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Aim and Scope

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 covering the scope of the journal will be evaluated by properly competent referees.

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Original Article
Review Article
Case Report
Short Communication
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Letters to Editor
Neurological Images
Neurological Videos
Iranian Neurological Events
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Details

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

Case reports: Case reports will be accepted only as Letter to the Editor.

Short communications: The maximum word number of short communications should be below 1200 words with maximum one table or figure and 10 references. The manuscript should be structured including introduction, materials and methods, results, discussion, and conclusion with a structured abstracts as original articles.

Neurological images or videos: Interesting cases as
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The text should not be formatted. 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.

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   - 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.
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3. **Page three and subsequent pages** of the original paper and short communication should include the text arranged in the following order (for other manuscript 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.
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5. **Conclusions:** These should be brief, follow directly from results presented above and correspond to the aim of the paper outlined in the introduction.

6. **Acknowledgements:** Should comprise information on sources of funding (grant numbers); acknowledgements should concern those who made a significant contribution to the paper, but who did not meet the criteria to be listed as authors.

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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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The efficacy of the ketogenic diet on motor functions in Parkinson’s disease: A rat model

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Keywords
Parkinson’s Disease; Pramipexole; Ketogenic Diet

Abstract
Background: The ketogenic diet (KD), high in fat and low in carbohydrate and protein, provides sufficient protein but insufficient carbohydrates for all the metabolic needs of the body. KD has been known as a therapeutic manner intractable epilepsy. In recent years, the effectiveness of KD drew attention to the treatment of some other disorders such as Parkinson’s disease (PD). This study has evaluated the efficacy of KD on motor function in Parkinsonian model of rat and compared it with pramipexole.

Methods: A total of 56 male Wistar rats weighing 200-240 g between 12 and 14 weeks of age were randomized in seven 8-rat groups as follows: Control group; sham-operated group; KD group; Parkinsonian control group; KD-Parkinsonian group; pramipexole-Parkinsonian group; and KD-pramipexole-Parkinsonian group. The results of bar test, beam traversal task test, and cylinder task test were compared between the groups.

Results: The mean number of ketone bodies had increased significantly in the rats blood after KD. Regarding the results of the triad tests, no statistically significant difference was found between the controls and the sham-operated group. Among the Parkinsonian rats, better results were found in KD groups compared to the non-KD group. The KD enhanced the effect of pramipexole for motor function but did not reach a statistically significant level.

Conclusion: The KD reinforced the motor function in Parkinsonian rats in our study. When the diet was combined with pramipexole, the effectiveness of the drug increased in enhancing motor function.

Introduction
Parkinson’s disease (PD) is the second most common neurodegenerative disease that affects almost 1% of individuals over 60 years of age. First described in 1920,1 the ketogenic diet (KD) comprises fat (80-90%), carbohydrate, and protein and metabolically induces a fasting-like condition.2,3 Some studies have shown the usefulness of this diet in PD.2,4,5 Studies on experimental models of Modeling Parkinson’s disease in primates (MPTP)-induced Parkinsonism have shown that a restriction in glucose intake bolsters resistance of the cells located in the substantia nigra against neurotoxic effects of MPTP and prevents the progression of symptoms.
symptomatic treatment of PD in recent years. Noting dopamine receptors, which has been used for agonist with high affinity toward D2 and D3 agonist effects and binding to its receptor. PD motor symptoms through exerting dopamine in the substantia nigra, this medication can ameliorate cerebral dopamine levels after degradation of neurons in the mechanism of PD in which there is a decrease in oxidative stress, the prevention of the excitotoxicity due to neurotransmission escalation of excitatory amino acids, and fending off inflammatory processes and apoptosis.

Pramipexole is a non-ergo dopamine receptor agonist with high affinity toward D2 and D3 dopamine receptors, which has been used for symptomatic treatment of PD in recent years. Noting the mechanism of PD in which there is a decrease in cerebral dopamine levels after degredation of neurons in the substantia nigra, this medication can ameliorate PD motor symptoms through exerting dopamine agonist effects and binding to its receptor.

Because available treatments in PD are usually along with diminished symptoms without affecting progression of the disease and at the same time the potential of causing motor fluctuations, it is essential to use new therapeutic strategies in this regard.

Because there is no available study regarding the effects of the KD on motor symptoms in PD using rat model, this study seeks to examine the effect of this regimen on motor symptoms in rats with 6-hydroxydopamine (6-OHDA)-induced PD and to evaluate the efficacy of this regimen alone or in combination with pramipexole.

Materials and Methods

In this experimental study, a total of 56 Wistar rats weighing 200-240 g and aged 12-14 weeks were randomized in seven 8-rat groups including controls on a regular diet (negative controls), rats with 6-OHDA-induced PD on a regular diet, rats with 6-OHDA-induced PD on the KD for 25 days, rats with 6-OHDA-induced PD on a regular diet and pramipexole for 14 days, and rats with 6-OHDA-induced PD on the KD combined with pramipexole for 14 days.

This study was performed at Tabriz Neuroscience Laboratory (Iran) from July 2014 to September 2015. The exclusion criteria were an occurrence of any disease during the study period; the expiration of the rats due to intracerebral injections, and no documentation of ketonemia in rats after being on consecutive days of the KD.

This research was conducted in accordance with the latest ethical regulations for laboratory animal studies issued by Tabriz University of Medical Sciences in terms of providing an appropriate environment for animals, free access to water, and using painless stereotaxic injections.

Rats were first underwent a period of training for a standard bar test, beam traversal task test, and cylinder task test and then randomized in the aforementioned groups. To induce ketonemia, a KD containing medium chain triglycerides (MCTs) oils accounting for a total of 50% of the required calories plus a regular diet for the remaining calories was administered. The MCTs oil was administered orally through standard gavage feeding tubes.

To ensure induced ketonemia, serum levels of beta-hydroxybutyrate (BHB), as an index for the production of ketone bodies, were measured in both groups including rats on the KD and regular diets. In case of documenting a statistically significant difference between the two groups, an induced ketonemia was confirmed in rats on the KD.

In the present experiment, serum levels of ketone bodies were measured using biochemical kits of BHB at baseline and on the day 14 after being on the KD.

To induce experimental Parkinsonism, 11 days after the commencement of the KD and regular diets an intranigral injection of 6-OHDA (12 µg in 2 µl normal saline and 0.2% ascorbic acid) was carried out. 30 minutes before, this injection desipramine (25 mg/kg) was injected into the peritoneal cavity to preclude a possible reabsorption of 6-OHDA back into the noradrenergic neurons and subsequent injuries. In the sham surgical group, 6-OHDA was replaced with normal saline.

Finally, 14 days after induction of Parkinsonism the rats underwent a standard bar test, beam traversal task test, and cylinder task test.

Bar test
As illustrated in figure 1 to perform a standard bar test, the forearms of the animal were placed on a bar (9 mm in diameter) fixed at the height of 9 cm away from the platform of the testing device. The duration of maintaining this position (catalepsy time) was documented. In case of any exploratory head movements or displacement of one or both forearms, the test was considered terminated.

Beam traversal task test
As illustrated in figure 2, 5 cm wide and 1 m long wooden bridge fixed 50 cm above the ground was used. The animal was placed on one end of the bridge and released. The time needed for total crossing the bridge was documented.

Cylinder task test
As illustrated in figure 3, an animal was placed...
inside a seven-through glass cylinder, and the total number of forearm contacts with the wall was documented within a 10-minute period. Accordingly, the final score was calculated using the following formula:

\[ \text{Score} = 100 \times \left( \frac{\text{Number of forearm contacts on the lesion side} + \frac{1}{2} \text{of total forearm contacts}}{\text{total forearm contacts}} \right) \]

The KD was started from the 1st day of experiment and pramipexole (0.3 mg/kg once a day) was administered on the day 12 for 14 consecutive days in relevant groups.

The data were presented as mean ± standard error (SE) of the mean. The SPSS software (version 16, SPSS Inc., Chicago, IL, USA) was used. The one-way ANOVA test coupled with the Tukey post-hoc analysis was employed for comparisons. Levels of serum ketone bodies were compared between groups using the Wilcoxon test. A P < 0.050 was considered statistically significant.

**Results**

The mean level of serum ketone bodies in the group on the KD was 0.25 ± 0.03 mmol/L (range: 0.21-0.28) at baseline and 1.83 ± 0.17 mmol/L (range: 1.60-2.10) on the day 14. According to the results of Wilcoxon test, the mean serum level of ketone bodies increased significantly on the day 14 compared to that at baseline (P = 0.010).

**Results of the bar test (catalepsy time)**

Results of the bar test in different groups were as follows (Figure 4): The control group on a regular diet: 15.00 ± 1.18 seconds (range: 10-20); the surgical sham group: 18.75 ± 1.15 seconds (range: 15-25); the control group on the KD: 15.88 ± 1.30 seconds (range: 10-21); the PD group on a regular diet: 103.13 ± 2.65 seconds (range: 95-115); the PD group on the KD: 80.63 ± 1.21 seconds (range: 75-85); the PD group on a diet with pramipexole: 73.63 ± 1.87 seconds (range: 67-80); and the PD group on the KD with pramipexole: 72.50 ± 2.17 seconds (range: 65-80).

Comparing the controls on a regular diet with the sham surgical group showed no significant difference in terms of the mean catalepsy time (P = 0.730). A similar finding was found in the comparison between the controls on a regular diet and the controls on the KD (P = 0.990). Comparing unaffected groups with PD groups revealed that the mean catalepsy time was significantly shorter in the former (P < 0.001 for all paired comparisons). Similarly, the mean catalepsy time was significantly longer in the PD group on the KD compared to that in the remaining three PD groups (P < 0.001 for all paired comparisons). Comparing the PD group on the KD with the PD group on a regular diet with pramipexole did not show a statistically significant difference between the two groups in terms of the mean catalepsy time (P = 0.990). The PD group on the KD, however, had significantly longer mean catalepsy time than the PD group on the KD with pramipexole (P = 0.030). Finally, comparing the PD group on a regular diet with pramipexole with the PD group on the KD with pramipexole did not show a statistically significant difference between the two groups in terms of the mean catalepsy time (P = 0.990).
Results of the beam traversal task test

Results of the beam traversal task test in different groups were as follows (Figure 5): The control group on a regular diet: 3.61 ± 0.17 seconds (range: 3-4); the sham surgical group: 3.76 ± 0.13 seconds (range: 3-4); the control group on the KD: 3.64 ± 0.12 seconds (range: 3-4); the PD group on a regular diet: 6.25 ± 0.26 seconds (range: 5-8); the PD group on the KD: 5.41 ± 0.32 seconds (range: 4-7); the PD group on a diet with pramipexole: 5.08 ± 0.10 seconds (range: 5-6); and the PD group on the KD with pramipexole: 4.83 ± 0.06 seconds (range: 4.5-5).

There was not a significant difference between the controls on a regular diet and the sham surgical group in terms of the mean results of the beam traversal task test (P = 0.990); nor in the comparison between the controls on a regular diet and the controls on the KD (P = 0.990). Comparing unaffected and PD groups, however, showed that the mean results of the beam traversal task test were significantly lower in the former (P < 0.001 for all paired comparisons). Comparing the PD group on a regular diet with the three remaining PD groups showed that the mean results of the beam traversal task test were significantly higher in the former (P = 0.040 in comparison with the PD group on the KD and P < 0.001 for the other two comparisons). Comparing the PD group on the KD and the PD group on a regular diet with pramipexole showed no significant difference between the two groups as to the results of the beam traversal task test (P = 0.860). A similar finding was found in comparisons between the PD group on the KD and the PD group on the KD with pramipexole (P = 0.300), and between the PD group on a regular diet with pramipexole and the PD group on the KD with pramipexole (P = 0.960).
Results of the cylinder task test

Results of the cylinder task test in different groups are as follows (Figure 6): the control group on a regular diet: 48.38 ± 1.50% (range: 42-55); the sham surgical group: 50.38 ± 1.48% (range: 45-56); the control group on the KD: 49.88 ± 1.68% (range: 42-56); the PD group on a regular diet: 71.63 ± 1.86% (range: 62-80); the PD group on the KD: 64.13 ± 1.53% (range: 58-70); the PD group on a diet with pramipexole: 60.63 ± 1.10% (range: 57-65); and the PD group on the KD with pramipexole: 58.00 ± 1.48% (range: 52-65). Comparing the controls on a regular diet and the sham surgical group showed no significant difference between the two groups in terms of the mean results of the cylinder task test (P = 0.970). Similarly, no significant difference was found in the comparison between the controls on a regular diet and the controls on the KD (P = 0.990). Comparing the unaffected and PD groups showed significantly lower mean results of the cylinder task test in the former (P < 0.001 for all paired comparisons). In addition, comparing the PD group on a regular diet with the remaining three PD groups showed significantly lower mean results of the cylinder task test in the former (P = 0.020 in comparison with the PD group on the KD and P < 0.001 for the other two comparisons). There was no significant difference between the PD group on the KD and the PD group on a regular diet and pramipexole in terms of the results of the cylinder task test (P = 0.670). There was also no significant difference between the PD group on the KD and the PD group on the KD and pramipexole in this regard (P = 0.090). Finally, there was no significant difference between the PD group on a regular diet with pramipexole and the PD group on the KD with pramipexole regarding the results of the cylinder task test (P = 0.890).

Discussion

Nutritional and metabolic therapeutic strategies have been tried in a wide range of neurologic diseases such as epilepsy, headache, neurotrauma, Alzheimer’s disease, sleep disorders, brain cancer, autism, pain, multiple sclerosis (MS), and PD. The related incentive possibly originates from the ineffectiveness of available pharmacologic treatments in many of such diseases, as well as a general inclination toward more natural products.\textsuperscript{14}

The present experimental study on rats showed that the KD is significantly effective in promoting motor functions in PD animals and at the same time, it may enhance the therapeutic effects of concomitantly administered pramipexole, albeit in an insignificant fashion.

In accordance with these findings, using a standard scale, Vanitallie et al.\textsuperscript{6} showed that the KD was able to exert beneficial effects in 5 out of 7 PD patients.

One of the major limitations in the current study was using a small sample size that was unable to exclude the placebo effect. In a study by Tieu et al.,\textsuperscript{5} the injection of BHB acid also effectively prevented MTPT-induced neurodegenerative and aging processes in dopaminergic cells located in rat brain.

In another animal model used by Cheng et al.\textsuperscript{15} the employment of ketone bodies protected dopaminergic neurons located in the substantia nigra and other critical brain areas affected in PD. Furthermore, these ketone bodies may serve as an energy source for dopaminergic cells.

The KD has already been found to exert beneficial effects on PD-related motor disorders in rats and mice, as well as in recent human clinical trials. Research on the KD in neurodegenerative diseases such as PD is developing rapidly. For instance, Vanitallie et al.\textsuperscript{6} showed that the KD was significantly effective in promoting motor functions in PD animals and at the same time, it may enhance therapeutic effects of concomitantly administered pramipexole, albeit in an insignificant fashion.

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nigra against 6-OHDA-induced neurotoxicity. In a study by Yang and Cheng, the anti-inflammatory effects of ketone bodies were confirmed using a model of MPTP-induced neurotoxicity.

In a similar experiment by Beckett et al. using a rat model of Alzheimer’s disease, in conformity with our findings the KD managed to significantly improve some aspects of motor functions. In this study, all aspects of motor functions of the examined animals were not influenced equally. Although the underlying cause of this finding is not clear, it seems that various muscular groups are affected unequally by the KD (for example the quadriceps muscles vs. the paw flexors).

