STN DBS.[15,21,23,27] Motor symptoms of rigidity and bradykinesia can lead to sleep fragmentation and poor sleep functions and STN DBS may improve sleep by improving motor functions.[27]

Urinary symptoms

Nocturia is a common problem occurring in approximately 60% of PD patients.[28,29] In our study when we compared the frequency of all urinary symptoms, no significant difference was noted between cases and controls. However getting up regularly for urine at night or nocturia was significantly lesser in cases, a similar finding was noted by Halim et al.[30] In previous studies STN DBS has shown to improve bladder symptoms with decreased detrusor hyperreflexia and increased bladder capacity.[31,32] It has postulated that the improvement may be mainly due to modulation of bladder afferents and central sensory processing by STN DBS.

Cognitive impairment

Mild cognitive impairment is prevalent in 19-38% of PD patients[33-35] and these patients have a high risk of developing dementia.[35-38] In our study, we noted slightly higher frequency of cognitive impairment among cases (46.4%) compared to controls(32.%) but the difference was not statistically significant. Cognitive impairment has been noted after bilateral STN DBS.[39-42] However, Witjas et al. found significant improvement in fluctuations in cognitive functions after bilateral STN DBS.[14]

Anxiety/depression

Several studies have estimated that around 16-70% of PD patients suffer from neuropsychiatric problems, including depression, apathy, psychosis, and anxiety.[43-45] In our study anxiety or depression was significantly lower in cases compared to controls, similar findings were noted by others.[46,47] However, in few studies of PD patients followed up after STN DBS anxiety was shown to be same pre and post operatively.[48,49] The limitation of the previous studies was a lack of the control group, and other unknown factors could have influenced the outcome.

Sexual dysfunction

Several reports have found sexual dysfunction to be associated with PD.[50-53] The prevalence may range from 22% to 68.4%.[54-56] In our study, we found significantly higher frequency of sexual impairment in DBS patient compared to controls. This is in contrary to a prior study which showed improvement in sexual well-being in a cohort of 31 patients, 9-12 months after STN DBS.[57] The beneficial effect may be due to a reduction in dopaminergic medications which may cause erectile dysfunction, premature ejaculation, and reduced libido.[50,52,58,59] Compulsive sexual behavior as a part of impulse control disorders are noted in 3.5% of PD patients using a dopamine agonist.[60] A major setback of our study is that NMS-Quest does not

evaluate this aspect. However, a recent study has shown improvement in impulse control disorders after STN DBS.[61]

Miscellaneous

Symptoms in the miscellaneous domain were less common in DBS group compared to controls. This is a heterogeneous group consisting of symptoms pertaining to thermoregulation (excessive sweating), pain (unexplained pains), drug effect (swelling of feet), weight changes and diplopia.[4] On assessment of individual symptoms, complaints of pain were significantly less common in DBS group compared to medical therapy. Pain is a common complaint in PD and is worse in the "off" state.[62] The etiology is varied and may be secondary to rigidity, dystonia or changes in pain perception. Recent study they found improvement in pain after bilateral STN DBS was almost universal and persisted for 2 years after the surgery.[63] As is the case with many NMS, the effect may be secondary to improvement in motor functions but as DBS also seems to impact our sensory perception, it may be secondary to modulation of neural networks which may alter the central processing of pain.[64]

Our study compared the frequencies of various NMS among patients who have undergone DBS compared to those on medication alone. Reduction in dopaminergic dose is commonly seen after DBS and may contribute to the reduction in NMS such as orthostatic hypotension, cognitive impairment, depression and hallucinations, and gastrointestinal symptoms. Thus, DBS may help by directly stimulating the brainstem and by secondarily modifying medication.

Pitfalls of study

Our study used a simple tool in an attempt to identify the effect of STN DBS on the presence of NMS. However the NMS Quest only assesses the presence or absence, and does not evaluate the severity, of the NMS. NMS Quest does not cover certain areas such as gait, speech, dopamine dysregulation syndrome, and is subjective.

The second drawback is that we have used a case-control study which is fraught with selection biases. Moreover, we are using two groups of PD patients who are age and disease duration matched. Although the UPDRS 'on' scores were similar in both groups, the 'off' score was evaluated with the stimulator 'on' in the DBS group and hence does not give a clear picture of the disease severity. There is a possibility that the cases and controls have different disease severity and that itself might have contributed to the differences in NMS.

However, the only advantage of this design over a study comparing the symptoms before and after STN DBS in the same set of patients is that we were able to compare patients at the same time in the disease course. We also have undertaken the study considering the bilateral STN DBS group to be a homogenous one. Recent research has shown that surgical trajectory and final location of the electrode can significantly influence neuropsychological outcome and their effect on other NMS are not known.

Conclusion

Overall NMS and symptoms in the domains of cardiovascular, gastrointestinal, sleep and miscellaneous were significantly less frequent, in patients who underwent bilateral STN DBS while sexual disturbances were significantly more frequent, when compared to patients on best medical treatment. This may be due to an either a direct effect of DBS or secondary to a reduction in medication. The impact on these scores on the functional and occupational status of the patients has still not been established. Further longitudinal cohort studies and randomized control studied are required to confirm these findings and compute the effect of DBS on various domains and functional outcome.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Stroke specific quality of life questionnaire: Test of reliability and validity of the Persian version

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Keywords
Stroke, Quality of Life, Reproducibility of Results, Questionnaires

Abstract

Background: The aim was to assess the reliability and the validity of the translated version of the stroke specific quality of life (SS-QOL) questionnaire in Iranian post-stroke patients.

Methods: This project was performed at the Shiraz University of Medical Sciences, Shiraz, Iran, between 12 April 2010 and 24 February 2011. The English version of the SS-QOL was translated into Persian by "forward-backward" translation, cognitive inquiring and cultural adaptation process. The reliability and internal consistency were measured by Cronbach's alpha coefficient. Validity was assessed using convergent and divergent validity through Spearman's correlation coefficient.

Results: Our study included 117 post-stroke patients, consisting of 57 (48.7%) men and 60 (51.3%) women. The mean age of the patients was 81.60 ± 7.52 (range 60-88) years. The Persian version of the SS-QOL proved reliable (Cronbach's α = 0.96). Internal consistency was excellent for both demographic and patients' clinical characteristics (Cronbach's α ≥ 0.70). The scaling success rates were 100% for convergent validity of each scale. Divergent validity for all 12 scales was considered acceptable, whereas each scale had a 100% scaling success rate for convergent validity.

Conclusion: The Persian version of SS-QOL should be mentioned as a noteworthy instrument to specify different aspects of health related QOL of patients suffering stroke and hence that clinicians, researchers and epidemiologist can exploit it trustfully.

Introduction

Stroke is the foremost cause of adult disability worldwide. Although the stroke considered as the third cause of mortality in developed countries,[1] it is ranked as the second cause of death in developing counties.[2] The socioeconomic importance of this non-communicable disease is growing in ageing populations.[3] It also represents a major cause of long-term disability with a potentially major impact on patients, their families, and health-care services by various emotional and socioeconomic aspects.[4] Stroke mortality data from multiple countries reveal that, as a whole, mortality rates have decreased in recent decades.[5,6] Stroke incidence, as first ever event of its kind, was estimated between 22.7 and 103.23/1,00,000 individuals in all age ranges. These statistics showed that approximately 70% of the patients survived the acute initial phase. The increasing number of long-term post-stroke survivors due to improved medical and social care, successful and effective secondary

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prevention especially by antihypertensive agents and incremental overall life expectancy demonstrate the unique and specific role of stroke in the drafting and implementation of healthcare strategies.[7,8]

The majority of the surveys evaluating the quality of life (QOL) after stroke have applied generic instruments such as the Short Form-36, the well-being scale, the sickness impact profile, the EuroQOL, or the Nottingham Health Profile. These scales enable researchers compare patients with different diseases, but are less sensitive regarding the specific effects of a specific disease, such as stroke, on the patient's QOL or the response to a specific treatment.[9] The stroke specific QOL (SS-QOL) questionnaire is one of the noteworthy specific scales for the determination of QOL after stroke, which is significantly more valid and sensitive as compared to traditional instruments.

Currently, there are approximately more than 80 million persons who speak Persian worldwide. They live in Iran, Afghanistan, Tajikistan, Uzbekistan and several other countries. There has been no valid and reliable questionnaire with official Persian language to evaluate QOL in stroke patients in Iran. The current study was conducted in order to translate and validate the Persian version of the SS-QOL.

Materials and Methods

The SS-QOL, which is a disease-specific QOL measure, consists of 49 items encompassing 12 domains, which include the social role (five questions), mobility (six questions), energy (three questions), language (five questions), self-care (five questions), mood (five questions), personality (three questions), thinking (three questions), upper extremity function (five questions), family role (three questions), vision (three questions), and work/productivity (three questions). Each item is ranked on a five-point Likert scale in which level one means completely agreed while level five means completely disagree. The summary score of this scale is an un-weighted average of the 12 domains. The total score ranges from 49 to 245, with higher scores indicating a better QOL.

This face-to-face interview survey was performed at the Stroke Special Clinic, Department of Neurology, Shiraz University of Medical Sciences, Shiraz, Iran between 12 April 2010 and 24 February 2011. For translating the questionnaire from English to Persian, the standard forward-backward method was used, as described by our previous studies.[10,11] All 49 items were translated by expert bilinguals into Persian and afterwards, the preliminary version was again translated into English. Cultural adaptation was performed in order to obtain a version of the questionnaire that is practically as similar as possible to the main English one, along with patients' perception and understanding. The Persian version of SS-QOL was filled out by 20 patients. All these patients were asked to evaluate the transparency and clarity of each question. All the findings of this pilot study and the interviews with the patients were gathered. Based on the results of this pilot study, unclear or questionable items were modified.

