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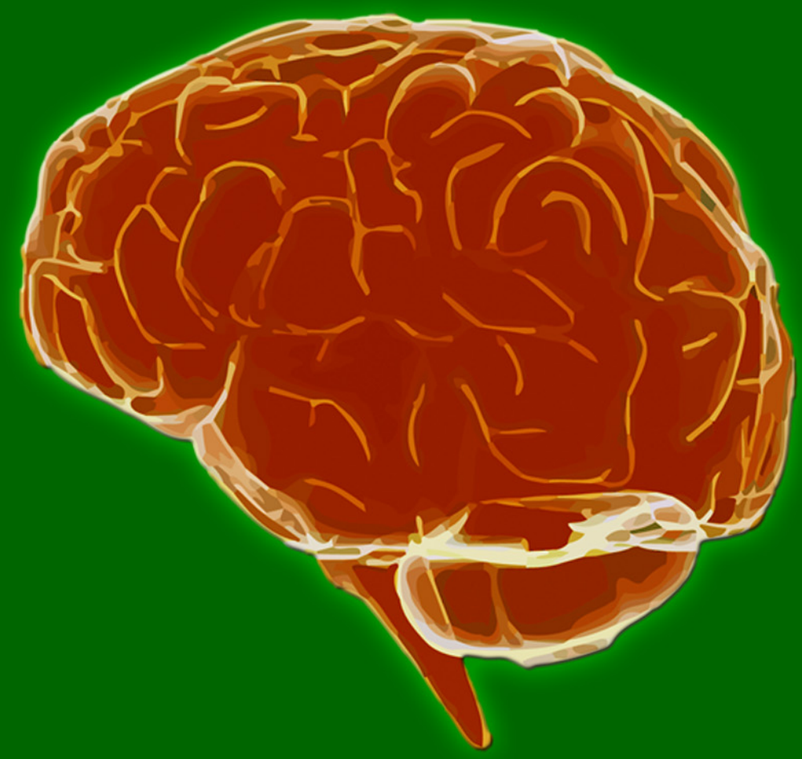

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Iranian Journal of Neurology

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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.

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Each section of the paper should begin on a new page

The manuscript must include:

Page 1: Title Page

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1. Title page:

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

2. Abstract page:

The length of the abstract should be at least 200 and not more than 250 words for original papers and not more than 150 words for review papers and case reports. Abstracts of original papers should be structured to include the background, methods, results and conclusion.

Below the abstract authors should provide between three and six keywords conforming to Medical Subject Headings (Index Medicus).

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

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Proofs: The proofs will be sent via email and must be accordingly corrected and get back within 48 hours.

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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2017; 16(4): 164-7

Determination of cut-off point of cross-sectional area of median nerve at the wrist for diagnosing carpal tunnel syndrome

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Keywords
Carpal Tunnel Syndrome; Electrophysiology; Ultrasonography

Abstract

Background: The most common entrapment mononeuropathy of the upper extremity is carpal tunnel syndrome (CTS). It consists 90% of entrapment neuropathies. The purpose of this study was to compare cross-sectional area (CSA) of the median nerve at the wrist in CTS patients and healthy controls and define the best cut-off point of CSA to differentiate patients and controls in Iranian population.

Methods: In this study, 45 patients with confirmed idiopathic CTS and 62 healthy controls were evaluated. Based on electrophysiological findings, patients were divided based on CTS severity into three groups of mild, moderate and severe. The largest CSA was measured at the level of distal wrist crease which is consistent with carpal tunnel inlet.

Results: Mean CSA was 0.124 ± 0.031 mm^2, 0.146 ± 0.028 mm^2 and 0.194 ± 0.062 mm^2 in mild, moderate and severe CTS patients respectively, and 0.077 ± 0.011 mm^2 in controls. Our results showed that participants with CSA > 0.010 had CTS with 100% specificity and 83.12% sensitivity.

Conclusion: It is possible to diagnose CTS by measuring CSA and using above-mentioned cut-off point.