In another series by Brownlow et al., there was also a considerable improvement in motor functions in Alzheimeric rats using the KD. Ruskin et al. also showed that the administration of the KD could increase motor capabilities of animals with induced Huntington’s disease (HD).

Although the exact neuroprotective property of the KD is not known, some hypotheses have been suggested. The two major aspects in treating with Huntington’s disease (HD).

Although the KD is an increase in the production rate of ketone bodies in the liver and a decrease in serum glucose levels. An increased level of ketone bodies is assumed to be related to fatty acid oxidation. Certain polyunsaturated fatty acids such as arachidonic acid (AA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) may regulate the stimulatory properties of the neural sheaths through inhibiting voltage-dependent calcium and sodium channels, decreasing inflammation and inducing mitochondrial uncoupling proteins that could lead to production of reactive oxygen species (ROS). Ketone bodies themselves may also bear neuroprotective properties.

This effect develops through increasing the levels of adenosine triphosphate and decreasing ROS production via enhancing nicotinamide adenine dinucleotide hydrogen (NADH) oxidation and preventing mitochondrial permeability change. Along with other enhanced bioenergetics pathways, ketone bodies are able to stimulate mitochondrial biogenesis and stabilize synaptic functions. The second major biochemical feature of ketone bodies is diminishing glycolytic flow. This condition is the main feature in calorie intake limitation that could elongate the life of various species including primates. It seems that the observed neuroprotective effect is due to a diminished incidence of the brain-derived neurotrophic factor and its principle receptor the tyrosine kinase B, an improved mitochondrial function, diminished oxidative stress, a compromised activity of pro-apoptotic factors, and the prevention of inflammatory mediators such as interleukins and tumor necrosis factor-alpha.

Possible mechanisms involved in the effectiveness of the KD in relieving PD symptoms could be summarized as follows:

- Providing an efficacious source of energy, which is capable of preventing local hypometabolism in the brain
- Diminished oxidative injury
- Increasing mitochondrial biogenesis pathways
- Exploiting ketone capacities to bypass a failure in the Complex I activity.

Noh et al. showed that one of principle mechanisms of the KD in preventing neurodegeneration was via impeding neural apoptosis by caspase-3.

The early pathophysiology of PD is an excitotoxic degeneration of the dopaminergic neurons located in the substantia nigra. On the basis of some findings, ketone bodies may bypass defects in mitochondrial Complex I activities, which are possibly involved in the pathogenesis of PD. Therefore, it seems that mitochondrial abnormalities play a pivotal role in this regard.

Kashiwaya et al. used an analog of heroin to destroy dopaminergic cells. The suggested mechanism involved in this process was the blockade of a mitochondrial NADH dehydrogenase multi-enzyme complex. Accordingly, much of previous studies on the role of the KD in PD have been focused on this aspect of the disease (i.e., mitochondrial abnormalities). For example, in a study by Kashiwaya et al. on an animal model of PD induced by MPTP, the administration of BHB reduced mitochondrial respiration cycle lesions, which are usually induced by the used toxin.

In a study by Kim et al. the protective effects of ketone bodies against mitochondrial respiratory complex lesions developed by inhibitors of complex I (rotenone) and II (exogenous 3-nitropropionic acid) were examined. They suggested their findings as potential neuroprotective mechanisms of ketone bodies in PD.

Nevertheless, the current study is one of the rare experiments that examine the effect of the KD on one aspect of PD in a rat model. The observed results are promising and could pave the way for further human studies. For instance, recently some commercial treatments have been available which are based on development and exacerbation of ketonemia such as a formulation using medium-chain triglycerides. It is not clear whether such treatments are effective against PD as much as they are against Alzheimer’s disease. Further studies are needed in this regard.

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Conclusion
According to the findings of the present study, since the KD is effective in improving motor function in PD rats further human studied are recommended in this regard.

Conflict of Interests
The authors declare no conflict of interest in this study.

Acknowledgments
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References
Musculoskeletal disorders are common in patients with hypothyroidism,\(^1\) and carpal tunnel syndrome (CTS) is the most common compression syndrome in hypothyroid patients: A cross-sectional study

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Keywords
Carpal Tunnel Syndrome; Ultrasonography; Hypothyroidism

Abstract
Background: Carpal tunnel syndrome (CTS) is a common peripheral entrapment neuropathy in patients with hypothyroid. The diagnosis of CTS is usually clinical and confirmed by electrodiagnostic (EDX) procedures. This study aimed to describe the diagnostic accuracy of high-resolution ultrasonography (US) as an alternative method to nerve conduction study (NCS) for the diagnosis of subclinical CTS in patients with hypothyroidism.

Methods: Between April 2013 and November 2014, from the patients with the diagnosis of hypothyroidism referring to the Institute of Endocrinology and Metabolism of Firoozgar Hospital, Tehran, Iran, those who met our inclusion criteria entered this cross-sectional study. The patients divided into two groups of subclinical CTS with the age- and gender-matched control group. US measurements of the median nerve cross-sectional area (CSA) in the CT inlet were compared with the NCS results as the gold standard diagnostic test.

Results: A total number of 152 wrists of 76 hypothyroid patients were examined in this study. The mean of median nerve CSA at the tunnel inlet was 9.96 ± 2.20 mm\(^2\) for the CTS group and 7.08 ± 1.38 mm\(^2\) for the control group (P < 0.05). 31 wrists (20.4%) were diagnosed as CTS using NCS while US diagnosed 19 wrists (12.5%) as CTS. Using receiver-operating-characteristics analysis, the sensitivity and specificity of US at the diagnosis of CTS were 45.0 and 95.8%, respectively, with a median nerve CSA cutoff point of 9.8 mm\(^2\). Positive and negative predictive values of US were 87.2 and 85.5%, respectively, with a test accuracy of 85.5%.

Conclusion: According to our findings, US has an acceptable diagnostic value to confirm CTS in hypothyroid patients. However, it may not replace NCS due to low sensitivity.

Introduction
Musculoskeletal disorders are common in patients with hypothyroidism,\(^1\) and carpal tunnel syndrome (CTS) is the most common compression syndrome in
the upper extremities. The recent American Academy of Orthopaedic Surgeons Clinical Guidelines define CTS as asymptomatic compression neuropathy, which is characterized by decreased median nerve function at the level of wrist accompanying with physiologically increased pressure in the CT. With a prevalence of about 50 per 1000 subjects, the incidence of CTS has been estimated 1-3 per 1000 cases per year in the United States. Current literature reports a higher prevalence of hypothyroidism and diabetes in patients with CTS. The prevalence of CTS is estimated to be 5.8% in women and 0.6% in men, in the general population while its prevalence in hypothyroid patients is reported about 28.5%. A retrospective review of patients who underwent surgery for CTS over a 3-year period by Vashishtha et al. in the UK showed that CTS is associated with thyroid dysfunction and diabetes.

The British Society for Surgery of the Hand advises screening CTS patients for thyroid and glucose dysfunction before surgery. Considering the high prevalence of CTS in hypothyroidism, early diagnosis of this disorder to prevent nerve changes is very important. CTS is characterized by typical anatomic changes, the most probable swelling of the median nerve in the proximal part of the CT. The diagnosis is usually clinical using Tinel’s sign and Phalen’s maneuver and is confirmed by nerve conduction study (NCS). Although NCS is the method most frequently used in practice to confirm a clinical diagnosis of CTS, it is known to be painful or unpleasant for patients, and false negatives and false positives occur even if the most sensitive methods are used. In addition, NCS does not provide anatomical information about the nerve or its surroundings that could help in determining its etiology. Recently, using high-frequency ultrasonography (US) for CTS has emerged as an alternative confirmatory test with a sensitivity of 44-95% and a specificity of about 57-100%. Various studies suggested different cut-off points to have the best sensitivity and specificity for median nerve cross-sectional area (CSA) as the most reliable finding for the diagnosis of CTS.

Yet, no study has been conducted to evaluate the diagnostic value of high-frequency US in the diagnosis of CTS in patients with hypothyroidism. To determine whether these findings are reliable and can be used to establish the diagnosis, we aimed to evaluate US as an alternative procedure for diagnosis of subclinical CTS in hypothyroid patients in a cross-sectional study.

Materials and Methods

This study was approved by the Local Ethics Committee of the Firoozgar Clinical Research Development Center, Iran University of Medical Sciences, Tehran, Iran. Informed consent was taken from the patients before the diagnostic procedures. No invasive method was used in this study and all the diagnostic procedures were harmless. The patients’ information remains confidential and would be used only for analytical study.

Between April 2013 and November 2014, from the patients with the diagnosis of hypothyroidism referring to the institute of endocrinology and metabolism of Firoozgar Hospital, those who met our inclusion criteria entered the study. The patients with CTS or injection, wrist fractures, median nerve neuropathy and cervical radiculopathy, or polyneuropathy were excluded. In addition, the patients with diseases and conditions associated with CTS including pregnancy, rheumatoid arthritis (RA), diabetes mellitus (DM), renal failure, gout, tenosynovitis, tumors, ganglion cysts, amyloidosis, and median nerve with two or more branches were also excluded from the study. Bilateral wrist US at the CT inlet was done for the included patients using a MyLab™40 - Esaote with an 18 MHz ultrasound probe by an expert in the neurology clinic to measure the median nerve CSA.

To compare the US measurements with the standard values, NCS was done for all patients as the gold standard test. Other variables such as age, body mass index (BMI), disease duration, wrist circumference, and median nerve CSA were recorded for each patient in the data collection form. The patients were divided into two groups of subclinical CTS and the control group according to the clinical Tinel’s sign and Phalen’s tests, confirmed by NCS. The median nerve CSA at the forearm CT inlet was assessed by an expert investigator blinded to the clinical and NCS data.

The subjects were seated facing the examiner with their arms extended, their wrists on a flat surface, their forearms supine, and their fingers semi-extended. The transverse US of the median nerve was performed at the inlet of the CT. The pisiform bone was used as an anatomical landmark to measure the median nerve CSA at the CT inlet, by tracing a continuous line within the hyperechogenicity boundary of the nerve.

A t-test was used to compare these data with those with previous normal wrists. P < 0.05 was considered as statistically significant. Positive and negative predictive values were calculated using SPSS software (SPSS Inc., Chicago, IL, USA). To compare the accuracy of US, sensitivity and specificity were measured using receiver-operating characteristic curve analysis and other diagnostic
test evaluations. Quantitative variables expressed as mean ± standard deviation (SD) and frequency was used for qualitative data.

Results
A total number of 76 patients (152 wrists bilaterally) were recruited in the study including 70 women and 6 men. The mean age of the subjects was 43.1 ± 13.8 years (range from 19 to 81) with a mean BMI of 27.5 ± 3.8 kg/m² (minimum 20 and maximum 45). The mean duration of disorder was 7.5 ± 3.3 years (from 2 to 15). The average wrists surface area was 20.0 ± 1.7 cm² (minimum 16 and maximum of 24), and the average of median nerve CSA at the CT inlet was 7.6 ± 1.9 mm² (minimum of 4 and maximum of 15). About 31 wrists (20.0%) had CTS diagnostic criteria in the NCS, which were considered as subclinical CTS. The median nerve CSA was more than 9 mm² in 14 cases (9.0%) (Figure 1). The mean median nerve CSA at the tunnel inlet was 9.96 mm² (SD: 2.2) for the CTS affected wrists and 7.08 mm² (SD: 1.38) for the normal wrists (P < 0.05). The average of median nerve CSA was 8 mm² in left and 7.34 mm² in right wrists. The same parameter was 8 mm² in males and 7.6 mm² in females (The difference was not significant). The average of median nerve CSA seemed also not to be associated with age, BMI, wrist circumference and duration of the disease. According to the NCS findings, 31 wrists (20.4%) were diagnosed as CTS while 19 wrists (12.5%) were diagnosed as CTS by the US. The sensitivity and specificity of US in the diagnosis of CTS was 45.0 and 95.8%, respectively, with a CSA cutoff point of 9.8 mm². Positive and negative predictive values of US were 73.7 and 87.2%, respectively, with a test accuracy of 85.5%.

Discussion
Although CTS is clinically diagnosed, moderate sensitivity and specificity have been reported for clinical symptoms and false negative and positives results for NCS. A some of the CTS symptoms such as paresthesia may appear before nerve fiber changes, which can justify the false negative results of NCS. According to different studies, NCS has a sensitivity of about 56-85% and a specificity of 94% or more in the diagnosis of CTS. Although semi-invasive, NCS is the gold standard diagnostic procedure for CTS, while comparing to US, the electrical stimuli may not be pleasant for the patient.

In our study, the median nerve US had a sensitivity and specificity of 45% and 95.8% for diagnosis of CTS in patients with hypothyroid. The US measurements of median nerves were found to be increased significantly in patients with CTS when compared with controls, particularly in terms of CSA. As a result, high-frequency US can be used to confirm the diagnosis and due to high positive predictive value, it can be a suitable test to evaluate CTS in the majority of patients with clinical suspicion of CTS, reserving NCS only for with negative US findings. Current literature approves that patients with CTS have a higher prevalence of hypothyroidism and screening helps diagnosing new cases of this condition in this selected group. A random-effects meta-analysis of the studies not controlling their estimates for any confounder confirmed an association between CTS and hypothyroidism.

In an interesting study by Kolovos and Tsiotas to establish US examination as a method with at least of the same accuracy with electrodiagnostic (EDX) study, 60 healthy individuals and 30 patients suffering from CTS were scanned. The authors suggested that ratios over the value 1.0 could be considered as a definite diagnosis of CTS. While, ratios up to 0.79 would be surely refers to a healthy wrist and the intermediate ratios between 0.79 and 1.0 refers to a gray zone, which is practically considered healthy.

![Figure 1. Transverse ultrasonographic image of median nerve (outlined) at level of carpal tunnel (CT) inlet](image-url)
Recent studies have demonstrated advantages of US in the diagnosis of CTS; however, its role is limited due to lack of adequate data relative to EDX testing. The wide variations of sensitivities and specificities reported in the literature, on the other hand, prevent meaningful analysis of US as either screening or confirmatory test in the diagnosis of CTS. The meta-analysis by Fowler et al. on 19 articles with a total sample size of 3131 wrists reported the sensitivity and specificity of US for the diagnosis of CTS, 77.6 and 86.8%, respectively. The study by Kwon et al. also showed a sensitivity of 66.0% and specificity of 63.0% for median nerve CSA of 10.7 mm² for the US, while the sensitivity and specificity of NCS were 78.0 and 83.0%, respectively. In another study by Mohammadi et al., the median nerve CSA at the CT inlet and outlet were examined bilaterally in 82 patients with electrophysiologically confirmed CTS to determine whether high-resolution US can be considered as an alternative diagnostic method to NCS in grading the severity of CT. The differences of the median nerve CSA in mild, moderate and severe CTS were not statistically significant either in the CT inlet or in outlet. According to this study, US of the median nerve CSA had a diagnostic value to confirm or exclude CTS, but could not be used for grading of its severity. In contrast, Azami et al. prospectively examined individuals with EDX proven CTS and healthy control subjects to determine the diagnostic value of US compared with NCS. With a sensitivity and specificity of 99.2 and 88.3%, CSA at the tunnel inlet with a threshold of 9.15 mm² had the best diagnostic accuracy. There was reported a significant difference in the median nerve CSA in mild, moderate and severe CTS in this study. In another cross-sectional case-control study, Ghasemi et al. assessed findings in US in correlation with severity of CTS. According to EDX, patients were classified as mild, moderate, and severe CTS and high-resolution US for CSA measurement at the tunnel inlet was performed for all patients. The mean of the CSA in mild, moderate and severe CTS wrists were 0.12 cm² in, 0.15 and 0.19 cm², respectively. A significant correlation between the median nerve CSA and the severity of CTS impelled the authors claiming that US may serve as a complementary and reliable method in assessing the severity of CTS.