In general, the patients reported that they had no problems in understanding and answering all of the questions of the Persian version of SS-QOL.

All demographic data including age, sex, marital status, dwelling place, educational and socioeconomic status were registered. A qualified neurologist was responsible for gathering clinical and medical data of patients related to stroke, comprising of the type of stroke, duration of disease, etc.

Patient inclusion criteria were age above 50 years and proved diagnosis of stroke. Stroke was defined according to National Clinical Guideline for Diagnosis and Initial Management of Acute Stroke and Transient Ischemic Attack (TIA)[12] and diagnosis was confirmed by clinical history, neurological examination and imaging via computed tomography scan and/or magnetic resonance imaging. The sample was selected from literate and illiterate people who accepted to participate in this study. Patients with any known vasculitis, thrombophilic diseases, infectious vasculopathy, arterial dissection, moyamoya disease, radiation induced vasculopathy, fibromuscular dysplasia, sickle cell disease, neurofibromatosis, reversible cerebral vasoconstriction syndrome, vasospasm after subarachnoid hemorrhage and cerebral venous sinus thrombosis were excluded from the study. Those with TIA without progression to stroke as well as those with severe heart, liver or renal disease that may considerably influence the QOL were also excluded.

Individuals were interviewed personally by family physicians under the full observation of a neurologist. The questions were asked during a face-to-face interview in Persian. The interviewer intervened only to clarify a question if required, but did not reveal any information about the value of each item or effect of each question on the outcome. No attempt was made to prompt the respondents by suggesting answers directly.

The questionnaire was filled out by literate subjects. For illiterate subjects, the questions were asked through an interview in Persian. The interviewer could only explain the meaning of questions for illiterate patients. The relevance and clarity of the questions were also assessed.

The approvals of the Institutional Review Board, as well as the Ethics Committee of the Shiraz University

of Medical Sciences, were obtained before the start of the study. All participants gave their written informed consents. This study was designed and performed according to principles of Helsinki Declaration.

Previous studies recommend that the acceptable sample size for testing the validity and reliability of QOL questionnaires are between 100 and 400.[13]

Statistical analyses were performed using the SPSS software, (version 17.0, SPSS Inc., Chicago, IL, USA). Results are reported as the mean ± standard deviation or n (%), as appropriate. The SS-QOL scale scores were measured using the Likert method for summed ratings, and the raw scores were linearly transformed into 49-245 scales: the higher the transformed score, the better the patient's health related QOL (HR-QOL).

The internal consistency and reliability were examined using Cronbach's alpha (recommended value $\alpha \geq 0.70$).[13-15] To assess the validity (convergence and divergence) of SS-QOL questionnaire, the Spearman's correlation coefficient was used.[14,15] Convergence validity assesses the relevance of each item with the subscale containing it. Divergence validity assesses the irrelevance of each item with the subscales not containing it. It is generally expected that an item has a high correlation with its subscale and low correlation with other subscales.

To determine the psychometric properties of the questionnaire's scales for ceiling effect, we counted the percentage of subjects who scored five for each item, and to determine the floor effect, we counted the percentage of subjects who scored one for each item.

Results

Overall, we included 117 post-stroke patients among whom there were 57 (48.7%) men and 60 (51.3%) women. The mean age of the patients was found to be 81.60 ± 7.52 (range 60-88) years. The majority of patients (82.1%) were married. Duration of the disease was 1.92 ± 1.86 years (range 0.8-12). 54 (47.8%) patients were illiterate, whereas 41 (36.3%) patients were semi-literate. Both high school graduates and university degrees included 9 (8%) patients. A total of 108 (92.3%) patients suffered ischemic stroke while the rest, 9 (7.7%) patients, suffered a hemorrhagic stroke (Table 1).

The reliability of the whole 49 questions was provided by the Cronbach's alpha coefficient ($\alpha = 0.96$), whereas the individual coefficients according to sex, marital status, residency, education, stroke type and duration of disease are shown in table 2.

Based on the correlation coefficients, there is an acceptable association between each scale and its items (recommended $r \geq 0.40$) while the scaling success rates were 100% for the convergent validity of each scale. Internal consistency for all scales, except for overall QOL is excellent ($\alpha \geq 0.70$; range: 0.74-0.94). On the other hand, each scale shows the least associations with other items in discriminate scales. Therefore, divergent validity for all scales (regarding corresponding discriminate scales) is satisfactory (Table 3).

Table 1. Demographic, socioeconomic and clinical characteristics of 117 post-stroke patients

Variable	n (%)	Mean ± SD
Sex		-
Male	57 (48.7)	-
Female	60 (51.3)	-
Marital status		-
Single	21 (17.9)	-
Married	96 (82.1)	-
Educational status		-
Illiterate	54 (46.2)	-
Semi-literate	41 (35.0)	-
High school	9 (7.7)	-
University degree	9 (7.7)	-
Residency		-
Urban	87 (74.4)	-
Rural	30 (25.6)	-
Type of stroke		-
Ischemic	108 (92.3)	-
Hemorrhagic	9 (7.7)	-
Age (Range)		81.60 ± 7.52 (60-88)
Disease duration (years) (Range)		1.92 ± 1.86 (0.8-12)
Disease severity (BI score) (Range)		79.00 ± 22.61 (20-105)

SD: Standard deviation; BI: Barthel Index

Table 2. Internal consistency of Stroke specific quality of life (SS-QOL) questionnaire in different demographic, socioeconomic and clinical subgroups

Variable	Number	Cronbach's coefficient
Age		
< 70	14	0.96
70-85	42	0.96
≥ 85	61	0.97
Sex		
Male	57	0.97
Female	60	0.95
Marital status		
Single	21	0.96
Married	96	0.96
Educational status		
Illiterate	54	0.96
Semi-literate	41	0.95
High school	9	0.89
University degree	9	0.98
Residency		
Urban	87	0.97
Rural	30	0.96
Type of stroke		
Ischemic	108	0.97
Hemorrhagic	9	0.96
Disease duration (year)		
< 1	45	0.97
1-3	36	0.96
≥ 3	36	0.95
Disease severity (BI score)		
Mild	71	0.94
Moderate	28	0.88
Severe	18	0.87

BI: Barthel index

Interestingly, the values of the Cronbach's alpha coefficients are all excellent in the subgroups according to gender and marital status (α ≥ 0.70; range: 0.70-0.95), except for that of family role subscale for singles (α = 0.39) (Table 4).

Concerning the internal consistency of each subscale of SS-QOL regarding stroke type and disease, the α values are interestingly excellent, with only one exception in the case of language subscale for patients with hemorrhagic stroke (α = 0.33) (Table 5).

Table 6 shows the floor and ceiling effects for each subscale of the questionnaire. The ceiling effects were generally greater than floor effects. However, the amount of values indicated that the variability to the subscales were generally acceptable and have not been affected by the accumulation of same responses in a specific item.

Discussion

The efficacy of interventions in stroke has been evaluated mainly on the basis of clinical endpoints, although patients and their families face a range of psychosocial issues. As a consequence, a variety of stroke-specific questionnaires has been developed for the assessment of HR-QOL,[16] an important concept to better understand the distress of people with stroke. Nowadays, it is widely used as a HR-QOL indicator for post-stroke individuals. It has been validated for use in Croatia,[17] Malaysia,[18] Taiwan,[19] the Netherland,[20] Brazil,[21] Denmark,[22] Germany,[23] Great Britain,[24] the United States.[25]

Table 3. Convergent validity for stroke specific quality of life (SS-QOL); Item scaling tests

Scale	Number of items per scale	Convergent validity (range of correlation)	Scaling success*	Scaling success**	Internal consistency (Cronbach's alpha)	Divergent validity (range of correlation)
Energy	3	0.75-0.89	3/3	100	0.80	0.08-0.49
Family role	3	0.68-0.88	3/3	100	0.74	0.03-0.78
Language	5	0.75-0.83	5/5	100	0.94	0.13-0.47
Self-care	5	0.77-0.91	5/5	100	0.92	0.12-0.82
Social role	5	0.76-0.88	5/5	100	0.88	0.14-0.72
Thinking	3	0.82-0.87	3/3	100	0.81	-0.08-0.45
Mood	5	0.53-0.85	5/5	100	0.80	0.14-0.53
Personality	3	0.85-0.90	3/3	100	0.86	0.14-0.58
Upper extremity function	5	0.79-0.84	5/5	100	0.92	0.11-0.79
Vision	3	0.82-0.86	3/3	100	0.85	0.06-0.37
Work (Productivity)	3	0.81-0.92	3/3	100	0.86	0.11-0.78
Mobility	6	0.79-0.93	6/6	100	0.94	0.05-0.78

Spearman's correlation coefficient was used for assessing convergent and divergent validities of each scale and corresponding items

* Number of correlations between items and hypothesized scale corrected for overlap > 0.4/total number of convergent validity tests; ** Scaling success rate of previous column as percentage

Table 4. Internal consistency (Cronbach's alpha) of each subscales of stroke specific quality of life (SS-QOL) questionnaire by gender and marital status