Introduction

The most frequent entrapment neuropathy is the neuropathy of median nerve at the wrist, called carpal tunnel syndrome (CTS), which occurs as a result of compression of the median nerve at the carpal tunnel. CTS is one of the leading causes of hand dysfunction. Median nerve entrapment in the carpal tunnel causes clinical symptoms such as pain, numbness, and tingling.[1-4] The prevalence of CTS has been shown to be 5.8% and 0.6% in women and men, respectively.[5] A few studies conducted in the United States of America showed 0.2% of all outpatient visits had been due to CTS.[6] Although electrophysiological tests have been considered as the gold standard for CTS diagnosis and distinguishing the different severities of disease,[7,8] their sensitivity ranges from 49% to 86% and their false negative range is between 16% and 34%.[9,10] This variability seems to be attributed to different study methods and measurement

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techniques, in addition to demographic factors such as gender, age and weight.[11]

In the last few years, it has been shown that ultrasonography is a useful diagnostic tool for CTS diagnosis because of its noninvasiveness, lower cost and wide availability.[3,12] The cross-sectional area (CSA) of the median nerve at different locations, can be measured for this aim. Different studies showed that CSAs of the median nerve at different levels of the carpal tunnel are significantly greater in CTS patients as compared to normal population. Various studies suggested different cut-off points for the diagnosis of CTS.[13,14] In previous studies, cuto-ff point of cross-sectional area at tunnel inlet in CTS patients ranged from 6.5 to 15 mm^2.[15-18]

The aim of this study was to compare CSA of the median nerve at the wrist in patients with CTS and normal controls and define the best cut-off point of CSA to differentiate patients and controls in Iranian population.

Materials and Methods

This case-control study was conducted in a one-year period in the neuromuscular department of teaching hospitals of Isfahan, Iran. According to sample size estimation, at least 14 patients were needed to be enrolled in each group, but for more accurate results we enrolled 45 patients with established idiopathic CTS (within two weeks of electrophysiological examination) in 77 of their wrists and 62 healthy controls, with 124 normal wrists.

All electrodiagnostic (EDX) studies were done before ultrasonography evaluation by a neurologist with neuromuscular expertise. According to EDX results, patients were categorized as mild, moderate, and severe CTS based on the following criteria.[8] Mild: Prolonged distal sensory nerve action potential-latency (SNAP-L) and/or median mixed nerve action potential-latency (MNAP-L), and normal distal compound muscle action potential-latency (CMAP-L), and normal amplitudes of all responses. Moderate: Prolonged SNAP-L and CMAP-L, and with or without diminished amplitudes of all tested responses. Severe: Unobtainable median sensory nerve action potential plus low-amplitude or unobtainable median compound muscle action potential and, if present, prolonged CMAP-L.

Patients with underlying diseases that may affect CSA of median nerve independent of CTS, such as wrist trauma, cervical radiculopathy, polyneuropathy, and CTS patients with previous corticosteroid injection were excluded.

All participants filled out an informed consent before the study. All ultrasonography evaluations were done by means of a 13-MHz (SonoSite) linear array Transducer. The examiner was blinded to clinical symptoms and EDX results. Patients were asked to lie on the bed while their forearms are extended. They were rested in the supine position on a smooth surface, and their fingers were semi-extended. The largest CSA was measured at the wrist as described by Ziswiler, et al.,[19] at the beginning of the examination by performing gray scale examination.

Data were analyzed by using SPSS software (version 18, SPSS Inc., Chicago, IL, USA), presented as the mean ± standard deviation (SD). The analysis of variance (ANOVA) was applied for comparing continuous variables. Receiver operating characteristic (ROC) curve was used to determine optimal cut-off values of the median nerve inlet CSA. In addition, we used analysis of covariance (ANCOVA) to neutralize the confounding effects of different factors on CSA. The area under the curve (AUC) was calculated. $P \leq 0.050$ was statistically considered significant.

Results

Table 1 and figure 1 both show the descriptive statistics of the median nerve CSA at the wrist.

Table 1. Descriptive statistics of median nerve cross-sectional area (CSA) at the level of carpal tunnel inlet in mild, moderate, and severe carpal tunnel syndrome (CTS)

Subjects	Mean ± SD	Range
Control	0.077 ± 0.012	0.05-0.10
Mild	0.124 ± 0.032	0.08-0.18
Moderate	0.147 ± 0.028	0.08-0.19
Severe	0.195 ± 0.063	0.11-0.32
Total	0.106 ± 0.049	0.05-0.32

SD: Standard deviation

As the aim of our study was a differentiation between healthy controls and CTS patients using CSA, ROC curve was used to define a cut-off point for the diagnosis of CTS. Different values of CSA were considered as cut-off points. Sensitivity and specificity (percent of correct detection of controls and patients) were determined for each cut-off point (Figure 2).