Yazdchi et al. also studied the sensitivity and specificity of median nerve US in diagnosis of CTS in 90 Iranian patients with clinically suspected CTS. The median nerve CSA at the three levels of the CT could fairly differentiate severe CTS from other cases. Their results suggested that median nerve US cannot replace the NCS because of an overall low sensitivity and specificity. Dejaco et al. prospectively studied 135 consecutive patients with diagnosis of CTS in order to compare US measurement of median nerve CSA. They measured CSA using US at five different levels at forearm and wrist. The US of median nerve swelling revealed a good reliability with an intraclass correlation coefficient of 0.90, allowing a fairly reliable diagnosis of CTS.

Kim et al. studied 187 patients, to determine the criteria for US measurement of the median nerve CSA and differential diagnosis of patients with CTS with or without diabetic polyneuropathy. All the CSAs in this study were larger in the diabetic polyneuropathy group compared with those in the control group. The cutoff value for the CSA at the wrist that yielded the highest sensitivity and specificity was 11.6 mm². They concluded that diagnosing the comorbidity of CTS with diabetic polyneuropathy could be done according to the median nerve CSA at the wrist and the wrist-forearm ratio. In another similar study, Kanikannan et al. compared the diagnostic accuracy of high-resolution US and electrophysiology in the diagnosis of CTS in patients with CTS and CTS associated with peripheral neuropathy. High-resolution US showed a good correlation with EDX studies in all grades of CTS in these patients with the sensitivity, specificity, positive predictive value and negative predictive values of 76.4, 72.7, 89.5 and 68.0 percent, respectively. They claimed that US can be used as a complementary screening tool to EDX.

Although US is an operator-dependent procedure and should be done by or under supervision of an expert, it may be preferred by patients since it is painless and easily accessible. The high-resolution US allows direct imaging of the involved nerves, in addition to documentation of nerve shape changes that occur in compressive syndromes. US can also diagnose a spectrum of entrapment causes such as tenosynovitis, ganglia, soft-tissue tumors, bone and joint abnormalities, and anomalous muscles. According to our study, US may not replace EDX testing as the most sensitive and specific diagnostic test for CTS diagnosis in hypothyroid patients, but it can be used as the first line confirmatory test as its accuracy was detected 85.5% in our study.

**Conclusion**
We conclude that the results of US are reliable, and the diagnosis of CTS in hypothyroid patients can be established based on US findings. Further studies are recommended with wider series to evaluate the ultrasound in CTS of hypothyroid patients and confirm our preliminary results.
Conflict of Interests
The authors declare no conflict of interest in this study.

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References
The assessment of proinflammatory cytokines in the patients with the history of cerebral venous sinus thrombosis

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Keywords
Cerebral Thrombosis; Venous Thromboembolism; Interleukin; Cytokine; Erythrocyte Sedimentation Rate

Abstract
Background: Evidence is accumulating that venous thromboembolism is not limited to coagulation system and immune system seems to be involved in formation and resolution of thrombus. Some studies have demonstrated the role of inflammatory factors in deep venous thrombosis (DVT) of limbs; however, there has not been such study in the patients with cerebral venous sinus thrombosis (CVST). The purpose of this study was to evaluate inflammatory cytokines including interleukin-6 (IL-6), IL-8, IL-10, and tumor necrosis factor-alpha (TNF-α) in the patients with the history of CVST.

Methods: In a cross-sectional study, 20 patients with the first episode of CVST and 20 age- and sex-matched healthy controls were included. The patients were seen only after anticoagulant treatment had been discontinued for at least 3 months. IL-6, IL-8, IL-10, TNF-α levels, and erythrocyte sedimentation rate (ESR) were measured in two groups.

Results: The median age of patients was 37.0 [interquartile range (IQR) = 31.75-42.75] and in control group was 42.0 (IQR = 38.0-40.6) (P = 0.18). In patients group, 14 (70%) were females and in control group, also, 14 (70%) subjects were female (P = 0.01). It is significant that the level of IL-6 was significantly higher in the control group [patients: median: 9.75, IQR: 8.98-10.65; controls: median: 11.45, IQR: 10.28-13.10; P = 0.01]; however, the ESR level was higher in the patients. On the subject of IL-8, IL-10, and TNF-α, no significant difference was detected.

Conclusion: We did not find higher concentrations of inflammatory ILs in the patients with the history of CVST that is contradictory with some findings in venous thrombosis of the extremities; however, the studies with larger sample size may be required.

Introduction
Classic risk factors for venous thrombosis are divided into two main groups of acquired factors such as immobilization, surgery and cancers, and genetic risk factors, like activated protein C resistance, and deficiencies of protein C or S and antithrombin.¹ Evidence is accumulating that venous thromboembolism is not limited to coagulation system and immune system seems to be involved in formation and resolution of thrombus.²³

Cytokines are different groups of soluble short acting proteins, glycoproteins, and peptides produced by numerous immune cells and vascular
cells, and act in picomolar to nanomolar concentrations to trigger specific receptors and modulate the functions of many cells and tissues. Interleukins (ILs) are cytokines synthetized by one leukocyte and acting on other leukocytes. Anti-inflammatory cytokines are involved in the down-regulation of inflammatory reactions such as IL-10 and some others such as tumor necrosis factor-alpha (TNF-α). IL-6 provokes stimulation of acute-phase reactants or chemotactrant such as IL-8.4

There is evidence that elevated levels of ILs could be associated with venous thrombosis.5-7 Elevated plasma levels of IL-8 were previously shown to be associated with recurrent venous thrombosis.8 In addition, in particular, IL-6, IL-8, and TNF-α play an important role in the process of inflammation and thrombosis formation. IL-6 provokes a prothrombotic effect by increasing expression of tissue factor, fibrinogen, factor VIII and Von Willebrand factor (VWF), activation of endothelial cells and accumulating platelet creation; in addition, it decreases the levels of inhibitors of hemostasis such as anti-thrombin and protein S.9

Cerebral venous sinus thrombosis (CVST) is an uncommon cerebrovascular disease representing approximately 1% of all strokes, marked by clotting of blood in cerebral venous or dural sinuses, and in rare cases, cortical veins.10 A great many of risk factors have been previously described for the CVST patients.10 Previously, local and generalized infections had an important role in the pathogenesis of CVST; but the studies in recent years have shown that in addition to acquired risk factors such as oral contraceptive pills, inherited blood coagulation disorders play an important role in the development of CVST.10

Some studies have demonstrated the role of inflammatory factors in deep venous thrombosis (DVT) of limbs; however, there has not been such study in CVST patients. We tested the hypothesis that a chronic inflammatory state following a proinflammatory stimulus, regardless of origin, could precede future thrombotic events. The purpose of this study was to evaluate proinflammatory markers including IL-6, IL-8, IL-10, and TNF-α in the patients with the history of CVST in comparison with healthy individuals.

Materials and Methods

This was a cross-sectional study conducted between January 2013 and June 2015. A total of 20 patients with a first episode of objectively demonstrated CVST and 20 age- and sex-matched healthy controls were included. The patients had been previously hospitalized in Shariati Hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran.

The patients were seen only after anticoagulant treatment had been discontinued for at least 3 months. This was always at least 6 months after the event because oral anticoagulant treatment was routinely given for 3-9 months in unprovoked CVST patients. The healthy control subjects were acquaintances of patients or partners of other patients and were selected according to the following criteria: same sex, same age (± 5 years), no biological relationship, no history of venous thromboembolism, no use of warfarin-derivatives for at least 3 months, and no known malignancies.

Inclusion criteria for the patients were definite diagnosis of CVST according to history, clinical exam, and brain magnetic resonance imaging (MRI) and magnetic resonance volumetry. The clinical records and objective documentation of CVST were reviewed by a neurologist to confirm the diagnosis. The age was between 18 and 65 years.

The exclusion criteria were the CVST patients with the history of surgical intervention, stupor or coma during hospitalization, history of ischemic heart disease, intermittent claudication and arterial stroke or transient ischemic attacks, history of acute or chronic renal failures, the previous diagnosis of autoimmune disorders previous to CVST or diagnosed after CVST, secondary thromboses as a result of malignancy, pregnancy, infectious disorders, and thrombophilia, recent immobility, history of diabetes mellitus (DM), smoking and hypertension. Of utmost importance, the patients who required life-long anticoagulation (due to hereditary thrombophilia, recurrent thrombosis, and unresolvable thrombophilic risk factor) were not enrolled in the study.

We drew 10 ml blood and transferred to the laboratory during 1 hour. Enzyme-linked immunosorbent assay (ELISA) kits for IL-6, IL-8, IL-10 and TNF-α were used from Diaclone Company, France. Whole-blood samples were collected in the early morning after overnight fasting. The samples were stored for 15 hours at room temperature and then centrifuged at 1000 × g for 20 minutes. The supernatant was then separated and stored at −70 °C until testing. Repeated freezing and thawing were avoided for all samples. The procedures for the measurement of IL-6, IL-8, IL-10, TNF-α level followed the instructions provided by the kit manufacturers. Erythrocyte sedimentation rate (ESR) was measured with Westergren method.

All patients or their caregivers/relatives provided signed consent to participate in this study. This study was approved by Ethical committee of Tehran University of Medical Sciences.
Data analysis was performed using RStudio (version 3.2.2). Since the data did not follow normal distribution, we used the non-parametric Mann–Whitney test for analysis (comparison of the factors between patients and controls). The significance level below 0.05 was regarded significant. The data are presented as median [interquartile range (IQR: 25-75th percentiles) range].

Results
The median age of patients was 37.0 years (IQR = 31.8-42.8) and in the control group was 42.0 years (IQR = 38.0-40.6) (P = 0.18). In patients group, 14 (70%) were females and in the control group, 14 (70%) subjects were female (P = 0.01). In CVST group, 5 women consumed oral contraceptive pills before the episode. Patients were included in the study at different time intervals after the thrombotic episode [median 10.5 months (IQR = 9.0-12.0)]. All patients had received during acute-phase and the median duration of warfarin consumption was 6 months (IQR = 5.0-6.3).

The comparison of blood levels of measured factors (IL-6, IL-8, IL-10, TNF-α, and ESR) are shown in table 1 and figure 1. It is significant that the level of IL-6 was significantly higher in the control group (Table 1, Figure 1); however, the ESR level was higher in the patients. On the subject of IL-8, IL-10, and TNF-α, no significant difference was detected.

Table 1. The measured factors between patients and controls

<table>
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<tr>
<th>Factors</th>
<th>Patients (n = 20)</th>
<th>Controls (n = 20)</th>
<th>Mann-Whitney U</th>
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<td>IL-6 (pg/ml)</td>
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<td>IL-8 (pg/ml)</td>
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<td>IL-10 (pg/ml)</td>
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<td>9.05 (8.38-9.83)</td>
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<tr>
<td>TNF-α (pg/ml)</td>
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<td>8.80 (7.98-10.68)</td>
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<td>ESR (mm/hour)</td>
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<td>9.50 (8.00-11.25)</td>
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</tbody>
</table>

ESR: Erythrocyte sedimentation rate; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; IQR: Interquartile range

Figure 1. The comparison of measured factors between two groups of patients and controls (the levels are in pg/ml)
Discussion

According to our results, we could not confirm the hypothesis that pro-inflammatory cytokines are higher in the patients with the history of CVST; however, there have been some studies in favor of this hypothesis in DVT of extremities.

In van Aken et al. study, the patients with the first event of objectively demonstrated DVT were involved in whom anticoagulant treatment had been discontinued for at least 3 months (at least more than 6 months after the event). The study demonstrated that higher concentrations of IL-8 were related to venous thrombosis. Plasma concentrations of IL-8 (above the 90th percentile) lead to around two-fold increased risk of venous thrombosis, and this association was most noticeable between 40 and 51 years. However, in our study, we did not find such difference between CVST patients and controls.

It is significant that in a population of cancer patients with abdominal malignancies, the C-reactive protein, IL-6, nuclear factor-κB, and E-Sel levels in patients with DVT were meaningfully higher than the control group. The IL-10 level was higher in patients with DVT than in controls. Another study demonstrated that IL-10 -1082A/G polymorphism is associated with increased risk of DVT.

In a case-control study, the association of venous thromboembolism and levels of IL, IL-6, IL-8, and monocyte chemotactic protein-1 (MCP-1) was examined. Blood was collected > 7 months after the thrombotic episode. Odds ratios (OR) adjusted for age and sex were 1.520 for IL-6, 1.1 for IL-8, and 1.0 for MCP-1. Polymorphisms did not affect the thrombotic risk and the cytokine levels in study participants.

In another study, it was demonstrated that patients with idiopathic venous thrombosis had significantly lower levels of IL-10. Patients also had increased levels of proinflammatory cytokines such as IL-6 and IL-8. In patients with trauma, an elevated serum P-selectin to IL-10 ratio was associated with the development of venous thromboembolism.

It is noticeable that in our study the level of IL-6 was lower in the CVST patients in comparison with the control group that may stem from the chronic consumption of warfarin by the patients. According to some previous studies, warfarin may directly influence inflammatory signal transduction, in lower concentrations lessening such signaling but in higher concentrations provoking proinflammatory reactions; in other words, low-dose warfarin may have anti-inflammatory effect through suppression of IL-6 secretion and obstructing the immune-associated signals. The most important limitation of our study was the small sample size that is, as a result of scarcity of CVST in comparison with other forms of venous thrombosis such as DVT in the extremities. Conducting study as multi-center study may solve this problem.

For future, we propose the measurements of ILs in a larger population; what is more, we suggest the measurements in acute phase as well as measuring more widespread vascular factors such as vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and E-selectin and other related factors.

Conclusion

According to our results, we did not find higher concentrations of pro-inflammatory cytokines in the patients with the history of CVST that is contradictory with some findings in venous thrombosis of the extremities; however, the studies with larger sample size may be required.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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A migraine, a major cause of chronic headaches, is a common neurovascular disorder with multifactorial and polygenic inheritance. It affects about 12% of the adult population which is more prevalent in females.\textsuperscript{1,2} Migraine is recurrent unilateral pulsatile

Keywords
Headache; Lp-PLA2; Migraine; Gene Polymorphism; Questionnaires

Abstract
Background: Migraine is a common neurovascular disorder with multifactorial and polygenic inheritance. The aim of this study was to investigate the association of a migraine without aura and Ala379Val polymorphism of lipoprotein-associated phospholipase A2 (Lp-PLA2) gene in the Iranian population.

Methods: In this study, 103 migraine patients and 100 healthy controls were enrolled. DNA samples were extracted and the Ala379Val polymorphism of Lp-PLA2 gene was investigated. To assess severity of a headache, patients filled out the headache impact test (HIT-6) and migraine severity (MIGSEV) questionnaires.

Results: Allele V had significantly lower frequency in the case group than control subjects [P = 0.001, odds ratio (OR) = 0.25, confidence interval (CI): 0.15-0.40]. The frequency of migraine patients that were a carrier of V allele (V/V and A/V) was statistically significant lower than the control group (P = 0.003, OR = 2.39, CI: 1.35-4.23). There was no significant difference of alleles frequency between three grades of MIGSEV (P = 0.316). Furthermore, total HIT-6 score was not significantly different between different genotypes (P = 0.466).