Scale	Cronbach's alpha			
	Male	Female	Single	Married
Energy	0.87	0.87	0.76	0.81
Family role	0.77	0.72	0.39	0.79
Language	0.94	0.93	0.93	0.93
Self-care	0.93	0.92	0.94	0.92
Social role	0.90	0.84	0.85	0.89
Thinking	0.80	0.83	0.90	0.79
Mood	0.82	0.76	0.70	0.82
Personality	0.86	0.85	0.94	0.84
Upper extremity function	0.93	0.91	0.95	0.91
Vision	0.76	0.90	0.75	0.87
Work (productivity)	0.92	0.79	0.86	0.87
Mobility	0.95	0.92	0.95	0.93

Table 5. Internal consistency of each subscale of stroke specific quality of life (SS-QOL) questionnaire regarding stroke type and duration of disease expressed in years)

Scale	Cronbach's alpha				
	Ischemic	Hemorrhagic	Disease duration (< 1)	Disease duration (1-3)	Disease duration (≥ 3)
Energy	0.80	0.80	0.80	0.80	0.82
Family role	0.74	0.79	0.79	0.73	0.70
Language	0.94	0.33	0.93	0.95	0.93
Self-care	0.92	0.88	0.95	0.91	0.88
Social role	0.88	0.92	0.92	0.82	0.89
Thinking	0.80	0.92	0.79	0.81	0.84
Mood	0.80	0.77	0.79	0.80	0.84
Personality	0.87	0.72	0.89	0.84	0.83
Upper extremity function	0.92	0.84	0.94	0.91	0.85
Vision	0.84	0.96	0.90	0.81	0.69
Work (productivity)	0.84	0.72	0.85	0.86	0.88
Mobility	0.94	0.89	0.95	0.94	0.92

Table 6. The ceiling and floor effect for the subscales of stroke specific quality of life (SS-QOL) questionnaire

Subscale	Floor effect (%)	Ceiling effect (%)
Energy	23.1	8.5
Family role	20.5	15.4
Language	3.4	34.2
Self-care	1.7	36.8
Social role	12.0	12.8
Thinking	1.7	33.3
Mood	1.7	20.5
Personality	29.9	13.7
Upper extremity	5.2	32.8
Vision	1.7	54.7
Work product	11.1	20.5
Mobility	4.3	16.2

This survey was conducted with the purpose of translating the SS-QOL questionnaire into Persian and to evaluate its reliability and validity among Iranian post-stroke patients. The psychometric characteristics of the Persian adaptation of the SS-QOL questionnaire were highly satisfactory and compatible to those of the Croatian,[17] Malaysian,[18] Taiwanian,[19] Dutch,[20] Brazilian,[21] Danish,[22] German,[23] and English[24,25] versions.

This study investigated the issue of validity specifically based on convergence and divergence of items in the questionnaire. Our confident finding on the internal validity can be followed by the other

researchers to assess the external validity of Persian version of the questionnaire.

Cronbach's alpha coefficient was applied for determining the reliability, and it was excellent ($\alpha \geq 0.70$) for all 12 subscales, making our findings compatible with those of a previous study in Denmark.[22]

The internal consistency of the whole 49 items of the SS-QOL was excellent for both literate and illiterate patients. Cronbach's alpha was excellent regarding age, sex, marital status, residency, educational status, stroke type and duration of disease.

The present study shows a high convergent validity for all subscales of the SS-QOL questionnaire.

In correspondence to a German trial,[23] the scaling success rate for all subscales was 100% in our study, whereas the divergent validity for all subscales was acceptable. However, it is interesting to note that this finding has not yet been reported by other surveys.

One limitation of our study was that we were unable evaluate reliability through test-retest analysis. This setting claims for further studies in order to examine the test re-test reliability in order to find more reliable results. Another possible limitation of our study is that minority of the respondents were interviewed while others filled the forms by themselves. This was inevitable due to the fact that some of the stroke patients were illiterate and could not fill out the forms by themselves. It might be a source of bias in our tool validity survey.

Currently, to the best of our knowledge, this is the first study to show the reliability and validity of the Persian version of SS-QOL. The results of our survey proved that the Persian version of SS-QOL has an efficiently structured specification and convergent validity. In addition, this instrument can be used for assessing the effects of stroke on the QOL reliably and confidently.

Conclusion

In conclusion, we may thereby declare to have accomplished the translation, cultural adaptation and testing of reliability and validity of the SS-QOL questionnaire for Iranian patients. Consequently, the Persian version of SS-QOL should be mentioned as a noteworthy instrument to specify different aspects of HR-QOL for patients suffering a stroke and clinicians, researchers and epidemiologist can exploit it trustfully.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Development, cross-cultural adaptation, and validation of the Persian Mississippi Aphasia Screening Test in patients with post-stroke aphasia

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Keywords
Stroke, Aphasia, Mississippi Aphasia Screening Test

Abstract

Background: The Mississippi Aphasia Screening Test (MAST) is a brief screening test for assessing the expressive and receptive language abilities in patients with aphasia. The objective of the study was to develop and validate the Persian version of the MAST (MASTp) as a screening test for language disorders in patients with post-stroke aphasia.

Methods: This study used a cross-sectional design to cross-culturally adapt the MASTp following the guidelines for the process of cross-cultural adaptation of measures. A total of 40 subjects (20 patients with post-stroke aphasia and 20 healthy subjects) were included. The MASTp was tested for floor or ceiling effects, internal consistency reliability, intra-rater reliability, discriminative validity, and factor structure.

Results: There were no floor or ceiling effects for MASTp total score. The MASTp yielded values for internal consistency reliability that were not adequate (Cronbach's alpha 0.64 and 0.66 for test and retest, respectively. The intra-rater reliability of the MASTp within a 7 day-interval was excellent for total score (ICC $_{agreement}$ = 0.96) and both expressive index (ICC = 0.95) and receptive index (ICC $_{agreement}$ = 0.98). here were statistically significant differences in MASTp total scores and both indexes between patients and healthy subjects suggesting the discriminative validity of the MASTp (P < 0.001). Factor analysis revealed a 3-factor solution, which jointly accounted for 72.06% of the total variance. Additional factor analysis suggested 6-item MASTp as a unidimensional measure.

Conclusion: The MASTp is useful as a valid and reliable screening tool for evaluation of language abilities in Persian speaking patients with aphasia after stroke.

Introduction

Aphasia is one of the most common and devastating consequences of stroke. It is reported that the aphasia is present in 21-38% of patients with acute stroke.[1] A prospective, population-based study of the epidemiology of aphasia found that 43 of 100,000 inhabitants are affected per year from first ischemic stroke.[2] The burden of aphasia is high. Aphasia is associated with higher mortality, morbidity, and worse functional outcomes.[1,3] Communication problems in patients with post-stroke aphasia can impair their quality of life.

It is important to identify the aphasia early after stroke to maximize the therapy gain and to improve language outcomes. Screening assessment using tools with sound psychometric and administrative properties can provide a quick and efficient means to diagnose the presence of aphasia post-stroke. There are several

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screening instruments reported in the published stroke literature. The Mississippi Aphasia Screening Test (MAST) is one of the most valuable screening devices to identify the patients withaphasia.[4]

The MAST is a valid and repeatable screening tool for quickly measuring the expressive and receptive language abilities in patients with aphasia. The MAST has 9 subtests ranging from 1 to 10 items per sub-scale (naming, automatic speech, repetition, yes/no accuracy, object recognition from a field of five, following verbal instructions, reading instructions, verbal fluency, and writing/spelling to dictation).[5] The scores from each item of MAST are summed to produce sub-scale scores (receptive and expressive, each range 0-50). The scores from both sub-scales are summed to provide total score (range 0-100). The MAST is a simple and brief measure, and time required to administer the MAST is ~5-15 min.[5]

The MAST is developed and validated in English language. To be used in different languages other than English, the MAST is required to be translated and cross-culturally adapted to ensure that the translated version is appropriate and relevant in the target language. The translation and validation process following standard guidelines tries to produce the equivalency of the source MAST conceptually and semantically and the target language.[6] Although the MAST is translated into Czech,[7] Spanish,[8] and Telugu language,[9] no Persian version exists.

Therefore, the aim of the present study was to translate and cross-culturally adapt the MAST into Persian language (MASTp). The floor or ceiling effects, internal consistency reliability, intra-rater reliability, discriminative validity, and factor structure were examined.

Materials and Methods

A cross-sectional study was used to develop and cross-culturally adapt the MASTp, and to assess the reliability and validity of the MASTp. The study design was approved by the Review Board, School of Rehabilitation, and the Ethical Committee of Tehran University of Medical Sciences, Iran.

The translation of the MASTp was performed following proposed guideline by Beaton et al.[6] Two bilingual translators whose native language was Persian independently forward-translated the MAST into Persian, and another two bilingual translators whose native language was English independently back-translated the synthesized Persian version into the English. An expert committee reviewed the all documents and produced the pre-final version. Ten speech-language pathologists (SLP) expert in aphasia therapy were invited to evaluate the pre-final version of the MASTp to give their comments on the clarity and meaningful of the translation. The feedbacks from the experts were reviewed by the committee, and some proposed changes were applied to produce the final MASTp (sub-scale of Verbal fluency: "knowledge is power" was substituted for "three strikes"; sub-scale of Repetition: "table" was substituted for "pot"; sub-scale of writing to dictation: "go" and "machine" was substituted for "sit" and "airplane", respectively. The final MASTp is shown in Appendix.