As high sensitivity and specificity were very important in this study, a point of ROC curve which had the highest sensitivity and specificity was defined using Youden index, as the cut-off

point. So our results showed that participants with CSA > 0.01 had CTS with 83.12% sensitivity and 100% specificity. AUC of ROC curve was calculated equal to 0.962, which is statistically significant (P < 0.001), and showed the prediction ability of CSA is not based on chance.

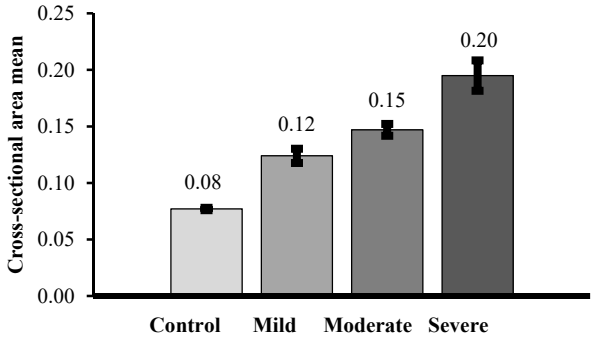

Figure 1. Mean cross-sectional area (CSA) of median nerve in different groups

ANOVA showed that mean CSA-D has a statistically significant difference between controls and different groups of patients (P < 0.001). Our analyses showed that the mean age has a significant difference between case and control groups; therefore, ANCOVA was used to adjust this difference. However, there was still a significant difference of mean CSA-D between two groups with adjusting to age (P < 0.001).

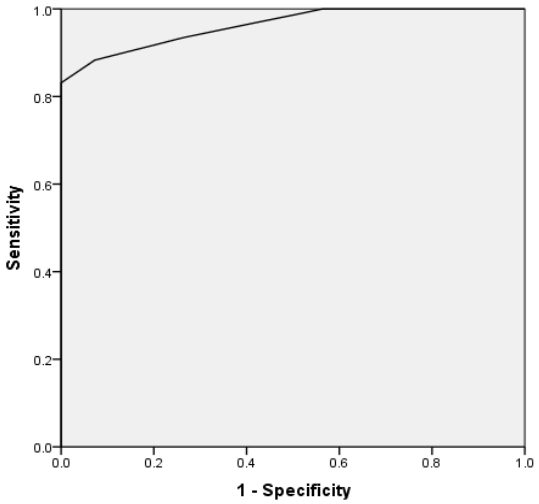

Figure 2. Receiver operating characteristic (ROC) curve

Discussion

Our results demonstrated that the largest mean value of CSA is (0.194 mm^2) in severe CTS patients and the smallest mean value is (0.124 mm^2) in mild CTS patients. Thus, there is the statistically significant difference between the mean CSA in severe and mild CTS patients. In addition, the results of this study showed that mean CSA of the median nerve at the wrist in CTS patients was significantly different from healthy controls and the best cut-off point of CSA for diagnosing CTS is 0.543 mm^2, which is an appropriate value.

Mohammadi, et al. studied the diagnostic significance of median nerve CSA in severity grading of CTS. Unlike our results, they found that the difference in CSA of the median nerve in different severities of CTS was not statistically significant in either the tunnel inlet or outlet. They also concluded that ultrasonography does not have any diagnostic value for grading the severity of CTS.[16]

Similar to our study, Sarraf, et al. studied the best cut-off point for the median nerve CSA at the level of carpal tunnel Inlet. According to their results, mean CSA and perimeter in patients and healthy controls were significantly different and the best cut-off point for CSA was 10.5 mm^2 with 80% and 76% sensitivity and specificity, respectively. Ultimately, they believed that median nerve CSA at the wrist is helpful as a diagnostic tool for CTS.[18]

Dalili, et al. concluded that the CSA of median nerve at both inlet and outlet of the carpal tunnel has a considerable association with CTS diagnosis and could be used for diagnosis of CTS, which is similar to our findings.[7]

Also, we found that the sensitivity and specificity of CSA equal to 0.105 for diagnosing CTS is 83.1%, 100%, respectively.