Conclusion: Our results showed that Ala379Val gene polymorphism of LP-PLA2 is associated with lower risk of migraine but not with severity of headaches in an Iranian population.

Introduction
A migraine, a major cause of chronic headaches, is a common neurovascular disorder with multifactorial and polygenic inheritance. It affects about 12% of the adult population which is more prevalent in females.\textsuperscript{1,2} Migraine is recurrent unilateral pulsatile
headache and can be accompanied by nausea, vomiting, phonophobia, and photophobia.3 Furthermore, some patients have transient neurologic attacks known as “aura.”4 The pathogenesis of the migraine is still unclear, but evidence suggests role of inflammation and vascular dysfunction in pain generation.5 Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor (PAF) acetylhydrolase, is a calcium-independent serine lipase involved in many physiological actions and is produced by inflammatory cells such as macrophages, monocytes, and T-lymphocytes.5,7 It is known that mass and activity of Lp-PLA2 associated with race (white is more than black) and sex (in male is more than female).8 Lp-PLA2 is an enzyme that circulates in blood and classified as a new inflammatory marker and atherosclerosis risk factor because of the production of oxidized free fatty acids and lysophosphatidylcholines during oxidation of low-density lipoprotein.6,9 The proatherogenic effect of Lp-PLA2 may be through its role in the generation of lysophosphatidylcholine and oxidized fatty acids and also hydrolysis of the proinflammatory mediator PAF.10 Lp-PLA2 activity and mass were correlated with increased ultrasound determined carotid intima-media thickness. Moreover, there is an association between Lp-PLA2 and cardiovascular diseases.7,8

The Lp-PLA2 gene is located in the 6 q21.2-p12 chromosome and different polymorphisms have been described for this gene. Studies have shown that some polymorphisms exist in one race that is not shown in others. Val279Phe and Gln281Arg are two polymorphisms of this gene that have only seen in Japanese populations; however, Arg92His, Ile198Thr and Ala379Val, other polymorphisms of this gene have been described more in European populations.11,12 The different polymorphisms of Lp-PLA2 have association with some diseases. For example, G994T has an association with polycystic ovary syndrome and also has increased susceptibility to oxidative stress and inflammation.13 Studies have shown that V279F variant in the Lp-PLA2 gene is associated with the increase of myocardial/cerebral infection and also shown an association between this variant and an increased of coronary artery disease (CAD) and infarction. On the other hand, some other polymorphism of this gene like V379 allele of the Ala379Val polymorphism reduced the risk of CAD.14 By reducing the Lp-PLA2 protein production, the risk of coronary heart disease (CHD) may decrease. Studies have shown that in individuals homozygous for Ala379Val this enzyme production had reduced and it may lead to less risk for CHD.15 As migraine is a vascular disorder and Lp-PLA2 has some vascular effects, the aim of this study was to investigate the association of migraine without aura and Ala379Val polymorphism in Iranian population.

Materials and Methods
We conducted a case-control study enrolling patients that were recently diagnosed as without aura migraines based on the International Headache Society (IHS) criteria16 and also controls that were matched for age, education, sex, and socio-economic status with the cases. The patients were selected from three outpatient neurology clinics between November 2011 and June 2012 in Isfahan, Iran. The socio-demographic and headache characteristics of all the subjects including age, sex, level of education (with and without academic degrees), residency (urban/rural), frequency of headaches, the effect of menstruation on the migraine, and positive family history were asked. Patients who had at least a 3-month history of headaches before the diagnoses and had not have received any medications for their migraine were consecutively enrolled. Controls were selected from healthy people who accompanied the patients that were referred to the neurologic clinics (including patients with migraine and other neurologic disorders) who did not have any history for migraines and also any family history of migraine in the first degree relatives. An informed consent was taken from participants before entering the study.

Headache impact test (HIT-6) questionnaire
To assess the severity of headaches, each patient filled HIT-6 questionnaire. HIT-6 questionnaire consists of six questions that show six dimensions: pain severity, role functioning, social functioning, vitality, emotional distress, and cognitive functioning. Each question has 5 available answers: never, rarely, sometimes, very often, and always. Choices have been scored between 6 and 13. The total score is between 36 and 78.17

Migraine severity (MIGSEV) questionnaire
Each migraine patient completed an MIGSEV questionnaire as a valid scale for assessing headache severity. The MIGSEV scale, developed by EL Hasnaoui in 2003,18 is a simple severity scale with four items including intensity of pain, disability in daily activity, tolerability and nausea that categorize patients in three groups of intensity: mild, moderate, and severe. This instrument is highly reliable, reproducible and sensitive, and we have used its Persian translation in our previous study as a valid scale.18,19
DNA extraction and genotyping

A value of 2 ml of venous blood was collected from each participant. Genomic DNA samples were extracted from peripheral whole blood using the AccuPrep Genomic DNA Extraction kit (Bioneer Inc., Korea) according to the manufacturer’s protocol.

The single-nucleotide polymorphisms (SNPs) rs1051931 (A379V) were identified by the National Center for Biotechnology Information (NCBI) data bank and primers were designed by Beacon Designer 8.00 to flank the coding regions (PREMIER Biosoft International, USA and synthesized by TIB MOLBIOL, Germany).

The forward primer was 5’- TTCTCTTTATGGGTTTACGT-3’ and reverse primer was 5’- CATCTGGTTAGGTCATGAAA-3’.

Genotyping was done by high-resolution melt (HRM) assay using a Rotor-Gene 6000 instrument (Corbett Life Science, Australia). Polymerase chain reactions (PCRs) were carried out in duplicate in 20 µl of final volume using the type-it HRM kit (Qiagen), HRM PCR buffer, HotStarTag Plus DNA Polymerase, nucleotides and EvaGreen dye, and 30 ng DNA.

The PCR program consisted of an initial denaturation-activation step at 95 °C for 5 minutes, followed by a 40-cycle program (denaturation at 95 °C for 15 seconds, annealing conditions 55 °C for 5 seconds, 72 °C for 15 seconds; a HRM step from 70 to 95 °C rising at 0.1 °C per second). Curves for each duplicate were checked on the shape and peak temperature. HRM PCR buffer, HRM PCR buffer, HotStarTag Plus DNA Polymerase, nucleotides and EvaGreen dye, and 30 ng DNA.

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We analyzed our data with SPSS software (version 18, SPSS Inc., Chicago, IL, USA). An independent t-test was used for quantitative variables between two groups. The relation between polymorphism (homozygous and heterozygous) and different categorized variables, (age, sex, case-control) was established using chi-square test and calculation of odds ratio (OR) [confidence interval (CI) = 95%]. The significant level was considered as P < 0.050.

The study was approved by the Ethical Committee of Isfahan University of Medical Sciences.

Results

In this study, 103 subjects with migraine and 100 healthy subjects were enrolled, and DNA samples were analyzed for LP-PLA2 Ala379Val gene polymorphisms. In the case and control group, 82.6 and 78.0% were female, respectively, and distribution was not statistically significant. Total mean age of the subjects was 34.42 ± 0.73 (34.08 ± 1.01 and 34.77 ± 1.06 in the case and control groups, respectively, P = 0.639). There were no significant differences in the mean ages, education level (40.0 vs. 36.0% without academic degrees) and residency (51.5 vs. 57.6% urban) between case and control groups, respectively. The migraine characteristics of the case group are shown in table 1.

Table 1. The migraine characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache per month (mean ± SE)</td>
<td>8.32 ± 0.81</td>
</tr>
<tr>
<td>Age onset of migraine (years) (mean ± SE)</td>
<td>26.28 ± 0.94</td>
</tr>
<tr>
<td>Family history of migraine [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>64 (77.1)</td>
</tr>
<tr>
<td>No</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Menstrual effect [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (51.9)</td>
</tr>
<tr>
<td>No</td>
<td>39 (48.1)</td>
</tr>
<tr>
<td>Total HIT-6 score (mean ± SE)</td>
<td>53.51 ± 1.93</td>
</tr>
<tr>
<td>MIGSEV grade [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>9 (12.9)</td>
</tr>
<tr>
<td>Grade II</td>
<td>27 (38.6)</td>
</tr>
<tr>
<td>Grade III</td>
<td>34 (48.6)</td>
</tr>
</tbody>
</table>

HIT-6: Headache impact test; SE: Standard error; MIGSEV: Migraine severity

The analysis of allele frequency in the case group shows no significant difference in the distribution of A and V alleles in the two genders (P = 0.282), but in control group, V allele frequency in male subjects was significantly more than females (P = 0.008). Another analysis in the case group showed that the distribution of alleles A and V was not associated with family history of migraine and also menstruation effect (P = 0.209 and P = 0.516, respectively). The patients were classified into three groups according to the MIGSEV grade. There was no significant difference of alleles frequency between three grades of MIGSEV (P = 0.316).

The total frequency of allele A and V in the study population were 287 and 119, respectively. Allele V had lower frequency in the case group than control subjects, and the difference was statistically significant (P < 0.001, OR = 0.25) (Table 2). The frequency of A/A, A/V and V/V genotypes in all subjects were 117, 53 and 33, respectively.

The frequency of migraine patients that were carrier of V allele was statistically significant lower than control group (P = 0.003, OR = 2.39, 95% CI: 1.35-4.23).

Table 3 shows comparison of mean age of onset, frequency of headache per month and total HIT-6 score between A/A and A/V genotypes of LP-PLA2 Ala379Val gene polymorphism in patients. Our results revealed that there are no significant differences between the mean of mentioned factors in the two genotypes (P > 0.050).
Table 2. Distribution of allele and genotype of LP-PLA2 Ala379Val gene polymorphism in the case and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case [n (%)]</th>
<th>Control [n (%)]</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allele</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>173 (84)</td>
<td>114 (57)</td>
<td>&lt; 0.001</td>
<td>0.25 (0.15-0.40)</td>
</tr>
<tr>
<td>V</td>
<td>33 (16)</td>
<td>86 (43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>70 (68)</td>
<td>47 (47)</td>
<td>0.003</td>
<td>2.39 (1.35-4.23)</td>
</tr>
<tr>
<td>A/V</td>
<td>33 (32)</td>
<td>20 (20)</td>
<td>0.051</td>
<td>1.88 (0.99-3.58)</td>
</tr>
<tr>
<td>V/V</td>
<td>0 (0)</td>
<td>33 (33)</td>
<td>0.000</td>
<td>2.53 (2.10-3.05)</td>
</tr>
</tbody>
</table>

LP-PLA2: Lipoprotein-associated phospholipase A2; OR: Odds ratio; CI: Confidence interval

**Discussion**

As migraine is a vascular disorder and Lp-PLA2 has some vascular effects, the aim of this study was to investigate the association of migraine without aura and Ala379Val polymorphism in Iranian population. Our results showed that frequency of V allele (mutant allele) was lower in case group than control group. We classified our subjects into three genotypes of A/A, A/V, and V/V. The frequency of migraine in the subjects who are carrier of V allele was statistically significant lower than non-V allele carriers (OR = 2.39, CI: 1.35-4.23), so the current study suggests that V allele of Ala379Val polymorphism of LP-PLA2 will be related to decreased risk for migraine. We also investigated the association of Ala379Val polymorphism with severity and frequency of headaches in migraine patients. Our results revealed no association between the polymorphism and mentioned factors. To the best of our knowledge, there is no study conducted to assess the association of Ala379Val polymorphism of LP-PLA2 and migraine. But according to results of a study conducted on the genetic of migraine although they could not find a relation between Lp-PLA2 gene and migraine, but they have reported that a predisposing haplotype spanning 10 Mb on the chromosome 6p12.2-p21.1 that contains the Lp-PLA2 gene, was inherited with all migraine patients in the pedigree that they have studied.\textsuperscript{20}

There are some other studies designed to assess association of other disorders and Ala379Val polymorphism of LP-PLA2. Abuzeid et al. in their study have reported that homozygosity for the V379 allele was associated with lower risk of myocardial infarction (MI), but the risk of MI in the AA and AV subjects was very similar.\textsuperscript{15} Similar to this report, our results showed that there was no significant difference between AA and AV groups in the frequency of migraine. However, VV genotype was associated with lower risk of migraine. Results of another study conducted by Oei et al. revealed that activity of Lp-PLA2 is associated with risk of CHD and also ischemic stroke.\textsuperscript{21} This report confirms the Abuzeid et al.\textsuperscript{15} conclusion as we know that V379 allele is associated with lower activity of Lp-PLA2 protein.\textsuperscript{21}

In a study by Kardara et al.\textsuperscript{22} that was designed to investigate the association of Ala379Val polymorphism with hypertension and thrombotic markers, results showed that A/V genotype is associated with lower risk of essential hypertension. But both A/A and V/V genotypes were at higher risk of developing essential hypertension. Their results also showed that in hypertensive patients, A/V genotype carriers have elevated level of fibrinogen. They have reported that in hypertensive patients, A/V genotype is associated with increased inflammatory and thrombotic burden.

**Conclusion**

Our results showed that Ala379Val gene polymorphism of LP-PLA2 is associated with lower risk of migraine without aura in Iranian population. However, it has no effect on the severity of migraine and also frequency of headaches in migraine patients. We had a small sample size and it reduced the power of our study especially in analysis of association of the polymorphism with frequency of headache and severity of migraine. Therefore, this is a preliminary conclusion. Further studies with larger sample sizes are needed.

Table 3. Comparison of mean age of onset, frequency of headache per month and total headache impact test (HIT-6) score between A/A and A/V genotypes in patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Genotype</th>
<th>P</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/V</td>
<td>A/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td>28.56 ± 1.88</td>
<td>25.38 ± 1.08</td>
<td>0.131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of headache</td>
<td>7.86 ± 1.70</td>
<td>8.49 ± 0.93</td>
<td>0.739</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total HIT-6 score</td>
<td>51.24 ± 3.77</td>
<td>54.40 ± 2.26</td>
<td>0.466</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HIT-6: Headache impact test; SE: Standard error

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Ala379Val polymorphism & migraine without aura in Iranian population

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Conflict of Interests
The authors declare no conflict of interest in this study.

Acknowledgments
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Amyotrophic lateral sclerosis mimic syndromes

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Keywords
Amyotrophic Lateral Sclerosis; Motor Neuron Disease; Differential Diagnosis

Abstract
Amyotrophic lateral sclerosis (ALS) misdiagnosis has many broad implications for the patient and the neurologist. Potentially curative treatments exist for certain ALS mimic syndromes, but delay in starting these therapies may have an unfavorable effect on outcome. Hence, it is important to exclude similar conditions. In this review, we discuss some of the important mimics of ALS.

Introduction
Amyotrophic lateral sclerosis (ALS) is a progressive and almost always devastating neurodegenerative disorder. It is a kind of a heterogeneous group of disorders known as motor neuron diseases (MNDs). The most common MND of adults is ALS. The prototypic form of this lethal disorder simultaneously involves both upper motor neuron (UMN) and lower motor neuron (LMN) which progresses from a region of neuraxis to others and final death, typically from respiratory involvement.1

In populations of European origin, ALS is the more common in men than in women (1.2-1.5:1).2 On the other hand, most studies show that bulbar-onset ALS displays a female predominance.3,4 In contrast to other neurodegenerative disorders, the risk of developing ALS peaks between the ages of 50 and 75 years, and declines thereafter.2,5 This feature suggests that aging is not a single risk factor of ALS. The incidence of sporadic ALS is reported to be between 2.16 per 100000 person years population (average 1.89 per 100000/year), with a uniform incidence across Europe. It is estimated that the general risk of ALS for lifetime is 1:400 for women and 1:350 for men. Incidence decreases quickly after age of 80 years.2 The Research Group of World Federation of Neurology on MNDs have build up the “El Escorial” diagnostic criteria in 1994.6 Moreover, the revised in 2000 (Airlie House Criteria)7 to aid in diagnosing and classifying ALS patients specially for research studies (Tables 1 and 2).