Patients were included with the following inclusion criteria: (1) age 18-65 years; (2) first-ever stroke resulted in aphasia; (3) stroke duration of at least 1 month; (4) able to read and write Persian language. Patients with severe visual/auditory and cognitive deficits were excluded. Healthy and neurologically intact subjects were also included. All participants agreed and signed written informed consent prior to participate in the study.

Patients were tested by an experienced SLP familiar with the MASTp. The SPL administered the MASTp in all patients and healthy subjects. Patients were tested again with 1-week interval for intra-rater reliability.[10] The Edinburgh inventory Laterality was used to assess the handedness in all subjects.[11]

Kolmogorov-Smirnov test was performed to assess whether continuous data have a normal distribution. Demographic characteristics were compared between groups using the independent *t* test (continuous data) or Mann–Whitney U-Test (categorical data). The independent *t* test was applied to estimate the discriminative validity by comparing MASTp scores between patients and healthy subjects. The Cronbach's alpha statistic was used to calculate internal consistency reliability. The Cronbach's alpha between 0.7 and 0.95 was considered high.[10] To measure intra-rater reliability, the intraclass correlation coefficient (agreement) ($ICC_{agreement}$) (two-way random effects model, single measure) was calculated. A minimum of 0.7 was regarded for reliability. An ICC coefficient of more than 0.75 was interpreted excellent reliability; 0.60-0.75, good reliability; and 0.40-0.59, fair reliability.

The percentage frequency of lowest or highest possible score achieved by subjects were calculated as floor or ceiling effect. The floor or ceiling effects > 15% were considered to be significant. The data were analyzed using the SPSS software (version 18.0, SPSS, Inc., Chicago, IL, USA). An alpha of < 0.05 was considered as statistically significant.

Results

All the continuous variables were normally distributed. In this study, 20 patients [13 male and 7 female; mean age ± standard deviation (SD) = 52.3 ± 8.2 years, range = 36-65] and 20 healthy subjects (10 male and 10

female; mean age ± SD = 49.6 ± 8.8 years, range = 27-65) were participated. The mean education ± SD in patients and healthy subjects was 11.2 ± 5.5 years (range = 1-18) and 10.3 ± 4.0 years (range = 5-18), respectively. Eighteen patients (90%) and 19 healthy subjects (95%) were right handed. There were no significant differences between 2 groups for age (P = 0.210), education (P = 0.560), gender (P = 0.340), and laterality (P = 0.550). Duration since stroke in patients group was 27.2 ± 50.75 months (range 1-224).

Floor or ceiling effects

Floor or ceiling effects were not seen for MASTp total score in test (44.60 ± 16.11, range = 6-70) and retest (46.0 ± 16.14, range = 6-67).No patients were scored the lowest or highest possible score on MASTp.

Discriminative validity

There was a statistically significant difference in MASTp total scores (Levenes' test for equality of variances: F = 25.32, P < 0.001; t = −14.80, df = 19.49, P < 0.001), expressive index scores (Levenes' test for equality of variances: F = 44.57, P < 0.001; t = −14.41, df = 19.94, P < 0.001, and receptive index scores between the 2 groups (Levenes' test for equality of variances: F = 23.84, P < 0.001; t = −9.49, degree of freedom (df) = 19.46, P < 0.001) (Table 1).

Internal consistency

The Cronbach's alpha was 0.64 for test, and the Cronbach's alpha if item deleted ranged between 0.52 and 0.72 (Table 2). For retest, the Cronbach's alpha was 0.66, and the Cronbach's alpha if item deleted ranged between 0.56 and 0.73 (Table 2).

Intra-rater reliability

The ICC $_{agreement}$ for the intra-rater reliability of the MASTp total score was excellent (0.96, 95% CI = 0.90-0.98, P < 0.001). The intra-rater reliability for the expressive MASTp (0.95, 95% CI = 0.88-0.98, P < 0.001) and receptive MASTp (0.98, 95% CI = 0.94-0.99) delivered excellent results.

Table 1. Mean ± standard deviation of Mississippi Aphasia Screening Test (MAST) scores by group for test (n = 20)

MAST scale	Healthy subjects (Mean ± SD)	Patients (Mean ± SD)	P
Naming	9.09 ± 0.44	3.90 ± 4.27	< 0.001
Automatic speech	9.07 ± 0.73	4.45 ± 3.64	< 0.001
Repetition	9.09 ± 0.47	4.20 ± 2.96	< 0.001
Yes/No responses	19.08 ± 0.61	13.03 ± 6.16	< 0.001
Object recognition	10.00 ± 0.00	9.00 ± 2.55	0.080*
Following instructions	10.00 ± 0.00	1.01 ± 2.63	<0.001
Reading instructions	9.04 ± 0.94	5.08 ± 2.50	< 0.001
Verbal fluency dictation	9.75 ± 1.11	0.75 ± 1.83	< 0.001
Writing/spelling	9.08 ± 0.89	2.10 ± 3.21	< 0.001
Expressive index	49.15 ± 1.63	15.40 ± 10.34	< 0.001
Receptive index	49.01 ± 1.02	29.20 ± 9.32	< 0.001
Total score	98.25 ± 1.83	44.60 ± 16.11	< 0.001

* Not significant; MAST: Mississippi Aphasia Screening Test; SD: Standard deviation

Table 2. Cronbach's alpha if item deleted for Mississippi Aphasia Screening Test (MAST)

Subtests	Scale mean if item deleted		Scale variance if item deleted		Corrected item-total correlation		Squared multiple correlation		Cronbach's Alpha if item deleted	
	Test	Retest	Test	Retest	Test	Retest	Test	Retest	Test	Retest
Naming	40.70	42.00	171.91	188.00	0.62	0.56	0.87	0.87	0.52	0.57
Automatic speech	40.15	41.25	191.71	187.15	0.54	0.59	0.73	0.70	0.56	0.56
Repetition	40.40	41.90	201.10	196.62	0.59	0.63	0.76	0.76	0.56	0.57
Yes/No Responses	31.30	32.00	178.22	177.68	0.26	0.29	0.56	0.66	0.67	0.68
Object recognition	35.60	37.10	202.57	197.46	0.70	0.73	0.65	0.65	0.55	0.56
Following verbal instructions	38.80	40.00	241.85	237.47	0.15	0.24	0.55	0.57	0.64	0.65
Reading instructions	43.50	44.90	234.05	241.04	0.23	0.15	0.64	0.68	0.63	0.66
Verbal fluency dictation	43.85	45.25	236.03	239.04	0.36	0.32	0.57	0.57	0.62	0.64
Writing/spelling	42.50	43.60	271.74	266.78	-0.21	-0.16	0.53	0.57	0.72	0.73

Factor structure

The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was 0.56. Bartlett's test of sphericity was 79.15 (P < 0.001). A principal component analysis with varimax rotation loaded 3 latent factors with Eigen values greater than 1, which jointly accounted for 72.06% of the total variance. The first factor (expressive) included 6 items, which explained 37.76% of the total variance (Eigen value = 3.40). The second factor (receptive) included 3 items, which explained 20.09% of the total variance (Eigen value = 1.81). The third factor (writing) included 2 items, which explained 14.22% of the total variance (Eigen value = 1.28). The item of "Object recognition" was loaded with all factors but slightly more on the first factor. The results are illustrated in table 3. The scree plot for MASTp is shown in figure 1.

The Cronbach's alpha for the extracted factors were 0.83, 0.60, and 0.42, respectively. Since the alpha value was acceptable only for the first factor, we thus further proceeded to test it for the factor structure. A principal component analysis with varimax rotation produced 1 homogenous measure for 6-item scale, which explained 54.68% of the total variance (KMO = 0.66, Bartlett's test = 50.60, P < 0.001, Eigen value = 3.28). Figure 2 shows the scree plot for 6-item MASTp.

Table 3. The factor structure of the Mississippi Aphasia Screening Test (MAST)

MASTp items	Factors		
	Expressive	Receptive	Writing
Naming	0.884		
Automatic speech	0.878		
Repetition	0.848		
Yes/no responses		0.871	
Object recognition	0.549	0.509	0.516
Following verbal instructions		0.842	
Reading instructions	0.556		
Verbal fluency dictation	0.584		
Writing/spelling			0.865