In contrast to our results, Yazdchi, et al. concluded that the sensitivity and specificity of the median nerve ultrasonography for diagnosing CTS were low and ultrasonography could not replace nerve conduction study which is the gold standard of this diagnosis, but it might provide useful information.[13]

Ziswiler, et al. investigated the largest CSA of the median nerve at the wrist and found a mean value of 12.2 mm^2 in CTS patients and 7.9 mm^2 in controls. Moreover, a cut-off point of 10 mm^2 showed 82% and 87% sensitivity and specificity, respectively.[19]

In Nakamichi and Tachibana study, with the median nerve CSA cut-off point value of 12 mm^2, 67% sensitivity, 97% specificity, and 82% accuracy were reported.[20]

Ulasli, et al. studied the reasons for using

swelling ratio in sonographic diagnosis of CTS and a liable method for its calculation. Their results showed that the greatest sensitivity (99%) of the median nerve CSA is where the cut-off point is considered 10 mm^2. However, it had a low specificity value (71%), which increased the false positive rate.[21]

Conclusion

The current study showed that diagnosis of CTS is possible by measuring CSA. According to our findings, the most excellent cut-off point of median nerve CSA at the the wrist is 0.105 (with 100% specificity and 83.1% sensitivity) and 0.095 (more sensitive than the first cut-off point). It is an appropriate method in order to diagnose CTS.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We are grateful to all of those with whom we have had the pleasure to work during this and other related projects, especially our patients for their great cooperation.

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Iranian Journal of Neurology

Original Paper

Iran J Neurol 2017; 16(4): 168-72

The relationship of multiple sclerosis and cerebral developmental venous anomaly with an advantageous role in the multiple sclerosis diagnosis

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Keywords
Multiple Sclerosis; Cerebral Venous Angioma; Pathogenesis; Intracranial Central Nervous System Disorders; Venous Insufficiency; Magnetic Resonance Imaging

Abstract

Background: There is a suggestion for a role of abnormal cranial venous drainage in the etiopathogenesis of multiple sclerosis (MS). Moreover, it seems that cerebral developmental venous anomaly (DVA), a cerebrovascular malformation, is frequently seen in the magnetic resonance imaging (MRI) of MS patients. This study is set out to evaluate the relationship between MS and cerebral DVA, with its possible role in the MS diagnosis.

Methods: We compared MRI of 172 MS patients and of 172 age- and sex-matched subjects without MS. Then, we recorded and analyzed the presence, number, and location of developmental venous anomalies.

Results: Frequency of DVA did not have a significant statistical difference (P = 0.148) in subjects with MS (12.21%) and without MS (7.55%). Moreover, a difference of anatomic distribution of supratentorial developmental venous anomalies was not statistically significant (P = 0.690, for juxtacortical, P = 0.510 for subcortical, and P = 0.420 for periventricular DVAs) in two groups.

Conclusion: Our investigation does not provide supporting evidence for a relationship between etiopathogenesis of MS and DVA. Furthermore, it may not be possible to use cerebral DVA as ancillary MRI finding to make MS diagnosis simpler and more accurate.

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system,[1,2] identified from more than one century,[3] but its etiology is still in doubt.[4] Recently, abnormal cranial venous drainage has been described to have a possible role in the etiopathogenesis of MS. On the other hand, it has been suggested that the area of brain affected by developmental venous anomaly (DVA), also

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known as venous angioma, does not have normal venous drainage.[5] Additionally, it seems that cerebral DVAs are frequently seen in the brain magnetic resonance imaging (MRI) of MS patients. These explanations raise the question whether MS and DVA have any association. Furthermore, there is an issue about the coincidence of MS and DVA as well as an advantageous role of DVA (as an ancillary finding in brain MRI) in the diagnosis of MS.

Histopathologically, there is perivenular inflammation and demyelination in MS plaques,[6,7] which are located characteristically in juxtacortical, periventricular, or infratentorial regions of the brain.[8] Moreover, categorization of DVAs into three groups of juxtacortical, subcortical, periventricular is relevant to their location and drainage pattern.[9] In fact, these explanations may support the relationship of MS and DVA.