In the early stages of disease patients are most likely to benefit from treatment, but these criteria may have low sensitivity to do definite diagnosis. Because of these limitations, the criteria have been modified to help early diagnosis and to optimize levels of diagnostic certainty.8-11

It is important to rule out treatable mimics. ALS misdiagnosis has many broad implications for the patient and the neurologist. Potentially curative treatments exist for certain ALS mimic syndromes, but delay in starting these therapies may have an unfavorable effect on the outcome.

The term ALS mimic syndrome has been used to describe a heterogeneous group of conditions that their presentation and clinical features may resemble...
Table 1. Diagnostic criteria for amyotrophic lateral sclerosis (ALS)

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>The diagnosis of ALS requires the presence of (positive criteria)</td>
</tr>
<tr>
<td>LMN signs (including EMG features in clinically unaffected muscles)</td>
</tr>
<tr>
<td>UMN signs</td>
</tr>
<tr>
<td>Progression of symptoms and signs</td>
</tr>
<tr>
<td>The diagnosis of ALS requires the absence of (diagnosis by exclusion)</td>
</tr>
<tr>
<td>Sensory signs</td>
</tr>
<tr>
<td>Sphincter disturbances</td>
</tr>
<tr>
<td>Visual disturbances</td>
</tr>
<tr>
<td>Autonomic features</td>
</tr>
<tr>
<td>Basal ganglion dysfunction</td>
</tr>
<tr>
<td>Alzheimer-type dementia</td>
</tr>
<tr>
<td>ALS “mimic” syndromes</td>
</tr>
<tr>
<td>The diagnosis of ALS is supported by</td>
</tr>
<tr>
<td>Fasciculations in one or more regions</td>
</tr>
<tr>
<td>Neurogenic changes in EMG results</td>
</tr>
<tr>
<td>Normal motor and sensory nerve conduction</td>
</tr>
<tr>
<td>Absence of conduction block</td>
</tr>
</tbody>
</table>

ALS: Amyotrophic lateral sclerosis; EMG: Electromyography; UMN: Upper motor neuron; LMN: Lower motor neuron

Table 2. El Escorial World Federation of Neurology criteria for diagnosis of amyotrophic lateral sclerosis (ALS)

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically definite ALS</td>
</tr>
<tr>
<td>UMN and LMN clinical signs or electrophysiological evidence in three regions</td>
</tr>
<tr>
<td>Clinically definite ALS-laboratory supported</td>
</tr>
<tr>
<td>UMN and/or LMN clinical signs in one region and the patient is a carrier of a pathogenic SOD1-gene mutation</td>
</tr>
<tr>
<td>Clinically probable ALS</td>
</tr>
<tr>
<td>UMN and LMN clinical or electrophysiological evidence by LMN and UMN signs in two regions with some UMN signs rostral to the LMN signs</td>
</tr>
<tr>
<td>Clinically possible ALS</td>
</tr>
<tr>
<td>UMN and LMN clinical or electrophysiological signs in one region only, or</td>
</tr>
<tr>
<td>UMN signs in at least two regions, or</td>
</tr>
<tr>
<td>UMN and LMN signs in two regions with no UMN signs rostral to LMN signs</td>
</tr>
</tbody>
</table>

ALS: Amyotrophic lateral sclerosis; LMN: Lower motor neuron; UMN: Upper motor neuron, SOD1: Superoxide dismutase 1

those of ALS at the beginning. It is different to ALS with laboratory abnormalities of uncertain significance, which is a subgroup of ALS that occurs in association with a defined laboratory abnormality that is of doubtful implication to the pathogenesis of ALS.11

To our knowledge, there have been few published studies of ALS mimic syndromes.12,13 Population-based studies have shown that almost 10% of patients with ALS diagnosis have had another disease.14

Mimics

Approach to the differential diagnosis of ALS (ALS mimic syndromes) can be in terms of the anatomy, symptoms, or clinical presentation. Here, we discuss mimics based on the nervous system anatomy.

Brain

Adult polyglucosan body disease (APBD) is a late-onset, slowly progressive disorder of both UMN and LMN, like ALS, but it has other neurologic sings such as cognitive decline, distal sensory loss, and disturbances of bladder and bowel function. Magnetic resonance imaging of the brain may reveal diffuse white-matter signal increase on T2-weighted images. The diagnosis is confirmed by the finding of characteristic pathological changes in samples from peripheral nerve, cerebral cortex, spinal cord, or skin. There are non-membrane-bound periodic acid-Schiff positive cytoplasmic polyglucosan bodies in axons and neural sheath cells.

Mutations of the glycogen-branching enzyme (GBE) gene are the cause of this disorder in Ashkenazi Jewish patients, but APBD occurs in many different populations, and considerable molecular heterogeneity has been noted, with otherwise typical cases lacking GBE mutations despite deficiency of enzyme activity.15,16

Brainstem and spinal cord

Adrenomyeloneuropathy present with spastic paraparesis, areflexia, sphincter disturbance, and sensory loss. It is a peroxisomal disorder caused by a defect in beta-oxidation of very long-chain fatty acids, presenting in their third or fourth decade of life. Increased plasma levels of very long-chain fatty acids make the diagnosis.17

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In multiple sclerosis a both of UMN and LMN involvement may be seen in the setting of plaque formation at root exit zones, combined with central nervous system (CNS) lesions. Lesions at the level of foramen magnum and medulla such as infarct, syrinx, demyelination, and neoplasm, may suggest the bulbar-onset ALS, so neuroimaging may be essential in the evaluation of suspected cases of ALS.

Syringomyelia may present with atrophy and weakness, but a characteristic pattern of dissociated sensory loss typically occurs, and the disease progresses at a much slower rate in a usually younger patient than ALS. Another consideration is vitamin B12 deficiency, but prominent sensory findings usually distinguishes it from ALS.

However, patients occasionally may lack sensory findings, so it is prudent to routinely measure a vitamin B12 level to exclude this treatable condition.

Allgrove or “Four-A” syndrome, a rare autosomal recessive disorder that derives its name from the combination of achalasia, alacrima, adrenal insufficiency, and amyotrophy.

It can manifest from the first decade of life with dysphagia and adrenal insufficiency and a broad range of neurological problems in later life.

A particular phenotype like ALS including pyramidal features and LMN involvement has been described in this disease. 18

The upper-limb amyotrophy, with predominance on the ulnar side of the hands, resembles that of ALS, and bulbar sign and symptoms (tongue atrophy and fasciculation, etc.) have led to the misdiagnosis of bulbar ALS. 19

The proximity of both UMN and LMN structures in the cervical spine, makes degenerative myeloradiculopathy an important diagnostic challenge in cases of suspected ALS.

On the other hand, incidental finding of cervical spondylosis is highly prevalent in ALS patients. 20

Symptoms such as emotional lability and abnormal signs of the cranial region are supportive in differentiate neck pathology from ALS. Furthermore, in contrast to ALS, cervical spondylosis is unlikely to cause LMN signs in the hand muscles or widespread fasciculations. 21

Specially, the presence of fasciculations in the bulbar and lumbosacral areas would be in contrast to the diagnosis of neck pathology.

Pure motor manifestations and without sphenicteric dysfunction are not rare in patients with cervical spondylotic myelopathy, which may be similar to the clinical manifestations of ALS, using such terms as dissociated motor loss or cervical spondylotic amyotrophy.

The pathogenesis of this syndrome may be selective damage to the ventral root due to compression by posterolateral osteophytes; on the other hand, vascular insufficiency of the anterior horn cells may be caused by dynamic cord compression. This condition is characterized by segmental muscular atrophy and neurogenic electromyography (EMG) changes, which may be multi-segmental but not as diffuse as is found in ALS. 21 Thus, we have to consider compressive radiculopathy as a cause of focal LMN signs in a limb. Furthermore, other causes of polyradiculopathies such as neoplasms (lymphoma or leukemia), radiation, and infections (viral and spirochetal) may mimic ALS.

In the differential diagnosis of slowly evolving spastic paraparesis, we have to consider hereditary spastic paraparesis. However, this disorder is differentiated by a family history together with very slow progression, sphincteric disturbance, and an absence of LMN, bulbar, and respiratory involvement. 21

Anterior Horn Cell

Kennedy’s disease, is an X-linked disorder of brainstem and spinal cord LMNs and classically presents in the third or fourth decade in males with atrophy and weakness of bulbar, facial, and limb girdle muscles; tremor; perioral fasciculations; mild cognitive impairment; sensory disturbance; and signs of endocrine dysfunction such as diabetes mellitus, gynecomastia, and testicular atrophy. 22,23

In addition of above-mentioned features, a moderately increased creatine kinase (CK) and low amplitude sensory nerve action potential (SNAPs) can help to differentiate it from ALS. To confirm the diagnosis, a genetic test for detection of CAG repeat expansion of the androgen receptor gene is recommended.

Hexosaminidase A (Hex-A) is a lysosomal enzyme that contributes in the degradation of the ganglioside GM2. Accumulation of GM2 leads to degeneration of nerve cells and produces a wide spectrum of neurological disorders. Total deficiency produces a fatal infantile disorder, Tay-Sachs disease. Partial deficiency of enzyme activity causes a variety of adult-onset neurological disorders, characterized by combined involvement of UMN and LMNs, cerebellar and extrapiramidal dysfunction, and psychosis or dementia. 23 It is commonly cited in the differential diagnosis of ALS, especially in atypical cases. In this disorder, EDX studies may reveal prominent complex repetitive discharges on needle EMG and abnormal SNAPs.

Benign monomelic amyotrophy is another
differential diagnosis, specially mimicking monomelic-onset ALS. It typically presents as focal atrophy and weakness of one limb, or part thereof, without sensory dysfunction, predominantly in second and third decades of young men. Fasciculations are prominent and reflexes may be either reduced or normal. It may progress for a few years with eventual stabilization. Needle EMG may reveal relatively sparse fibrillation potentials (in contrast to ALS) in affected muscles along with neurogenic motor unit action potentials (MUAPs) in both clinically affected and unaffected limbs.

Lymphoma may present subacutely with LMN manifestations typically in the lower extremities. Rarely lymphoma may present with a combination of both UMN and LMN signs, similar to ALS. Apart from lymphoma, Waldenstrom’s macroglobulinemia and myeloma may be present by MND.

Paraneoplastic encephalomyelitis may present with motor neuron disorder alone, like ALS, and sensory and autonomic features and ataxia occur later. Associated anti-neuronal antibodies, may be detected. The anti-ampiphysin presentation is usually PLS like, but unlike true PLS it rapidly deteriorates. The anti-Ma associated disorder varies but can be like progressive muscular atrophy.24 The association of ALS with solid malignancy is rather unclear.

Radiation toward the retroperitoneal area or spinal region can cause a pure LMN syndrome in the lumbosacral segment, simulating LMN onset ALS. It may appear many years after the irradiation. Myokymic discharges and non-resolving conduction blocks are distinguishing electrodiagnostic (EDX) features.25 Focal muscle weakness and wasting in post-polio syndrome progresses slowly to other regions over many years, and in contrast to ALS, it does not usually cause death. Moreover, it does not involve UMN.26

Peripheral neuropathies
Multifocal motor neuropathy with conduction block is another mimic of ALS. It presents by onset of focal motor weakness, usually in a distal upper extremity, accompanied commonly by fasciculations and cramps. It has a male predominance (3:1) younger age onset (mean 40 years), with no cases reported over age 70 years.

It is slowly progressive, usually over months or even years. An important clue to the diagnosis is the absence of muscle atrophy despite very significant weakness, until late in the disease course. In addition to above diagnostic clues, anti GM1 antibody and conduction block on nerve conduction study can differentiate this disorder.

Neuromuscular transmission (NMT) disorders
The most common NMT disorder in the context of isolated or near isolated bulbar dysfunction is myasthenia gravis (MG). MG is occasionally misdiagnosed as MND and viz. Muscle fatigue, although considered a characteristic feature of MG, occurs in patients with other neuromuscular disorders including MND. EDX study might not be diagnostic of MND in bulbar onset disease but should help to exclude primary NMT disorders, such as MG. Cholinesterase inhibitors used for the treatment of MG can provide transient symptom relief in MND.26

Muscle disorders
Oculopharyngeal muscular dystrophy may simulate bulbar-onset ALS, but in contrast to ALS, it usually involves the muscles of eyelids and extraocular. In those rare cases that present with bulbar manifestations and subtle or no extraocular involvement, a muscle biopsy may be required to differentiate it from MND.

Another attractive disorder is isolated neck extensor myopathy, which presents in older persons with dropped head and is associated with signs of active denervation in cervical paraspinal muscles like MND, but the weakness does not spread to other regions.

Because of distal muscle involvement, painless asymmetric weakness, and difficulty swallowing, inclusion body myositis (IBM) may mimic ALS. However, fasciculations and UMN signs obviously are absent. A raised serum CK beyond reasonable titers for denervation (> 1000 IU/L) may be a laboratory clue although it may be normal. In addition to phenotypical similarities, EMG may show neurogenic MUAPs with fibrillation potentials as seen in ALS.

Hence, it may be needed to perform muscle biopsy to confirm IBM by the presence of rimmed vacuoles and intranuclear inclusions.

Systemic disease
Hyperthyroidism may misdiagnoses as ALS. It presents with corticospinal tract signs (hyperreflexia), fasciculations, weight loss, and weakness. However, there usually are additional systemic signs such as heat intolerance, anxiety, tremor, tachycardia, and insomnia. It is prudent to include a thyroid function assay in the screening evaluation of ALS patients (Table 3). Weakness may be seen in hyperparathyroidism and mimic LMN onset ALS. Human immunodeficiency virus (HIV) infection may also clinically mimic ALS. A retrospective review of 1700 cases of HIV positive patients with neurological symptoms documented six cases presenting as an ALS-like syndrome.27
In each case, antiretroviral therapy was beneficial either in stabilizing or curing the disease. Overall, patients were younger than the typical ALS patients, by signs and symptoms of UMN and LMN involvement, and onset was characteristically in a monomelic pattern followed by rapid spread to other regions over a period of weeks.

Benign fasciculations usually occur under the age of 30 years, with a relapsing-remitting course over a period of months or years. It does not have any other neurologic abnormalities. They occur in a wide variety of disorders and are frequent in the normal population.

Fasciculations with MND typically is asymptomatic and do not recognize until detected by the physician. They are diffuse and rarely are the presenting symptom. It is in contrast to benign fasciculations.

Muscle fasciculation without weakness should be considered a benign phenomenon, although follow-up (sometimes 6 months or more), might be required to confirm benign nature of that.

Needle EMG has distinguishing features that can differentiate benign from MND-associated fasciculations.

The latter tend to have a complex waveform (neurogenic MUAP), may be induced by joint displacement, and are associated with other EDX features of a widespread disorder of anterior horn cells.