MASTp: Persian Mississippi Aphasia Screening Test

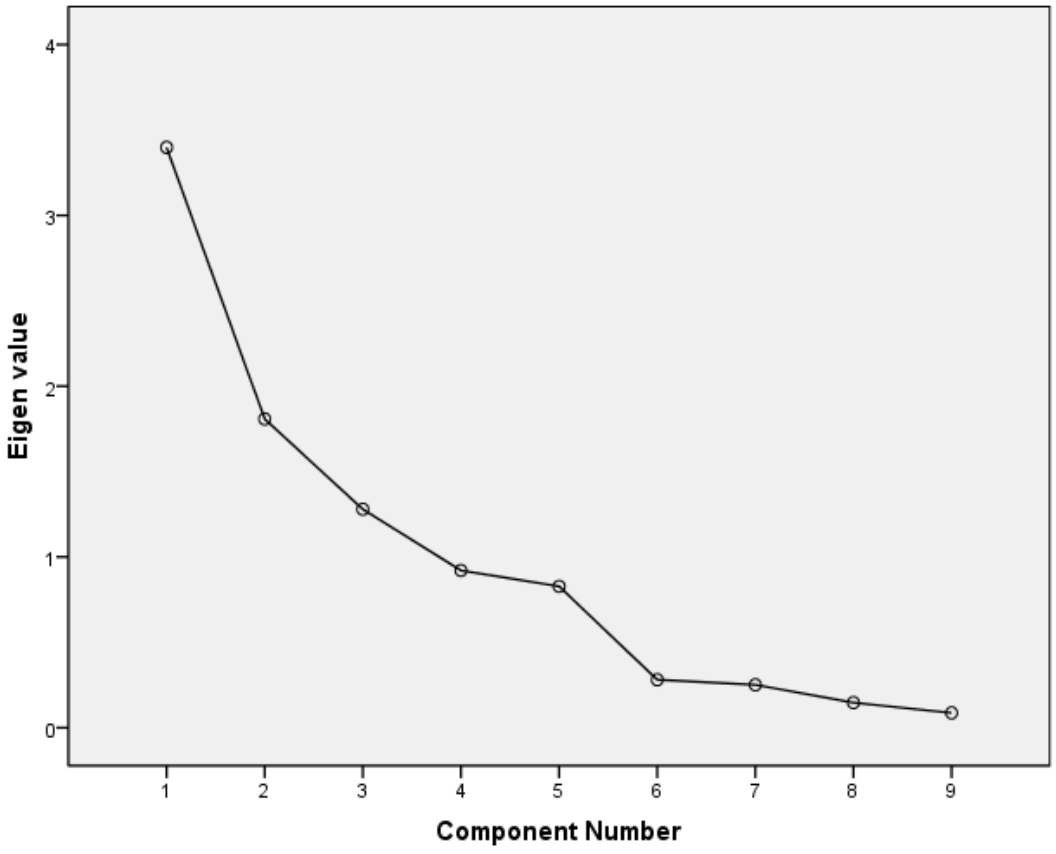

Figure 1. Scree plot for Persian Mississippi Aphasia Screening Test shows three latent factors

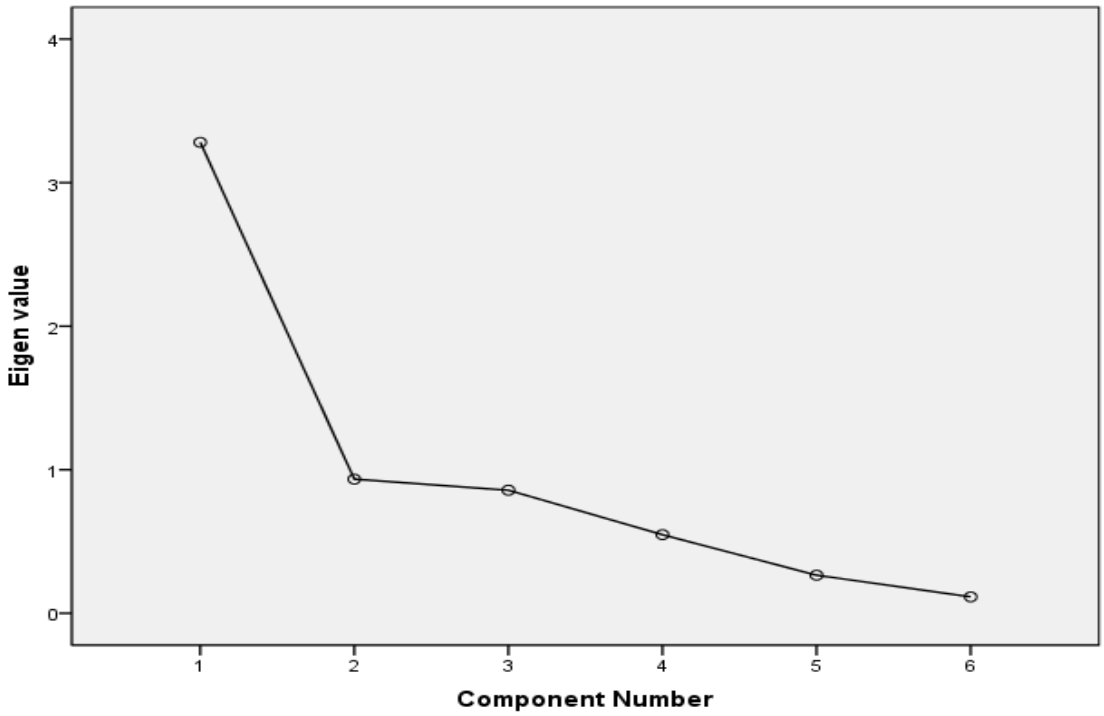

Figure 2. Scree plot for 6-item Persian Mississippi Aphasia Screening Test showing 1 homogenous factor

Discussion

This study presented the process of cross-cultural adaptation and validation of MAST for Persian speaking health professionals in particular SLPs to evaluate patients with post-stroke aphasia. The process of translation and cross-cultural adaptation in line with the translation versions of the MAST[7-9] was performed without any difficulty and resulted in a measure in Persian language, the MASTp. The equivalency of MASTp with the original English version ensures that a study that uses the MASTp can compare the results with those that used the MAST in English as well as other languages. The standard methodology used in developing the MASTp ensured the face and content validity of this screening instrument. This study further demonstrated that the MASTp has discriminative validity, internal consistency reliability, and intra-rater reliability. As far as we know, this is the first validation study of the MASTp.

Ceiling or floor effects

In this study, no patients scored 0 or 100 on the MASTp total score, and the MASTp total scores were well distributed. The ceiling or floor effects were not reported for the English[5] and the translated versions of the MAST.[7-9] The lack of ceiling or floor effects further verifies the content validity of the MASTp.

Discriminative validity

As expected, patients scored poorly than the healthy subjects on all MASTp subtests as well as the total score, expressive index, and receptive index. Current findings are consistent with those of the original and translated versions of the MAST[5,7-9] indicating the discriminative validity of the MASTp. This finding indicates that the MASTp was capable of discriminate between stroke patients with aphasia and healthy subjects.

The "Object recognition" subtest showed similar performance among patients with post-stroke aphasia and healthy subjects. This finding is in line with those of the Nagendar and Ravindra in the validation study of the Telugu language version of the MAST.[9] The similar performance on the "Object recognition" among patients and healthy subjects may be explained by the fact that the "Object recognition" subtest depends primarily on visual-perceptual abilities.[5]

Internal consistency reliability

The internal consistency reliability indicates the interrelatedness among the items assessing how each item relates to the other items.[12] Cronbach's alpha in this study did not quite reach the cut-off score of 0.7 for acceptable internal consistency reliability. Cronbach's alpha is not reported for the original English and translated versions of the MAST.[5,7-9] One reason could be that the internal consistency for culturally adapted measures might be typical to be lower compared to the original tool. Another reason for the lower value found in this study could be the small number of patients. We noticed that when the item of "Writing" omitted the Cronbach's alpha value improved, and the internal consistency reliability reached the acceptable level both for test (0.72) and retest (0.73). This suggests that the "Writing" might be redundant to the MASTp. The improvement of the

internal consistency reliability with removing "Writing" indicates that the items of MASTp are not homogeneous and thus not measuring the same concept.[10] A further study with larger sample size is needed to confirm the results.

Intra-rater reliability

The intra-rater reliability of the MASTp was excellent. A study to adapt the MAST to the Telugu language observed good inter-rater reliability and high test-retest reliability (r = 0.993).[9] Kostalova et al. evaluated the inter-rater reliability of the Czech language version of the MAST and found acceptable inter-rater reliability of MAST total score.[7] In another study to validate the MAST into Spanish language in patients with stroke, Authors reported excellent inter-observer reliability and test-retest reliability (ICC = 0.99).[8] In our study, the period between the two administrations was 1 week to prevent recall and to ensure that clinical changes have not occurred.[10] Excellent intra-rater reliability observed for the total MASTp as well as both the expressive and receptive indexes indicates that when the MASTp administered repeatedly by an examiner in stable stroke patients with aphasia can provide similar scores over time. Intra-rater reliability was not assessed for the original English and culturally adapted versions of the MAST.[5,7-9]

Factor analysis

Unidimensionality of a scale must be investigated with factor analysis to get an interpretable meaning for an internal consistency reliability statistic.[12] In the current study, it was found that the MASTp was not unidimentional, and the factor analysis yielded 3-factor solution (Expressive, Receptive, and Writing). It was noted that the "Writing" item was appeared as an independent factor. The performance on the "Writing" item was poor in this sample of patients with post-stroke aphasia compared to the healthy subjects. The reason could be that the "Writing to dictation" requires intact left hemisphere that is dominant for this task for right handed people. In the current study, 90% of patients were right handed, and "Writing to Dictation" requires optimized motor performance of the hand. Hemiplegia or muscle paralysis on one side of the body is a common outcome after stroke, and voluntary movements need commands from the cortex to be transmitted to the peripheral neuromuscular system via the descending tracts. It has been documented that the voluntary activation is impaired bilaterally in the upper limb after stroke, and cortical connectivity on the more affected side is reduced.[13] The Cronbach's alpha for MASTp improved when the "Writing" item was removed; this finding together with the results of factor structure analysis suggests that the "Writing" item is redundant for the MASTp. Further study is suggested to clarify the current results. The "Object recognition" was loaded on all the 3 extracted factors. To clarify to which factor that the "Object recognition" is related, we conducted internal consistency reliability analysis for all the extracted factors. Cronbach's alpha reached the acceptable level only for the first factor (Expressive subscale). Factor analysis for the first factor reduced the original 9-item scale to an 6-item scale and extracted 1 factor demonstrating the 6-item MASTp as a unidimensional screening instrument for patients with post-stroke aphasia. This finding indicates that when using MASTp for screening of patients with post-stroke aphasia, the 3 items of original MAST can be redundant (Writing, Yes/No responses, following instructions). The unidimensionality of the 6-item MASTp is an indication of construct validity. Factor analysis has not been performed to identify the possible latent subscales in previous studies with English and adapted versions of the MAST.[5,7-9]

Limitations

There are some limitations of the study, which have to be addressed. First, sample size of patients was small. At least 50 patients must be included in validation studies. Other psychometric characteristics such as inter-rater reliability, diagnostic accuracy of sensitivity and specificity, construct validity, responsiveness and changes over time with the MASTp will be necessary to be determined in future investigations.