Another area for consideration is the era of MS diagnosis. MRI is salient imaging modality for diagnosing MS with the use of McDonald criteria.[1,10] Although MRI is a sensitive tool to find MS plaques, its specificity is low and might lead to a fault in the diagnosis especially in the early period of MS.[1,7,10] The reason is that the other conditions such as a migraine and microvascular disease, which have hypersignal white matter foci, could simulate MS plaques.[7] Consequently, the recognition of ancillary findings in brain MRI might help to diagnose MS simpler and more accurately. During our daily work, the DVAs have been frequently encountered in brain MRI of patients with lesions suspicious to MS. It has been proposed the idea that one of the ancillary findings may be the presence of cerebral DVA. We believe that it is essential to conduct a study to address questions about the possible relationship and the coincidence of MS and DVA.

Although several studies have been carried out to evaluate the possible relationship between abnormal cerebral venous flow and MS, there is a controversy about this topic. Furthermore, it has been suggested that the coincidence of vascular malformation and MS might happen but little attention has been drawn to this topic in the literature.[11] A research, using transcranial color duplex sonography, concluded that altered venous flow could have a possible role in MS inflammatory process.[12] Another multicenter study with use of color Doppler sonography reported that there is a relationship between chronic cerebrospinal venous insufficiency and MS.[13] However, they have suggested using more reliable imaging modality due to variable data about the diagnosis of chronic cerebrospinal venous insufficiency in different centers.[13] By contrast, another study utilizing magnetic resonance venography (MRV) and MR flow quantification showed equal distribution of anomalous cranial venous outflow in MS patients and healthy subjects.[14] They finally concluded that mentioned anomalous cranial venous outflow probably stand for anatomical variations of venous drainage rather than abnormalities that might have relationship with MS.[14]

The purpose of this study is to compare the frequency and anatomical distribution of cerebral DVA in MS patients and healthy subjects in order to emphasize on the relationship of their etiopathogenesis along with identification of DVA as an ancillary MR finding. It may help to make MS diagnosis simpler and more accurate.

Materials and Methods

This case-control study was conducted to compare the frequency and anatomic distribution of DVAs in patients with MS and subjects without MS. A total of 344 participants were recruited for this study. Eligible cases consisted of 172 patients with definite diagnosis of MS were referred from neurology clinic. Control group consisted of 172 subjects without MS were referred to perform MRI with non-specific reason. Subject demographics are presented in table 1. The mean age ± standard deviation (SD) of the case group was 32.75 ± 0.57 years, while it was 32.44 ± 0.58 years for the control group (age range in both groups was 18-50 years). Case and control groups were matched by age and sex. The local ethical committee approved this study and written informed consent was obtained from the participants.

Table 1. Sex and age distribution in case and control groups

Group	Man [n (%)]	Woman [n (%)]	Age (year) (mean ± SD)	Age range (year)
Case (n = 172)	25 (14.5)	147 (85.5)	32.75 ± 0.57	18-50
Control (n = 172)	25 (14.5)	147 (85.5)	32.44 ± 0.58	18-50

Exclusion criteria for case group were the presence of pathologies other than MS, such as malignancy, meningoencephalitis, vasculitis, hematopoietic disorders and history of other immunological diseases. Exclusion criteria for the control group were suspicious MS (clinically or radiologically); the presence of any abnormality (except for DVA) in MRI, or previous history of malignancy, meningoencephalitis, vasculitis, hematopoietic disorders, and other immunological diseases.

Brain MRI images were acquired using MRI systems operating with a magnetic field strength of 1.5 Tesla (Magnetom Avanto mobile MRI 02.05, software version: Syngo MR B15; Siemens Ltd, Erlangen, Germany) and the following sequences were obtained: Axial and coronal T2-weighted sequences, axial FLAIR (fluid attenuated inversion recovery) sequence, sagittal proton density-weighted sequence, axial and sagittal pre-contrast T1-weighted sequences as well as axial, sagittal and coronal post contrast T1-weighted sequences after administration of 0.1 mmol/kg of gadolinium contrast agents including Magnevist (gadopentetate dimeglumine, Germany) or Omniscan (gadodiamide, Ireland) or Dotarem (gadoteric acid, France).

All the MRI images studied by one radiologist and the presence, number, and location of DVAs were recorded. The diagnosis of DVA was based on its appearance on MRI images as multiple enlarged enhancing vessels with star-like configuration draining into a collecting vessel. The DVAs were assorted as supratentorial and infratentorial. In addition, supratentorial DVAs were categorized into three subgroups as juxtacortical (within a gray matter or at the junction of gray and white matter), periventricular (adjacent to ventricles), subcortical (between the juxtacortical and periventricular area).