Table 3. Summary of amyotrophic lateral sclerosis (ALS) differential diagnosis

<table>
<thead>
<tr>
<th>Anatomical location of disorder</th>
<th>Disease</th>
<th>Clinical clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS ± PNS</td>
<td>Spino-cerebellar ataxia type 3</td>
<td>Prominent extrapyramidal and oculomotor signs</td>
</tr>
<tr>
<td></td>
<td>Multiple system atrophy</td>
<td>Ataxia, dysautonomia, sphincter disturbance, and oculomotor disturbances</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s disease</td>
<td>Tremor and response to levodopa</td>
</tr>
<tr>
<td></td>
<td>APBD</td>
<td>Cognitive decline, distal sensory loss, and disturbances of bladder and bowel function</td>
</tr>
<tr>
<td></td>
<td>Hex-A deficiency</td>
<td>Cerebellar ataxia, cognitive deterioration, EDX studies may reveal prominent complex repetitive discharges and abnormal SNAPs</td>
</tr>
<tr>
<td></td>
<td>Allgrome syndrome</td>
<td>Achalasia, alacrima, adrenocorticotrophic insufficiency, and a broad range of neurological problems</td>
</tr>
<tr>
<td>Brainstem and spinal cord</td>
<td>Kennedy’s disease</td>
<td>Mild cognitive impairment; sensory disturbance; and signs of endocrine dysfunction</td>
</tr>
<tr>
<td></td>
<td>Cervical spondylosis</td>
<td>Prominent neck pain especially with sphincter involvement</td>
</tr>
<tr>
<td></td>
<td>Adrenomyeloneuropathy</td>
<td>Increased serum VLCFA, sphincter disturbance, sensory loss</td>
</tr>
<tr>
<td></td>
<td>Hereditary spastic paraparesis</td>
<td>Family history, very slow progression, sphincter disturbance, absence of LMN, bulbar, or respiratory involvement</td>
</tr>
<tr>
<td></td>
<td>Syringomyelia</td>
<td>Dissociated sensory loss, slow progression, younger population</td>
</tr>
<tr>
<td></td>
<td>B12 deficiency</td>
<td>Prominent sensory findings</td>
</tr>
<tr>
<td>Anterior horn</td>
<td>Post-polio myelitis syndrome</td>
<td>History of paralytic poliomyelitis, paucity of UMN signs and slow rate of progression</td>
</tr>
<tr>
<td></td>
<td>Spinal muscular atrophy</td>
<td>Slowly progressive, symmetrical, proximal muscle weakness and atrophy without additional UMN signs</td>
</tr>
<tr>
<td></td>
<td>Monomelicamyotrophy</td>
<td>Young men in their second and third decades, relatively sparse fribillation on needle EMG</td>
</tr>
<tr>
<td>Neuropathies and plexopathies</td>
<td>Multifocal motor neuropathy</td>
<td>Absence of muscle atrophy despite very significant weakness, motor weakness is typically restricted to multiple separate peripheral motor nerves, anti GMI</td>
</tr>
<tr>
<td></td>
<td>Neuralgic amyotrophy</td>
<td>Preceded by significant deep, aching pain, involvement of motor nerve fibers can be curiously patchy</td>
</tr>
<tr>
<td>Disorders of the neuromuscular</td>
<td>MG</td>
<td>Absence of UMN signs and fasciculations, absence of fibrillation and fasciculation on needle EMG</td>
</tr>
<tr>
<td>junction</td>
<td>IBM</td>
<td>Absent fasciculations, no UMN signs</td>
</tr>
<tr>
<td>Myopathies</td>
<td>Oculopharyngeal muscular dystrophy</td>
<td>Involvement of eyelids and extraocular muscles</td>
</tr>
<tr>
<td></td>
<td>Isolated neck extensor myopathy</td>
<td>The weakness does not spread to other regions</td>
</tr>
</tbody>
</table>

EMG: Electromyography; LMN: Lower motor neuron; UMN: Upper motor neuron; IBM: Inclusion body myositis; MG: Myasthenia gravis; VLCFA: Very long chain fatty acids; SNAPs: Sensory nerve action potential; Hex: Hexosaminidase; EDX: Electrodiagnostic; PNS: Peripheral nervous system; CNS: Central nervous system
Conclusion
Although the essential diagnostic criteria of ALS are defined by the El Escorial criteria, there are still many misdiagnosis. Our misdiagnosis of ALS mainly relates to diagnostic difficulty, and, also to lack of skill and knowledge about MNDs. To reduce the misdiagnosis rate, enhanced knowledge of the potential alternative disease and MND diagnostic pitfalls are essential, particularly, if the key points are considered.
The differential diagnosis should rule out non-motor neuron similar diseases, especially treatable conditions and other adult-onset MND with limited or focal presentations (Table 4).

Table 4. Diagnosing amyotrophic lateral sclerosis (ALS)/ motor neuron diseases (MND): recommended investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Evidence class</th>
<th>Recommended mandatory tests</th>
<th>Recommended additional tests in selected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Hematological screen</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>AST, ALT, LDH</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Thyroid function test</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Vitamin B₁₂ and folate</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Serum immunoelectrophoresis</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>CK</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Creatinine</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Electrolytes (Na⁺, K⁺, Cl⁻, Ca²⁺)</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Glucose</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Lactate</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Hex A and B assay</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Ganglioside GM-1 antibodies</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Anti-Hu, anti-MAG</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>RA, antinuclear antibodies, anti-DNA</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Anti-acetylcholine receptor and anti-muscle-specific tyrosine kinase antibodies</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td><strong>Serology (Borrelia, virus including HIV)</strong></td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell count</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Cytology</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Total protein concentration</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Glucose, lactate</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Protein electrophoresis including IgG index</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Serology (Borrelia, virus)</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Ganglioside antibodies</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Lead (24-h secretion)</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Mercury</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Manganese</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Urine immunoelectrophoresis</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td><strong>Neurophysiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electromyography</td>
<td>III</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Nerve conduction velocity</td>
<td>III</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>tcMEP (TMS)</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Radiology</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI/computed tomography (cranium/cervical, thoracic, lumbar)</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Mammography</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>III</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Nerve</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>IV</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Lymph node</td>
<td>IV</td>
<td>–</td>
<td>×</td>
</tr>
</tbody>
</table>

ASAT: Aspartate aminotransferase, ALAT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CK: Creatine kinase; MAG: Myelin-associated glycoprotein; RA: Rheumatoid arthritis; Hex: Hexosaminidase; HIV: Human immunodeficiency virus; SBMA: Spinobulbar muscular atrophy; SMN: Survival of motor neuron; SOD1: Superoxide dismutase 1; FUS: Fused in sarcoma; TMS: Transcranial magnetic stimulation; MEP: Motor-evoked potentials; IgG: Immunoglobulin G, MRI: Magnetic resonance imaging
Conflict of Interests
The authors declare no conflict of interest in this study.

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None.

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37. Salajegheh M, Bryan WW, Dalakas MC.

ALS mimic syndromes

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Cerebral venous thrombosis (CVT) is found as a potential life threatening situation which needs prompt diagnosis and urgent treatment. It has been reported that this disease occurs moderately more frequent in South Asia and Middle East than western countries.\textsuperscript{1-3} Several lines of evidence demonstrated increasing incidence of CVT in Iran (10-12 per million),\textsuperscript{1,6} especially in Muslim women have a tendency to post-pone their menstrual period using a short course contraceptive pills (LD: Ethinyl estradiol 0.03 mg + levonorgestrel 0.15 mg) during Muslims fasting month, Ramadan.\textsuperscript{7-9} However, not all women choose this method. Indeed, the Islamic rule disallows women from taking part in some Islamic ceremonies such as fasting in the Ramadan during the menstrual period; therefore, they would like to utilize contraceptive pills as a tool to delay menstruation.

On the other hand, the known risk factors for CVT are normally divided into acquired [e.g., exogenous hormones such as oral contraceptive pill (OCP), pregnancy, puerperium, surgery, antiphospholipid syndrome (APS), trauma, and cancer] and genetic (inherited thrombophilia).\textsuperscript{5} Ashjazadeh et al. in a case series study of 124 patients, who referred to Nemazee Hospital, Shiraz, Iran, with CVT reported that taking oral contraceptives was the main risk factor associated with this phenomenon.\textsuperscript{10} The location of the potential life threatening situation which needs prompt diagnosis and urgent treatment. It has been reported that this disease occurs moderately more frequent in South Asia and Middle East than western countries.\textsuperscript{1-3} Several lines of evidence demonstrated increasing incidence of CVT in Iran (10-12 per million),\textsuperscript{1,6} especially in Muslim women have a tendency to post-pone their menstrual period using a short course contraceptive pills (LD: Ethinyl estradiol 0.03 mg + levonorgestrel 0.15 mg) during Muslims fasting month, Ramadan.\textsuperscript{7-9} However, not all women choose this method. Indeed, the Islamic rule disallows women from taking part in some Islamic ceremonies such as fasting in the Ramadan during the menstrual period; therefore, they would like to utilize contraceptive pills as a tool to delay menstruation.

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thrombosis in patients represents the clinical manifestations of CVT. They usually present headache, whereas some patients show a focal neurological deficit, seizures, decreased level of consciousness, or intracranial hypertension without focal neurological signs.\textsuperscript{11}

It is worth noting that according to the literature the rate of CVT seems to be high in Iran.\textsuperscript{5} According to the above subjects, this study was aimed to report the demographic and etiologic characteristics of patients with CVT admitted in Tohid Hospital of Sanandaj, Iran, during July-August 2014.

Materials and Methods

Case series

This is a retrospective case series of 9 patients who attended in the neurology ward of Tohid Hospital of Sanandaj from July to August of 2 consecutive years 2014-2015. CVT was diagnosed based on the clinical signs and confirmed by neuroimaging findings by magnetic resonance venography (Figure 1). In addition, the paraclinical assessments for thrombophilia including protein C and S, antiphospholipid antibody, vasculitis tests such as antinuclear antibody and anti-double stranded DNA (dsDNA) were conducted and were rollout. The results indicated that the most common clinical signs were headache, papilledema, seizures, sensorimotor deficit, decreased level of consciousness, and hemorrhage. Among these cases, one patient passed away. The clinical features of women with CVT in this study are presented in table 1.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Brain magnetic resonance venography In (Case 5) coronal view demonstrating absence of flow in right transverse sinus (arrow)}
\end{figure}

Discussion

The results of this study indicated that all patients suffered from CVT had used a short course OCP during Ramadan of 2 consecutive years (2014-2015). This result was in agreement with Ashjazadeh et al.\textsuperscript{10} who reported that the rate of CVT is significantly high in OCP consumer in Ramadan.

Previous studies reported several predisposing risk factors for CVT including pregnancy, use of oral contraceptives, autoimmune disease, thrombotic factors, trauma, malignancy, and infections.\textsuperscript{4,12,13} Several studies revealed that taking oral contraceptive is associated with numerous major side effects including cerebrovascular, cardiovascular, and peripheral vascular disorders.\textsuperscript{14,16} In recent years, the role of OCP consumption has greatly considered and limited evidences reported an upper incidence of CVT among OCP users in Ramadan.\textsuperscript{9,17,18}

Our results were in agreement with previous studies concerning the facts that headache, focal neurological deficit, seizures, muscle weakness, hemiparesis, vomiting, nausea, and decreased level of consciousness are the most symptoms of these patients. Among these symptoms, headache was the most common in 9/9 patients (100%), followed by vomiting 5/9 patients (55.5%) and vertigo in 4/9 patients (44.4%). This was similar to the previous study of Khomand et al.\textsuperscript{2} who reported headache as the most frequent and non-specific symptoms and was seen in 86.7% of cases. Furthermore, the incidence of mortality of this study (11.1%) was similar to Iranian studies in Ramadan\textsuperscript{1} which is higher comparing to western countries\textsuperscript{19} or the rate of mortality during the year (3.0%) in our province.\textsuperscript{5} The main reason of death in present study was large bilateral hemorrhagic venous infarction, which is in line with those of other studies.\textsuperscript{20}

We hypothesized that the possible reasons for greater incidence of CVT is associated to the OCP consumption which is concentrate in blood because of low water intake and dehydration during Ramadan fasting. Thus, a combination of dehydration and OCP use may be responsible for the higher risk of CVT occurrence in the Ramadan especially when this month falls in the summer and avoiding from water drinking is up to 16 hours. We found that the incidence of CVT was four time higher in Ramadan comparing to the other months of years according to our previous study.\textsuperscript{3} Therefore giving information and warning to all women especially those who have others risk factors should be considered.

Conclusion

Taking together our results reported nine cases of CVT who used contraceptive pills in Ramadan to delay women’s menstruation. This finding highlights the requirement for further studies with larger sample sizes, and we believe that it should be considered by healthcare system. We think there is an association between CVT and OCPs in fasting woman during Ramadan in this series.
Table 1. Demographic characteristics, investigations, treatments, and outcomes of cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Clinical manifestation*</th>
<th>Involved veins or sinus</th>
<th>Predisposing factor**</th>
<th>Treatment</th>
<th>Hospital discharge outcome</th>
<th>Duration of hospital stay</th>
<th>F/u period (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, vertigo, nausea, vomiting, papilledema, blurred vision and seizure</td>
<td>Superior sagittal sinus, bilateral cortical</td>
<td>Absent</td>
<td>Heparin and then warfarin and anticonvulsant</td>
<td>Recovered</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, vertigo, nausea, vomiting and bilateral papilledema</td>
<td>Superior sagittal sinus</td>
<td>Absent</td>
<td>Enoxaparin and then warfarin</td>
<td>Recovered</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, vertigo, weakness and drop attack, low blood pressure</td>
<td>Superior sagittal sinus</td>
<td>Absent</td>
<td>Heparin and then warfarin</td>
<td>Recovered</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, non-specific paresthesia in four limbs</td>
<td>Superior sagittal sinus</td>
<td>Absent</td>
<td>Enoxaparin and then warfarin</td>
<td>Recovered</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, vertigo, tinnitus and numbness of left face and limbs especially foot. Muscle weakness and seizure</td>
<td>Thrombosis of right transverse (lateral sinus) extending to the jugular vein</td>
<td>Absent</td>
<td>Enoxaparin and then warfarin and anticonvulsant</td>
<td>Recovered</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, vertigo, blurred vision and diplopia, papilledema</td>
<td>Left lateral sinus, bilateral sigmoid sinus and jugular vein</td>
<td>Absent</td>
<td>Heparin and then warfarin</td>
<td>Recovered</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, vertigo, vomiting</td>
<td>Left lateral sinus</td>
<td>Absent</td>
<td>Enoxaparin and then warfarin</td>
<td>Recovered</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>F</td>
<td>Kurdish</td>
<td>Headache, low blood pressure vertigo, nausea, vomiting papilledema, blurred vision and seizure</td>
<td>Left lateral sinus and bilateral sigmoid sinus</td>
<td>Absent</td>
<td>Heparin and then warfarin anticonvulsant</td>
<td>Recovered</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>F</td>
<td>Kurdish</td>
<td>Low level of consciousness (GCS = 3). Tachypnea and double Babinski extensor</td>
<td>Superior sagittal sinus, left transverse sinus and deep cerebral veins</td>
<td>Obesity BMI = 35</td>
<td>Mannitol and dexamethasone</td>
<td>Expired*** (due to hemorrhagic infarction)</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

*Clinical features of cases including headache (100%), vertigo (44%), nausea and seizure (33%), vomiting (55%), Papilledema (33%), blurred vision (22%);
**Predisposing factors, including coagulative disorders and inflammatory diseases and etc. were evaluated and excluded;
***The only one patient (11%) expired due to massive hemorrhagic infarctions and thrombosis. GCS: Glasgow Coma Scale; BMI: Body mass index
Conflict of Interests
The authors declare no conflict of interest in this study.