Conclusion

The Persian version of the MAST is a valid and reliable instrument to assess patients with post-stroke aphasia. The MASTp demonstrated face validity, content validity, discriminative validity, and intra-rater reliability. The psychometric properties of the MASTp suggest that this brief screening measure is appropriate for clinical and research studies in Persian speaking countries.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Iranian Journal of Neurology

Neurological Images

Iran J Neurol 2015; 14(2): 108-109

Unilateral cortical hyperintensity in diffusion-weighted MRI; New criteria for early sporadic Creutzfeldt-Jakob disease

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Keywords
Creutzfeldt-Jakob Disease, Magnetic Resonance Imaging, Electroencephalography

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rapidly progressive fatal prion disease. The proposed diagnostic criteria[1,2] are not sufficiently helpful for diagnosis in early stages of the disorder.

A 69-year-old female was brought to our hospital with a history of 3 weeks left side hemiparesis and the progressive loss of speech and attention. She was awake and mute without any purposeful behavior. Left side hemiplegia, hyperreflexia and Babinski sign was also detected. Brain magnetic resonance imaging (MRI) revealed asymmetric diffuse gyriform hyperintensity in right cortical area and fine signal changes in right caudate and putamen in diffusion-weighted imaging (DWI) sequence without any significant involvement in left side and no signal abnormality in other sequences (Figure 1).

Laboratory tests, including blood count, glucose, renal, hepatic and thyroid function tests, electrolytes, sedimentation rate, B12 and folic acid levels were normal. Human T-lymphotropic virus 1 (HTLV1) and 2, human immunodeficiency virus (HIV) and paraneoplastic antibodies, anti-thyroid peroxidase, anti-thyroglobulin and venereal disease research laboratory tests were negative. A repeated MRI 7 days later revealed fine hyperintense signals in left inferior frontal, angular and postcentral gyri on DWI sequences, although the signal changes were still clearly asymmetric, and no abnormality was present in other sequences. At fifteenth day of admission, she experienced myoclonic jerks and 2 days later, the typical pattern of periodic sharp wave complexes was appeared in electroencephalography.

Pathological study of right frontal cortical biopsy disclosed neuronal loss and spongiform changes (Figure 2).

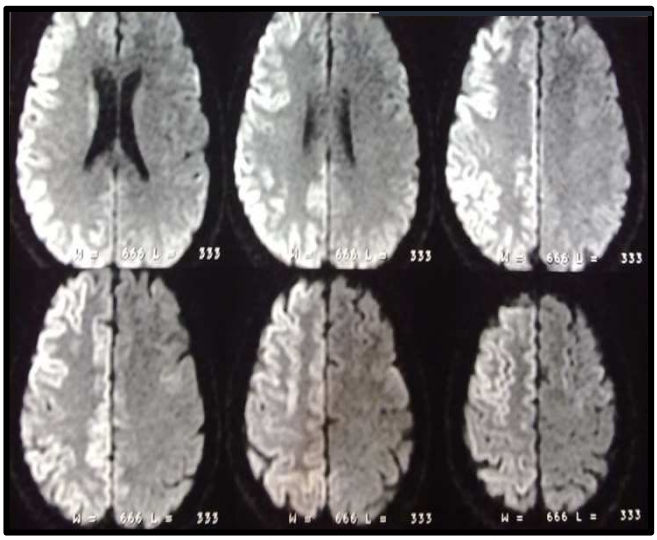

Figure 1. The brain magnetic resonance imaging diffusion (weighted imaging) shows right side diffuse cortical hyperintensity

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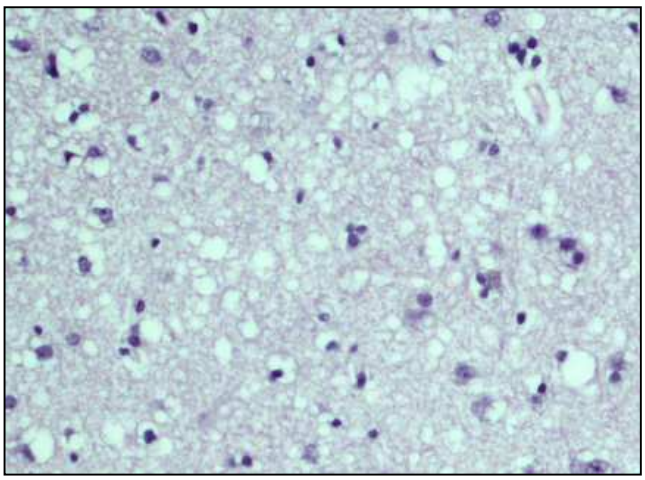

Figure 2. Spongiform changes in right frontal cortical biopsy (hematoxylin and eosin stain)

Based on World Health Organization (WHO) 1998 revised criteria,[1] the diagnosis of probable sCJD confirms for our case and according to University of California, San Francisco (UCSF) 2005 and 2010 proposal of MRI criteria,[2] the MRI is compatible with definite CJD. However, precentral and postcentral gyral involvement and the unilateral cortical hyperintensity merely in DWI sequences, even in late stages of the disease have made our case unique in the literature. Presence of unilateral gyral hyperintensity in DWI sequence should be considered as early imaging criteria for sCJD.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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Iranian Journal of Neurology

Neurological Image

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Cyclic headaches in β-thalassemia intermedia case presenting as moyamoya syndrome

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Keywords
Headache, B-Thalassemia, Moyamoya, Cerebrovascular

Moyamoya disease is a cerebrovascular disorder with unknown cause characterized by the occlusion of the bilateral internal carotid arteries (ICA) and proximal segments of ICA.[1,2] On the other hand, moyamoya syndrome (MMS) is a rare form of this condition with underlying several pathologies including hematologic disorders, congenital syndromes, vascular malformations or vasculitis after irradiation, infections, and head trauma.[1]

The symptoms of MMS are headache, seizure, and recurrent transient ischemic attacks. MMS frequently presents with the symptoms of occlusion in children, whereas in adults, the symptoms are mainly due to subarachnoid hemorrhage.[3] The collateral vessels which is a compensatory mechanism occur as a result of obstruction that resemble puff of smoke on digital subtraction angiography and magnetic resonance angiography (MRA).[1,2]

A β-thalassemia intermedia patient of 51 with cyclic headaches was investigated using MR imaging which demonstrated focal chronic infarcts and on MRA bilateral ICA were occluded at the level of petrous segment whereas vascular supply was from external carotid artery and by collateral development. At the posterior circulation, microangiopathic collaterals at thalamus and basal ganglia were detected originating from basilar artery and its branches (Figure 1a-c).

Few cases of MMS with β-thalassemia reported were under the age of 20 in our research of the literature. Among hemoglobinopathies, β-thalassemia intermedia is very rarely associated with MMS however, sickle cell anemia is the most frequent type.[4] Although silent strokes could be detected in the young patients, with the progression of moyamoya vessels we did not find any ischemic changes in our 51-year-old patient on MRI.[5] This β-thalassemia intermedia patient is an exclusive MMS case with the findings of cerebrovascular occlusion and collateral vessels demonstrated on MRA which is the preferred noninvasive imaging modality in the diagnosis.

Conflict of Interests

The author declares no conflict of interest in this study.

Acknowledgments

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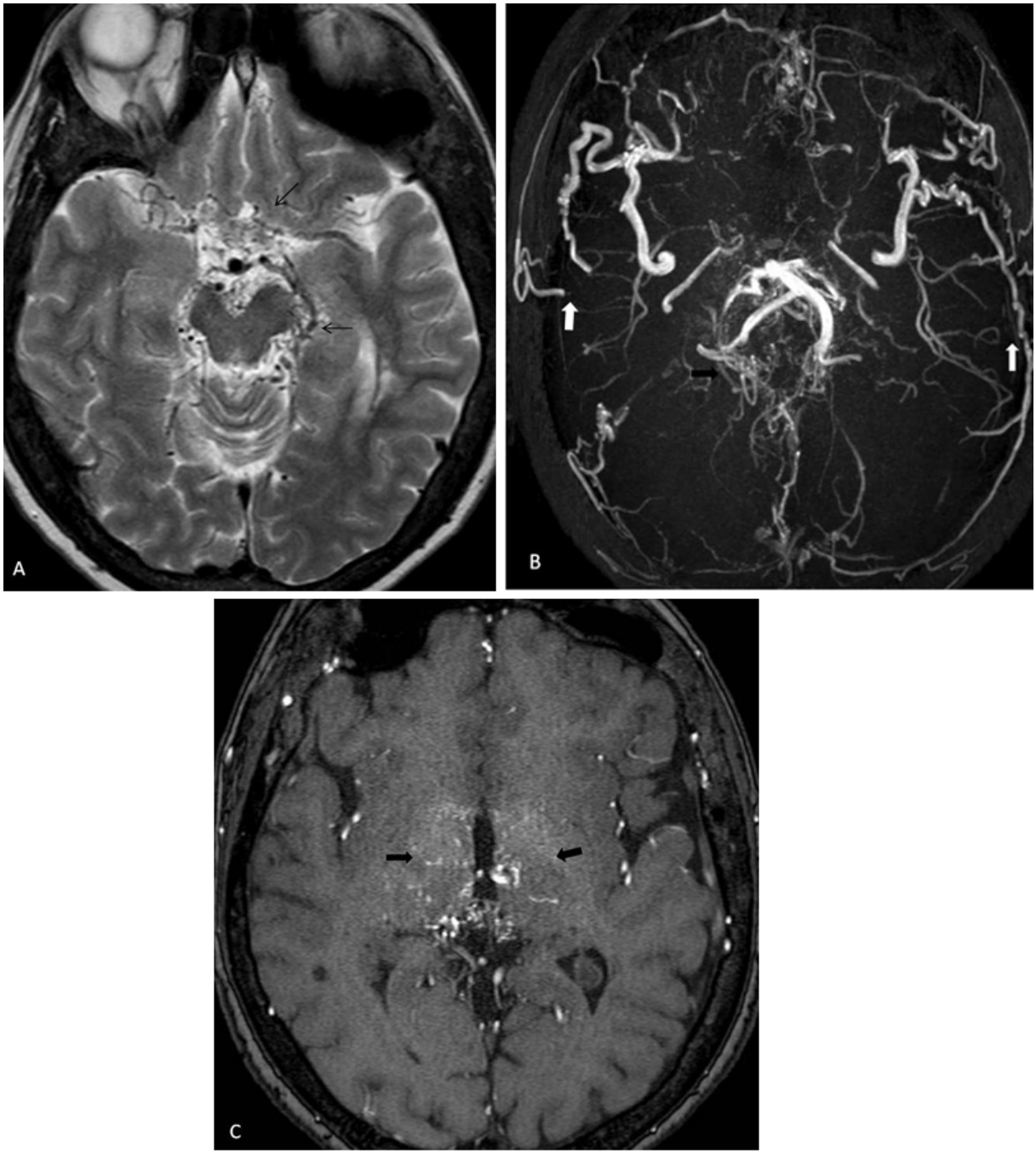

Figure 1. (a) Axial T2-weighted magnetic resonance (MR) image shows microvascular collaterals at the level of perimesencephalic cisterns and vascular supply to anterior cerebral artery and middle cerebral artery at the anterior circulation (arrows). (b) Axial MR angiography image reveals microangiopathic collaterals at the posterior circulation originating from basilar artery and its branches (black arrow). There was vascular supply from an external carotid artery by collateral development (white arrow) and bilateral internal carotid arteries occlusion at the petrous segment. (c) Axial MR angiography image demonstrates microangiopathic collaterals resembling puff of smoke (moyamoya vessels) at thalamus and basal ganglia (arrows).

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Iranian Journal of Neurology

Letter to Editor

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Intracranial hypertension and cerebellar symptoms due to Lhermitte-Duclos disease

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Keywords
Lhermitte-Duclos Disease, Dysplastic Gangliocytoma cerebellum, Magnetic Resonance Imaging

Lhermitte-Duclos disease (LDD) is a rare pathologic condition, which was first described in 1920 by Giorgianni et al.[1] This is a slowly growing tumor of the cerebellum, composed of granule Purkinje and glia cells. It evolves in a disorganized fashion and the cerebellum loses its normal architecture with no clear plane from normally structured cerebellar tissue.[2-5] We report a case of a young woman with hydrocephalus and cerebellar symptoms caused by a rare occurrence of dysplastic Gangliocytoma arising within the left cerebellar hemisphere and vermis.

A 19-year-old woman with uneventful medical history was admitted in March 2012 with a 6 months history of vertigo and the posterior headache and 2 months history of nausea, vomiting, and visual disturbance. On admission, the neurologic examination revealed edema in fundoscopy and an unsteady tandem gait with a tendency to fall to the left side. Other neurologic exams were normal. Computed tomography (CT) scan showed a hypodense area in the left cerebellar hemisphere and vermis with no calcification, reduced fourth ventricle, and obstructive hydrocephalus. Magnetic resonance imaging (MRI) with and without contrast revealed an irregular lesion, hypo signal on T1-weighted image and high signal on T2-weighted image with no enhancement (Figure 1). The patient was submitted to surgery through a left sub occipital craniotomy and a gross total resection of the tumor and subtotal left side of the cerebellum. Upon opening the dura matter a very large, wide, gray-colored cerebellar folia were visualized expanding throughout the left cerebellum and vermis. The patient recovered uneventfully with resolution of the neurologic symptoms. She was discharged from hospital 7 days after the surgery. The surgical piece showed enlargement and hypertrophy of the cerebellar cortex and folia. On histologic examination, the internal granular cell layer completely replaced the Purkinje cell. Normal Purkinje cell were absent (Figure 2). The final diagnosis was of dysplastic gangliocytoma of the cerebellum, World Health Organization (WHO) Grade 1.

LDD is a rare condition, usually affecting patients aged 30-50 years. There is no sex preference.[4] Around 220 LDD cases, have been reported in the literature.[1,5] This is a slowly evolving lesion that forms a mass. It is composed of granule, Purkinje and glia cell. LDD was found associated with phakomatosis, Cowden syndrome, systemic hamartomas and malignant neoplastic lesions of the breast, thyroid and genito urinary tract.[2,3] Imaging plays an important role. Hypo attenuated on unenhanced CT scan. No appreciable enhancement is seen on contrast-enhanced CT image.[1]

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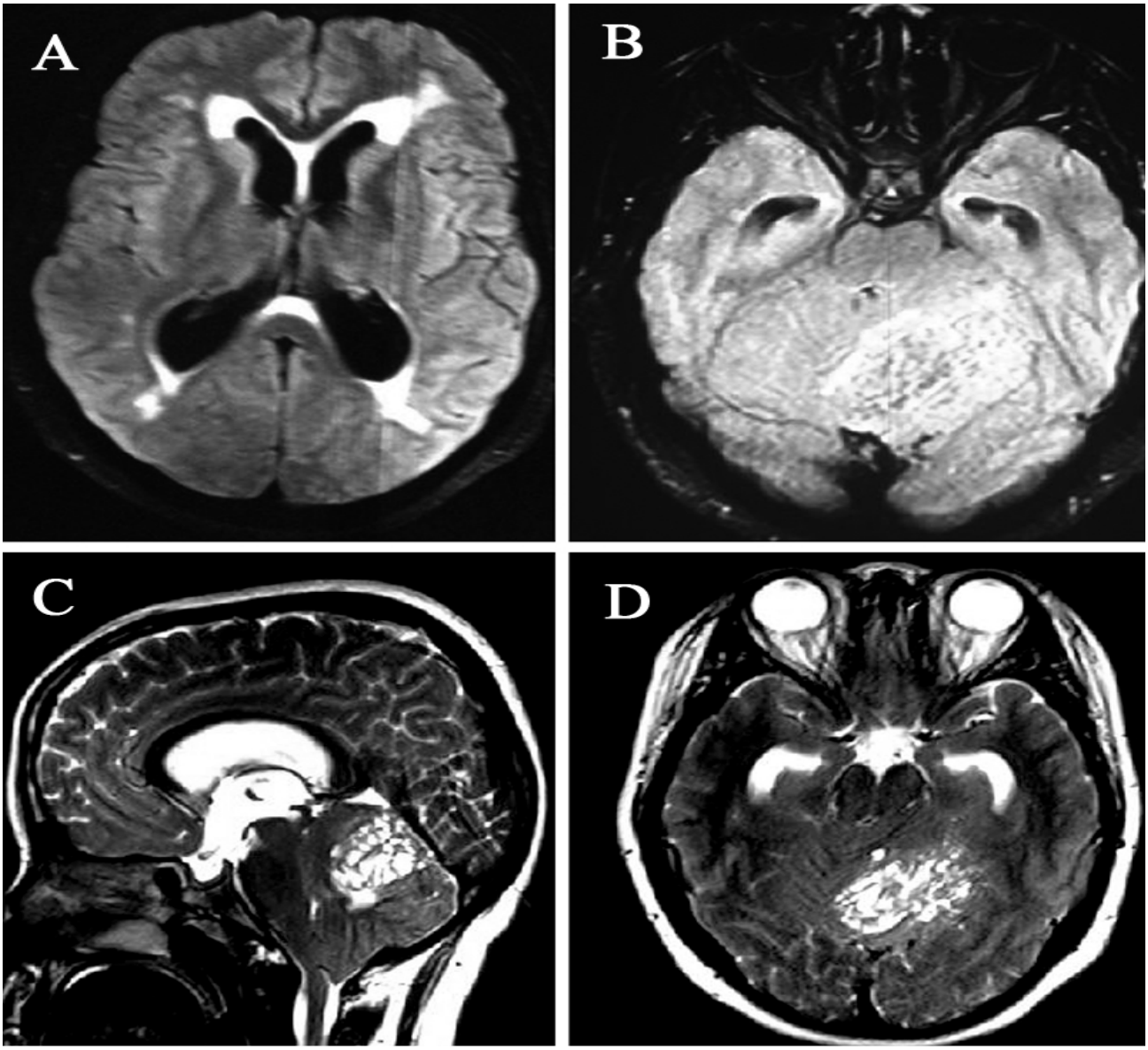