Acknowledgments
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References
Cerebral venous thrombosis (CVT) is a condition that affects about five people per million and accounts for 0.5% of all strokes. It results from thrombosis of the intracranial veins and dural venous sinuses that drain blood from the brain.

CVT is a neurological condition with nonspecific symptoms. Magnetic resonance imaging (MRI) in conjunction with MR venography (MRV) is the most sensitive technique for the diagnosis of CVT. The important finding in CVT on MRI images is the absence of normal flow void on T1 and T2-weighted images (WIs). Signal changes depend on the age of the thrombosis and the amount of residual flow. Common manifestations include headache, focal neurologic deficits, seizures, and variable consciousness. Other signs worth mentioning are obscuration of vision, nausea, papilledema, cranial nerve palsies, and coma. Most patients with deep venous thrombosis have a good outcome, with 60–70% recovering completely and 30–40% having residual neurologic deficits. The mortality rate is around 7–10%.
venous sinus thrombosis show signs of increased intracranial pressure. Isolated subarachnoid hemorrhage may also occur rarely due to CVT. Conventional T1 and T2-weighted spin echo (SE) sequences are not sensitive enough to exhibit CVT particularly in acute phases. Theoretically, T2-weighted gradient recalled echo (GRE) sequences can be more efficient in the depiction of CVT due to their higher sensitivity to magnetic susceptibility differences. In this study, we employed various MRI sequences to evaluate patients with CVT.

Materials and Methods

In this study, 17 patients with CVT were examined. All the patients had undergone MRI studies. MRI images were obtained using a 1.5 T MR scanner (MAGNETOM Avanto, Siemens) equipped with 18 receiver channels. The imaging sequences included T1-WI [repetition time/echo time (TR/TE), 430/9 ms], T2-WI [(TR/TE), 3720/100 ms], fluid attenuated inversion recovery (FLAIR) [TR/TE/inversion time (TI)], 7100/92/2232.4 ms], diffusion WI (DWI) [(TR/TE), 720/126 ms, flip angle (FA); 90°, matrix size; 192 × 192 and field of view (FOV); 230 × 230 mm].

T2-weighted conventional GRE images were obtained from all subjects (TR-720 ms; TE-26 ms; FA = 25°, axial planes; slice thickness, 5 mm; matrix size, 256 × 110; and FOV, 138 × 270 mm).

Afterward, three-dimensional enhanced MRV images [(TR/TE), 3/1 ms, FA = 25°] were acquired during injection of Dotarem. A dose of 0.1 mmol of Dotarem was injected at the rate of 2 ml/s. All MRI images were reported by two experienced radiologists and a neurologist. The reviewers were in strong agreement regarding the visualization of thrombosis on various evaluated imaging sequences. However, there were two conflicts in the detection of thrombosis on DWI sequences between the radiologists. One of the radiologists believed that the thrombosis was detectable in the two mentioned sequences for subacute cases. The final diagnosis was that the thrombosis was undetectable (not seen). Signal changes were evaluated relative to the gray matter for each pulse sequence. The data were entered into SPSS software (version 16, SPSS Inc., Chicago, IL, USA) and the following formulas were employed to evaluate confidence interval (CI) and intraclass correlation coefficient (ICC).

\[
CI = \text{Sensitivity} \pm 1.96 \times SE
\]
\[
ICC = \frac{\sigma^2_w}{\sigma^2_b + \sigma^2_w}
\]

\(\sigma^2_w\) is the pooled variance within subjects, and \(\sigma^2_b\) is the variance of the trait between the subjects.

Visualization of venous sinus thrombosis was assessed based on the following criteria:
1. Visible (1-1 high signal, 1-2 low signal)
2. Iso signal (insufficient for diagnosis)
3. Not seen.

Results

A total of 17 patients (75.5% female) with CVT were involved in this study with the mean age of 45 ± 18.76 ranging from 4 to 72 years (Table 1). Sensitivity tests were employed to evaluate the diagnostic value of T2-weighted GRE, FLAIR, T2-weighted, T1-weighted, and DWI sequences. Sensitivity value of T2-weighted GRE, FLAIR, T2-weighted, T1-weighted and DWI methods equaled 0.94, 0.82, 0.52, 0.64, 0.06, respectively. CI of the mentioned sequences was (0.85, 0.99), (0.69, 0.92), (0.38, 0.59), (0.53, 0.77), and (0.00, 0.09), respectively. Sensitivity value of T2-weighted GRE, FLAIR, T2-weighted, T1-weighted and DWI methods for subacute cases equaled 0.9, 0.55, 0.09 and for acute cases equaled 1, 0.5, 0.0 CI of the mentioned sequences for subacute cases was (0.57, 0.99), (0.77, 1), (0.25, 0.82), (0.76, 1), (0.04, 0.42) and for acute cases was (0.75, 1), (0.14, 0.86), (0.14, 0.86), (0.0, 0.048), (0.0, 0.48). ICC test showed significant agreement between all methods in the diagnosis of CVT (P < 0.05). ICC with the exact value of 0.27 indicates a weak agreement among the evaluated sequences.

T2-weighted conventional GRE sequences were superior in the detection of CVT in comparison with other techniques (Figure 1, A-F).

Discussion

CVT is a cerebrovascular disorder that most often affects young adults and children. Contrast enhanced MRV (CE-MRV) can perfectly demonstrate the thrombosis, small vein details, and collaterals. Conventional MRI is unreliable. It is sometimes difficult to decide whether the signal within a cerebral vein corresponds to the flow or to the thrombosis. An acute clot (up to 5 days) is isointense to the gray matter on T1-weighted and therefore easily missed and hypointense on T2-weighted.

In this study, areas of thrombosis were more prominently shown on GRE pulse sequence due to the high sensitivity of this sequence to tissue susceptibility differences. Other techniques were not as beneficial as T2-weighted GRE sequences. Previous investigations have evaluated T2-weighted GRE sequences in the diagnosis of CVT.
Table 1. Visual assessment of cerebral venous sinus thrombosis in various sequences

<table>
<thead>
<tr>
<th>Sex/age</th>
<th>Location of thrombosis</th>
<th>T₁</th>
<th>T₂</th>
<th>FLAIR</th>
<th>DWI</th>
<th>T₂*GRE</th>
<th>Stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/50</td>
<td>SSS + Straight sinus</td>
<td>1-1</td>
<td>1-1</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>F/4</td>
<td>SS</td>
<td>1-1</td>
<td>1-1</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Convulsion, variable consciousness</td>
</tr>
<tr>
<td>F/61</td>
<td>TS</td>
<td>1-1</td>
<td>3</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, cerebral palsy</td>
</tr>
<tr>
<td>F/26</td>
<td>SS + TS</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1-2</td>
<td>A</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>F/53</td>
<td>TS + SS</td>
<td>1-1</td>
<td>3</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, obscuration of vision, nausea</td>
</tr>
<tr>
<td>F/38</td>
<td>TS + SS</td>
<td>1-1</td>
<td>3</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, epilepsy</td>
</tr>
<tr>
<td>F/57</td>
<td>TS</td>
<td>1-1</td>
<td>2</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, nausea, seizure</td>
</tr>
<tr>
<td>F/30</td>
<td>SSS + TS + SS</td>
<td>1-1</td>
<td>2</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, seizure, nausea</td>
</tr>
<tr>
<td>F/64</td>
<td>TS</td>
<td>3</td>
<td>3</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>A</td>
<td>Headache, variable consciousness, nausea</td>
</tr>
<tr>
<td>F/49</td>
<td>TS</td>
<td>2</td>
<td>1-1</td>
<td>2</td>
<td>3</td>
<td>1-2</td>
<td>A</td>
<td>Headache, cerebral palsy, seizure</td>
</tr>
<tr>
<td>F/27</td>
<td>SS</td>
<td>1-1</td>
<td>1-1</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, nausea, convulsion</td>
</tr>
<tr>
<td>M/72</td>
<td>TS + SS</td>
<td>1-1</td>
<td>1-1</td>
<td>1-1</td>
<td>3</td>
<td>3</td>
<td>S</td>
<td>Headache, epilepsy, obscuration of vision</td>
</tr>
<tr>
<td>M/26</td>
<td>TS</td>
<td>3</td>
<td>3</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>A</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>F/48</td>
<td>SSS + TS</td>
<td>1-1</td>
<td>1-1</td>
<td>1-1</td>
<td>1-1</td>
<td>1-2</td>
<td>S</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>F/41</td>
<td>TS</td>
<td>2</td>
<td>1-1</td>
<td>2</td>
<td>3</td>
<td>1-2</td>
<td>A</td>
<td>Headache, convulsion</td>
</tr>
<tr>
<td>M/55</td>
<td>TS + SS</td>
<td>1-1</td>
<td>1-1</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>S</td>
<td>Headache, variable consciousness</td>
</tr>
<tr>
<td>F/71</td>
<td>SSS</td>
<td>2</td>
<td>1-1</td>
<td>1-1</td>
<td>3</td>
<td>1-2</td>
<td>A</td>
<td>Headache, nausea, convulsion</td>
</tr>
</tbody>
</table>

M: Male; F: Female; TS: Transverse sinus; SS: Sigmoid sinus; SSS: Superior sagittal sinus; GRE: Gradient echo; FLAIR: Fluid attenuated inversion recovery; DWI: Diffusion weighted imaging

1: Visible (1-1 high signal, 1-2 low signal), 2: Iso signal (insufficient for diagnosis), 3: Not seen, A: Acute (< 5 days), S: Sub-acute (5-15 days)

Figure 1. Cerebral venous thrombosis in a 50-year-old male with history of headache
Note the hypointense area on T₁-weighted gradient echo sequence (arrow) (A), thrombosis is invisible on T₂-weighted image (B), T₁-weighted image (C), fluid attenuated inversion recovery (D), diffusion weighted imaging (E), the absence of flow signal on contrast-enhanced magnetic resonance venography image represents the precise location of thrombosis (F)
Ihn et al.\textsuperscript{9} have assessed the efficacy of T$_2^*$-weighted GRE in 11 patients with CVT and compared the results with other conventional sequences. They reported that T$_2^*$-weighted GRE was able to visualize marked signal loss from CVT in all the studied patients.

Fellner et al.\textsuperscript{10} have evaluated the importance of T$_2^*$-weighted GRE MRI in the diagnosis of cortical vein thrombosis in six cases of CVT. In four cases, which involved superficial venous thrombosis, the susceptibility effect on GRE sequences in the thrombosed cortical veins was the most pronounced finding compared with those seen on other pulse sequences.

We found that conventional sequences were not satisfying in the detection of acute stage. CE-MRV can perfectly demonstrate the thrombus, small vein details, and collaterals. CE-MRV showed the extension and the exact location of thrombosis. SE-MRV revealed the clot in all of the assessed patients. It can be concluded that T$_2^*$-weighted GRE sequences are more sensitive to paramagnetic effects compared with the sequences based on SE. T$_2^*$-weighted GRE sequences are effective in the detection of CVT, particularly in acute stage.

**Conclusion**

These sequences can be used as a standard MR pulse sequence. MRV is impressively helpful in the diagnosis and the determination of the extent of CVT.

**Conflict of Interests**

The authors declare no conflict of interest in this study.

**Acknowledgments**

We acknowledge all patients that have participated in this study.

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**References**

Psychogenic nonepileptic seizures in adult neurology clinics in southern Iran: A survey of neurologists

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Keywords
Seizures; Epilepsy; Psychogenic; Diagnosis; Perception; Practice; Iran

Abstract
Background: We investigated the perceptions of the neurologists practicing in Fars province in Southern Iran about psychogenic nonepileptic seizures (PNES); their diagnostic processes and management strategies.

Methods: In this survey, all neurologists participating at the annual meeting of neurologists were asked to participate. These neurologists practice in Fars province. An anonymous questionnaire was specifically developed for this study.

Results: About 18 neurologists (14 males and four females), out of 20 attendees, agreed to participate in the study. The mean age of the participants was 41.6 ± 7.5 years. They estimated that 10.8% of patients attending their clinic had seizures or blackouts, whereas 4.4% of patients attending their clinic had PNES. The experiences of the participants about the manifestations that potentially differentiate PNES from epileptic seizures; the tests they use to diagnose suspected patients and their treatment strategies showed significant variability. For example, the tests the neurologists always used for the diagnosis of PNES in suspected patients included routine electroencephalographs (EEGs) by 9 (50%), video-EEG monitoring by 4 (22%), and serum creatine phosphokinase (CPK) measurement by 2 (11%).

Conclusion: There is much variability in the approaches to diagnosis and management of PNES in southern Iran. The participants in our study were aware of the many knowledge gaps in this area.

Introduction
Psychogenic nonepileptic seizures (PNES) are relatively common reason why patients attend epilepsy clinics. In patients with PNES, it takes a mean of more than 5 years to reach to a correct diagnosis and most of these patients receive inappropriate treatment with antiepileptic drugs (AEDs). This observation demonstrates that most physicians continue to struggle with the correct diagnosis of PNES and their distinction from epileptic seizures. Patients with PNES are at risk of iatrogenic harm, as they are more likely to receive inappropriate medications, hospital admissions, and emergency treatments.

In this study, we investigated the perceptions of the neurologists practicing in Fars province in Southern Iran about PNES, the diagnostic processes and management strategies for this disorder, to identify possible education and training needs.
Materials and Methods

In this survey, all 20 neurologists present at the annual meeting of the neurologists were asked to participate. These neurologists practice in Fars province. An anonymous questionnaire was developed for this study. This questionnaire included questions about the participant’s gender, age, years in practice, place of practice, and also questions with regard to the epidemiology of PNES at their clinics, manifestations and tests that potentially differentiate PNES from epileptic seizures in suspected patients, and their treatment strategy in patients with PNES. Their answers were summarized descriptively and analyzed anonymously. This study was conducted with the approval by Shiraz University of Medical Sciences Review Board.

Results

A total of 18 neurologists (14 males and 4 females) agreed to participate. All respondents completed over 90% of the individual items on the questionnaire. The mean age [± Standard deviation (SD)] of the participants was 41.6 ± 7.5 years. They were in practice for 8.9 ± 7.9 years (range: 1-30 years). Four participants were in academic practice, seven neurologists were in private, and seven others were both in academic and private practice.

They estimated that 10.8 ± 15.3% (range: 1-70%) of patients attending their clinic had seizures or blackouts, whereas 4.4 ± 6.8% (range: 0.1-30%) of patients attending their clinic had PNES. Their estimate was that 7.0 ± 9.5% (range 0-30%) of patients with PNES attending their clinic had both epilepsy and PNES. Finally, they said that 77.2 ± 15.2% (range: 40-90%) of patients with PNES attending their clinic were women.

The experiences of the participants about the manifestations that potentially differentiate PNES from epileptic seizures are shown in table 1.