Figure 1. Axial T2-fluid-attenuated inversion recovery magnetic resonance imaging showing hypersignal mass in the left cerebellar hemisphere (A) and hydrocephalus due to compression of forth ventricle (B). T2-sequence MRI sagittal and axial sections showing the characteristic "tiger stripe" appearance of this hamartomatous tumor in the left cerebellar hemisphere (C and D)

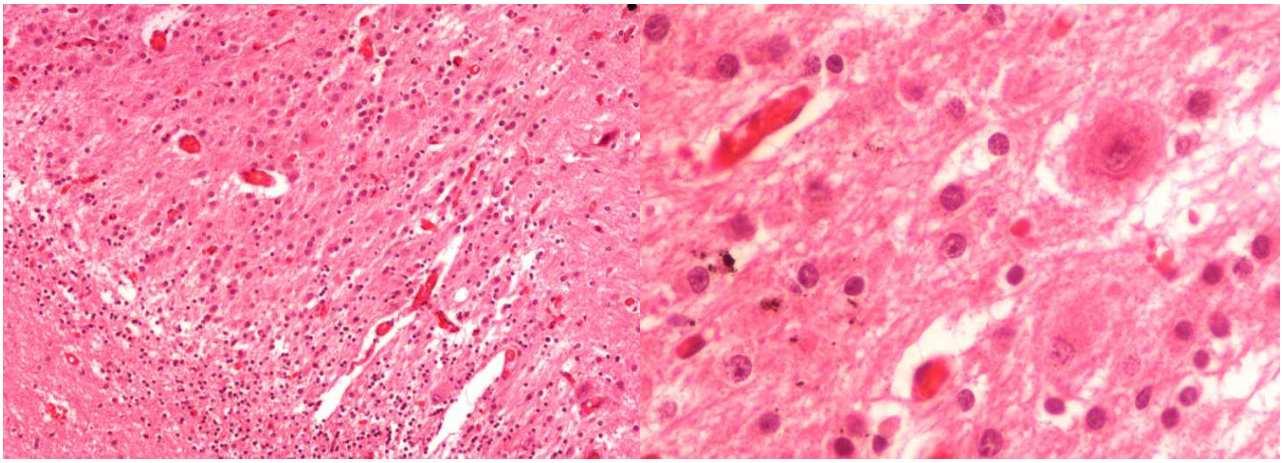

Figure 2. In histologic examination the internal granular cell layer was completely replaced Purkinj's cell

The appearance on MRI imaging is highly characteristic, showing tiger stripe appearance. LDD should be excised if symptomatic.[2]

In this case report, we presented a patient with dysplastic gangliocytoma of the cerebellum both as hemisphere and vermis with symptoms of cerebellum and raised intracranial pressure. The diagnosis of this rare entity should be considered in any young, and middle age adult presenting with signs of intracranial hypertension and cerebellar combined with characteristic radiologic features; however MRI cannot replace the histopathologic diagnosis. Surgery appears to be the only efficient treatment if symptomatic. Long-term follow up is advisable in order to reduce the probability of occasional symptomatic recurrence and to identify the possible sign of Cowden syndrome, which carries a risk of developing malignancy.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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Letter to Editor

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Coexistence of Ehlers-Danlos syndrome and multiple sclerosis

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Keywords
Ehlers-Danlos Syndrome, Multiple Sclerosis, Coexistence, Neurological Manifestations

A 26-year-old male patient was admitted to our outpatient clinic with complaints of numbness and weakness in his left arm and leg. These complaints had started about 10 days ago and were continuing. From his personal history, it was found out that he had been followed up with the diagnosis of Ehlers-Danlos syndrome (EDS) hypermobile tip for 10 years, and that he had had low vision in his left eye lasting for 15 days, but he had not consulted a physician for this complaint. After 1 year had passed from the complaint of blurred vision, he had had a weakness in his right arm and loss of balance, but again he had not sought medical advice. From his familial history, it was found out that his paternal grandmother, father, aunt, cousins, and younger sister were being followed up with the diagnosis of EDS. General physical examination revealed no pathological features except for several atrophic cicatrices on the face, back, and arms and hyperflexibility of the joints (Figure 1). No cardiologic or ophthalmologic involvement was detected in terms of EDS. Neurological examination revealed that the patient is conscious, cooperated and oriented. His cranial nerve examinations were normal. His muscle strength was 3/5 in the upper left limb, 4/5 in the lower left limb, and 5/5 in the upper and lower right limbs. Left-sided hemihypoesthesia including the face, and globally hyperactive deep tendon reflexes were seen. The patient had bilateral extensor plantar reflexes and reduced abdominal cutaneous reflex on the left side. His cerebellar tests were normal, and no urinary or fecal incontinence. His cranial magnetic resonance imaging (MRI) revealed several ovoid-shaped periventricular lesions located perpendicular to the ventricle, which is consistent with demyelinating plaques (Figure 2). His cervical MRI revealed several centrally-located, ovoid-shaped lesions aligned with C2-C3-C4 segments, which are consistent with demyelinating plaques. His thoracic MRI was considered to be normal. For the patient, who had blurred vision, a visual evoked potential (VEP) test was performed. p100 wave latency was lengthened for both VEP systems (right: 136, left: 132). Brainstem auditory evoked potential examination was normal. ANA, anti-dsDNA, Anti-cardiolipin IgG and IM, Homocysteine, Lupus Anticoagulant, Protein C, Protein S, Prothrombin II gene mutation, Factor 5 leiden mutation investigations revealed no significant pathologies. The patient was evaluated according to McDonald's criteria, an acute multiple sclerosis (MS) episode was considered, and pulse steroid therapy was prescribed for 10 days. Following the treatment, his symptoms at admission were recovered. He is now being followed up by our outpatient clinic.

EDS is a rare, inherited disease characterized by disturbed collagen synthesis and enzyme dysfunction. Central nervous system involvements are remarkable, mainly in vascular type EDS.[1] However, only one study could be identified that examined the potential association with MS, and it was emphasized in this study that MS prevalence is 10 to 11-fold greater in EDS patients compared to general population.[2]

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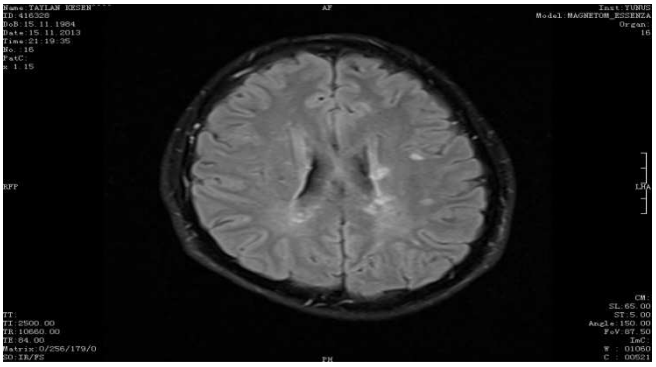

Figure 1. General physical examination revealed hyperflexibility of the joints

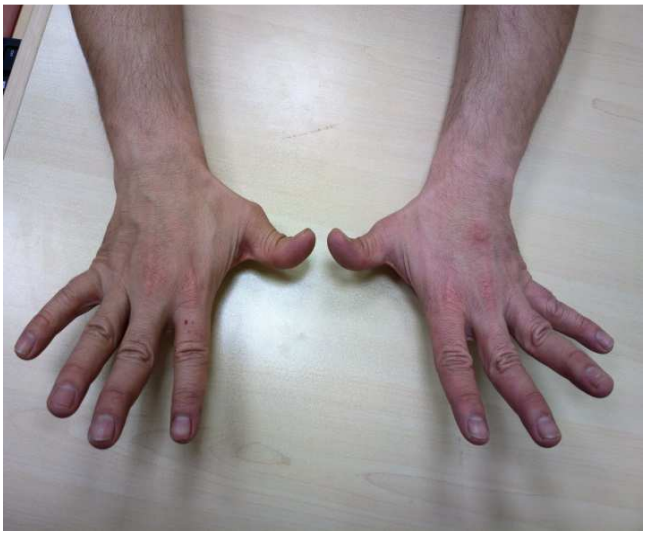

Figure 2. Hyperintense, ovoid-shaped, periventricular lesions located perpendicular to the ventricle

ECM is a structure that encloses and supports the cells. It has three major components. Structural proteins (mainly collagen), proteoglycan and hyaluronan, and specialized multi-adhesive proteins. ECM proteins were observed to involve in central nervous system inflammation and demyelination.[3] It is thought that in EDS, there are mutations in the genes coding ECM proteins. These are cells which ensure cell migration and organization, and EDS is seen when a synthesis defect occurs in their synthesis.[4,5] ECM proteins are produced by oligodendrocytes and astrocytes in the central nervous system, and were observed to be associated with the astroglial response in the MS lesions. According to a hypothesis, it can show effects on connective tissues and at the vascular level. Changes in the ECM proteins such as collagen and tenascin which are present in the blood vessel walls can cause myelin destruction by increasing the migration of the immune cells to the central nervous system. According to another hypothesis, MS-EDS association may be due to a suspicious gene. There may be a polygenic effect in MS, and one of these mutations may cause EDS. There are some points to be considered in the treatment of MS and EDS. These patients, who undergo physiotherapy due to MS, strong passive exercises can trigger pain or cause joint dislocations. Neck extension should be avoided to prevent carotid artery dissection.[2]

In our case, we discuss a rare association in terms of their underlying mechanisms and of the points to be considered in the treatment.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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