Table 1. The experiences of the participants about the manifestations that potentially differentiate psychogenic nonepileptic seizures (PNES) from epileptic seizures

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Only in epilepsy</th>
<th>Mostly in epilepsy</th>
<th>Equally common in epilepsy and PNES</th>
<th>Mostly in PNES</th>
<th>Only in PNES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized fine shaking (tremor)</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Generalized violent shaking</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Focal shaking (in one limb or one side of the body)</td>
<td>0</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asynchronous limb movements</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Out of phase clonic activity</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Intermittent or waxing and waning motor activity</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Pelvic movements (forward thrusting)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Side to side head movement</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Eyes closed during convulsive seizure</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Resisted eyelid opening</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Dystonic limb movements and opishtotonous back arching</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Gradual onset and cessation of seizures</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Ictal crying, weeping</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Postictal crying, weeping</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged seizures (more than 2-3 minutes)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Emotional or situational trigger for the seizures</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Seizures provoked by suggestion</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Aura</td>
<td>5</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>2</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Fecal incontinence</td>
<td>4</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nocturnal seizures</td>
<td>5</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ictal injury</td>
<td>3</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Seizures lasting more than 5 minutes</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>High seizure frequency (several per week)</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Clustering of seizures</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>No response to AEDs</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

*Some answers were missing.

AED: Antiepileptic drug; PNES: Psychogenic nonepileptic seizures
The tests the neurologists always used for the diagnosis of PNES in suspected patients included routine electroencephalographs (EEGs) by 9 (50%), video-EEG monitoring by 4 (22%), and serum creatine phosphokinase (CPK) measurement by 2 (11%). Only 5 (28%) neurologists said they always discontinue the AEDs and 12 (67%) said they always refer the patient to a psychologist or psychiatrist. 10 (56%) neurologists said that they tended to follow the patients up until AEDs are withdrawn, and 4 (22%) followed the patients up until seizures were controlled. 11 neurologists (61%) believed that it is very helpful and five persons (28%) said that it is somewhat helpful to attend a teaching course or symposium about different aspects of PNES to improve their practice.

Discussion

In this survey, we investigated the perception and the clinical approach of the participating neurologists to PNES in Southern Iran. The respondents’ estimate of the patients with PNES attending their clinics (4.4%) showed that PNES are relatively common even in general neurology clinics. This observation has been repeatedly mentioned in previous studies.1,8 The participants in our study thought that about 7.0% of patients with PNES attending their clinic had both epilepsy and PNES. This figure is different from what we observed in our previous study in the same region when the patients were investigated thoroughly with prolonged video-EEG recordings (17.0%).9 This difference probably reflects the challenges the neurologists face in making a correct diagnosis in suspected patients.10 This challenge was clearly highlighted when we asked about the experiences of the participants about the manifestations that potentially differentiate PNES from epileptic seizures (Table 1). In addition, we observed that there was confusion among the neurologists in our region with respect to the tests used for the diagnosis in patients suspected of having PNES. A similar observation has previously been reported from the UK.8

More frequent use of video-EEG monitoring may allow neurologists to make a definitive diagnosis more often. This will reduce the inappropriate use of AEDs and direct patients with PNES to more appropriate forms of treatment. A definitive diagnosis also reduces the risk of over diagnosing PNES in patients with epilepsy or emotional problems.8 When asked about their treatment and follow-up strategies, the variability of approaches among the neurologists was as great as that variability in their diagnostic processes. Again, this observation has been reported in previous studies.8

Conclusion

The findings of our study show that there is much variability in the approaches to diagnosis and management of PNES. The participants in our study were aware of the many knowledge gaps in this area: About 90% of the respondents endorsed the need to attend a teaching course or symposium about different aspects of PNES to improve their practice.

Conflict of Interests

The authors declare no conflict of interest in this study.

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References

Progressive ataxia due to alpha-tocopherol deficiency in Pakistan

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Keywords
Vitamin E Deficiency; Ataxia; Alpha-Tocopherol

Ataxia is a common neurological symptom defined as the loss of ability to control and coordinate bodily movements. It has multiple etiologies, among which vitamin E deficiency is a treatable and relatively reversible cause. Early diagnosis of vitamin E deficiency and vitamin E replacement can alleviate the symptoms, and halt the disease progression and even reverse ataxia associated with it. Ataxia resulting from vitamin E deficiency closely resembles Friedreich's ataxia. Patients should be screened for vitamin E deficiency, if they do not possess the diagnostic criteria for Friedreich's ataxia. There have been reports of vitamin E deficiency in Western literature, but a PubMed search did not show any case reports from Pakistan.

This case report presents a 15 year old boy referred to the neurology outpatient department for evaluation of multiple complaints. His complaints started 4 years back with clumsiness in walking which was followed by mood disturbance. After 6 months, his family noted he was being more aggressive which over the course of 4 years slowly progressed. Behavior changes included disinhibition with increased interest in sexuality. He started surfing explicit websites on the internet with pornographic material. He became more intuitive and more curious with increased interest in strangers and their personal belongings. He also had an increased appetite, and in the last 4 years, he had been having progressive weight gain. Past history was significant for paroxysmal nocturnal

General examination showed that he had a body mass index (BMI) of 33 kg/m², and his general physical examination was unremarkable. He was fully conscious, alert, and oriented with preserved memory. Gait was ataxic with impaired tandem walking. He had bilateral finger nose ataxia with past pointing. Cranial nerves were intact and vision was normal, pupils were 3 mm round and reactive to light. Ocular movements revealed impaired saccadic eye movements in all directions. Facial sensations and symmetry were normal as were hearing, and tongue and pharyngeal movements. There was no muscle wasting or fasciculations. His muscle tone was normal and power was 5/5 in proximal and distal muscle groups of arms and legs. His ankle reflexes were diminished (1+) with bilateral flexor plantar response. Sensations and joint position sense were normal.

Magnetic resonance imaging (MRI) of the brain showed prominent cerebellar folia (Figure 1). Electroencephalogram (EEG) was essentially unremarkable. Laboratory investigations revealed serum ceruloplasmin of 32 mg/dl (normal: 20-60 mg/dl), serum copper of 142.31 ng/dl (normal: 70-140 ng/dl), serum vitamin E of 2.5 mg/dl (normal: 8.9-18.3mg/l), serum fasting cholesterol of
181 mg/dl (normal: < 200 mg/dl), and serum alpha fetoprotein of 1.84 ng/ml (normal: 0.89-8.78 ng/ml). Serum vitamin E levels showed severe deficiency. Serum electrolytes, serum ceruloplasmin, serum alpha fetoprotein, and vitamin B12 were within normal limits. Moreover, lipid profile and thyroid profile were normal.

He was diagnosed as a case of alpha-tocopherol deficiency. He was prescribed 600 mg vitamin E capsules twice daily. On his subsequent follow-up 3 months later, his behavior had markedly improved with reduced aggressiveness, hypersexuality, and hyperphagia. Yet, his ataxic features still persist. He is currently on vitamin E supplementation (400 mg thrice daily).

Ataxia is a movement disorder characterized by incoordination of movements. Brain structures such as the cerebellum, brainstem, dorsal columns, and vestibular system may be involved. It can be hereditary, sporadic, or secondary to other diseases. Although Friedreich's ataxia is more common, it can easily be confused with other autosomal recessive cerebellar ataxias (ARCAs) which have similar clinical manifestations. One of the more treatable conditions among these is ataxia with vitamin E deficiency (AVED).

Alpha-tocopherol deficiency is associated with peripheral nerve damage. The condition associated with this deficiency is called AVED. The mechanism underlying this condition is not fully understood. One hypothesis is that vitamin E prevents tissue damage due to oxidative stress. A hereditary cause of vitamin E deficiency is isolated vitamin E deficiency which manifests as a progressive sensory and cerebellar ataxia that usually begins before 20 years of age. Its clinical signs are similar to those of Friedreich's ataxia which include dysarthria, lower extremity areflexia, loss of proprioception, gait ataxia, and positive bilateral Babinski sign. However, cardiomyopathy and glucose intolerance are usually absent from the clinical presentations of AVED as compared to Friedreich's ataxia. Thus, in the absence of a frataxin gene mutation, these signs should prompt the physician to consider vitamin E deficiency. As most ataxias are untreatable and progressive, it is necessary to search for causes which are treatable. A timely diagnosis and vitamin E replacement may reverse the condition. High doses of vitamin E supplementation (800 mg daily) have been shown to reverse the neurological signs of AVED. In this report, we have highlighted the importance of considering vitamin E deficiency as a cause of progressive but treatable ataxia in children and young adults.

Conflict of Interests
The authors declare no conflict of interest in this study.

Acknowledgments
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A 68-year-old diabetic female with a 30-year history of rheumatoid arthritis presented to our emergency department with a 2-month history of a headache, blurred vision, and subsequent hearing loss complicated with recent unilateral facial weakness and imbalance.

She has been taking prednisolone 5 mg/day and methotrexate 7.5 mg weekly for almost 20 years. Other medications included oral anti-hyperglycemic agents and calcium supplements.

The patient’s husband, with whom she lives, was diagnosed with tuberculosis (TB) 9 months ago and was treated according to the World Health Organization (WHO) treatment protocol.

Her systemic examination revealed no obvious abnormality. She was afebrile and had neck stiffness, which was performed cautiously regarding the risk of atlantoaxial dislocation, were negative. On neurologic examination, she was alert but not fully cooperative due to profound bilateral hearing loss. Both pupils were reactive to light without evidence of positive relative afferent pupillary defect. Optic discs were blurred in margins bilaterally with reduced visual acuity. Right sided peripheral facial palsy was detected. Deep tendon reflexes and motor forces were reduced globally, and an ataxic gait was notable.

Laboratory investigations revealed a raised total leukocyte count (15700/mm$^3$) with 70% neutrophils and normal serum electrolytes, renal function tests, and liver function tests. Human immunodeficiency virus (HIV) antibodies and repeated blood cultures were all negative. The erythrocyte sedimentation rate level was 22; rheumatoid factor and other collagen vascular related tests were negative. Chest X-ray and lateral cervical X-rays were all normal.

The cerebrospinal fluid (CSF) examination was a cellular with protein and glucose level of 61 and 43 mg/dl, respectively (corresponding blood glucose was 75 mg/dl). Brain magnetic resonance imaging (MRI) with contrast and diffusion-weighted (DW) sequences showed a small deep infarction of the right basal ganglia without obvious evidence of meningeal enhancement or Virchow-Robin space involvement (Figure 1).

During her admission, she became febrile and a second lumbar puncture was considered, which demonstrated raised leukocytes at 40/mm$^3$ with a lymphocytic predominance of 80%, low-CSF glucose (27 with a corresponding blood glucose of 110), and raised protein level (62 mg/dl). Regarding her
previous TB exposure and recent abnormal CSF analysis, anti-TB drugs were started. After 4 days, the second CSF Indian ink preparation and CSF culture were reported to be positive for Cryptococcus neoformans and we discontinued all anti-TB drugs and initiated long-term treatment with amphotericin B.

Repeated lumbar punctures revealed negative TB CSF culture, TB polymerase chain reaction, Wright, and Coombs-Wright. She continued on amphotericin B liposomal until day 54 when it was changed to fluconazole (200 mg, twice daily). Repeated brain MRIs at 6 weeks showed no new features. The brain MRI remained unchanged, but CSF fungal culture and Indian ink preparation were negative 11 weeks after initiating amphotericin B. CSF analysis showed mild lymphocytosis with a normal protein and sugar in this stage of the disease. Her condition improved and she was discharged after 14 weeks from admission.

The prevalence of cryptococcal meningitis, most commonly caused by C. neoformans, has increased in the past 20 years due to increased prevalence of HIV infection and use of immunosuppressives. Its presenting symptoms include fever, headache, fatigue, and a slow progressive mental decline. Frequently there are no symptoms; however, papilledema, meningismus, and cranial nerve palsy may be evident as manifesting signs. Diagnosis is facile in HIV positive patients due to a high fungal load in CSF, which results in a positive Indian ink preparation. However, repeated lumbar punctures and cultures may be indicated to distinguish the causative organism in immunocompetent patients, which was carried out in our patient.

As previously mentioned cranial nerve palsy is a probable presentation of cryptococcal meningitis and may present as sudden or progressive sensory neural hearing, either unilaterally or bilaterally. However, among the cranial nerves involved, facial nerves seem to be the least reported. Therefore, the presentation of our patient, including multiple cranial nerves palsies, is completely rare. Previous studies have reported isolated eighth nerve palsy or optic neuropathy; however, the combination of the two with facial palsy is rather uncommon.

![Image](http://ijnl.tums.ac.ir)
Krishnamoorthy et al. reported a case of bilateral abducent and facial nerve palsy completely resolved with antifungal treatment as well as degrees of visual acuity and hearing loss resolution were observed.\(^5\) In our patient, ataxia, facial palsy, headache, and bilateral blurred vision resolved. However, the bilateral hearing loss did not improve.

Cryptococcal meningitis is a rare but fatal complication of immunosuppressive agents. This disease should be considered in all patients receiving cytotoxic presented by cranial nerve palsy.

**Conflict of Interests**
The authors declare no conflict of interest in this study.

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None.

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**References**

Influenza vaccination in patients with multiple sclerosis is possible with some considerations

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Keywords
Multiple Sclerosis; Influenza; Vaccine

Introduction
Influenza is a disease of particular concern for patients with multiple sclerosis (MS). Is influenza vaccine good for MS?

Types of influenza vaccine
Two types of influenza vaccine are used. The first one includes inactivated (killed) influenza virus administered intramuscularly and the second, live, attenuated, virus administered intranasally via an aerosol sprayer. Live attenuated vaccine is not recommended for MS patients.

Risk of MS onsets after influenza vaccination
Studies of the onset of MS after influenza vaccination had very serious methodological limitation and did not report any association between influenza vaccination and the increased risk of MS in adults.2-5

Influenza disease in patients with MS
Two studies showed that the risk of influenza-related hospitalizations, mortality, morbidity and relapse increased in patients with relapsing-remitting MS (RRMS).6,7

Influenza vaccination and relapse
It seems that influenza vaccination has a protective effect on MS and does not seem to exacerbate or deteriorate neurological status.7,8 Nevertheless, there is a small case series reporting relapses within 3 weeks of simultaneous H1N1 and seasonal vaccination.9

MS drugs and influenza vaccination
Corticosteroid: Corticosteroids did not prove to impair the immune response following influenza vaccination.10

Interferon-beta (INF-β): Seasonal influenza vaccination is safe and effective in 90.9% and 93.0% INF-treated patients.11

Glatiramer acetate (GA): GA may present a lower protection after influenza vaccination compared to healthy individuals.12

Mitoxantrone: Mitoxantrone can impair influenza vaccine immunogenicity and efficacy.12

Teriflunomide: The TERIVA study showed that influenza vaccination was sufficient in providing the considered protection in patients treated with teriflunomide.13
Dimethyl fumarate: There is not any data on dimethyl fumarate and influenza vaccination.

Fingolimod: Influenza vaccination in fingolimod-treated patients could be safe and protective but need a booster dose.14

Natalizumab: Influenza vaccination could be safe and protective in natalizumab-treated patients.15

Cytotoxic: Azathioprine-treated patients with systemic lupus erythematosus (SLE) had a diminished antibody response following influenza vaccination.16

Intravenous immunoglobulin (IVIG): The immunogenicity of live vaccines was impaired by IVIG for 6-12 months.17

Rituximab: In rituximab-treated patients, vaccination with inactivated vaccines might be effective.18

Time of vaccination

Following corticosteroid pulse therapy, it is recommended to delay vaccination for at least 2 weeks. In patients with MS treated with mitoxantrone and cyclophosphamide, it should be done between drug cycles. In immunosuppressive therapy, antibody testing is recommended 4 weeks following the vaccination and if the antibody titers failed to rise, revaccination should be kept in mind.19

Conflict of interests

The authors declare no conflict of interest in this study.

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None.

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