Data analysis was performed using SPSS software (version 17, SPSS Inc., Chicago, IL, USA). The case and control groups were compared to each other by using the chi-square test and different variables were correlated with Pearson correlation. P less than 0.050 were regarded as statistically significant.

Results

A total of 344 participants (172 cases and 172 controls) were recruited for this study. Case and control subjects had similar age and sex distribution without significant difference (P = 0.070). Twenty-one (12.21%) patients of the case group and 13 (7.55%) subjects of the control group had DVAs. There was no significant difference between the two groups regarding frequency of DVAs (P = 0.148).

Of the 21 DVAs in the cases, 18 were supratentorial (Figure 1) and three were infratentorial. In the control group, three subjects had more than one DVA and a total of 17 DVAs (16 supratentorial, 1 infratentorial) detected in this group. The analysis did not reveal a significant difference between two groups on the subject of supratentorial DVAs (P = 0.400). Because of a limited number of infratentorial DVAs, they were not analyzed.

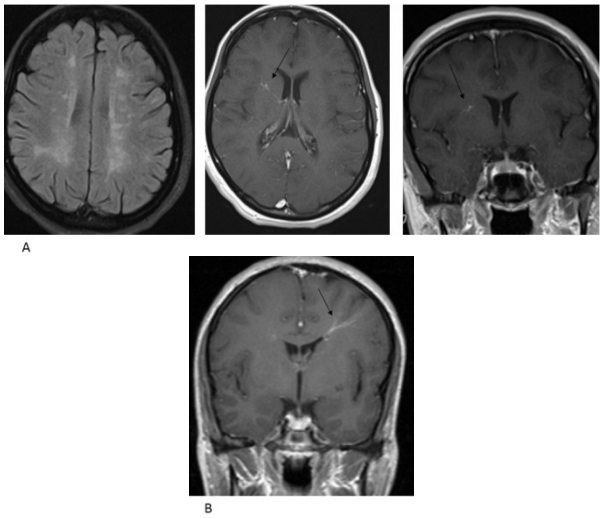

Figure 1. Developmental venous anomaly (DVA) in a patient with multiple sclerosis (MS). Axial fluid-attenuated inversion recovery image shows MS (multiple sclerosis) plaques and post-contrast T1-weighted images show enhancing vessels joining the collecting vein (arrows) (A), Developmental venous anomaly (DVA) in a control subject. Post-contrast T1-weighted image shows enhancing vessels joining the collecting vein (arrow) (B).

Table 2 summarizes the anatomical distribution of supratentorial DVAs. The difference between cases and controls on the subject of juxtacortical, subcortical, and periventricular DVAs was tested. P for juxtacortical DVAs was 0.690, for subcortical ones was 0.510, and for periventricular ones was 0.420. None of these differences was statistically significant.

Discussion

In this study, the frequency of DVA in patients with MS was 12.21% and in subjects without MS was 7.55%, in which their difference was not

significant statistically. Moreover, there was no statistically significant difference between cases and controls in terms of anatomic distribution of DVAs. We were surprised to find higher value for DVA frequency in subjects without MS, approximately 7.55%, as compared to previously reported frequency of DVA in the literature, which had been less than 2%.[5,15,16]

Table 2. Anatomical distribution of supratentorial developmental venous anomaly (DVA) in case and control groups

Supratentorial DVA	Case [n (%)]	Control [n (%)]	P*
Juxtacortical	3 (16.6)	3 (18.8)	0.690
Subcortical	7 (38.9)	8 (50.0)	0.510
Periventricular	8 (44.5)	5 (31.2)	0.420

*Chi-square test
DVA: Developmental venous anomaly

This investigation does not provide additional support for the association between anomalous cranial venous drainage and MS. Although the frequency of DVA in cases and controls was different, it was not statistically significant indicating that DVA is not more common in MS patients. Accordingly, it may not be possible to utilize cerebral DVA as ancillary MR finding for the diagnosis of MS. Moreover, anatomical distribution of DVA in the brain shows no significant correlation with the characteristic location of MS plaques. In fact, our results do not reinforce the association of MS and DVA, as an example of anomalous venous drainage.

Our results are consistent with previous works that claimed there is no relationship between chronic cerebrospinal venous insufficiency and etiopathogenesis of MS. In a study, using phase contrast MRI and with focus on the internal jugular vein, there was no supporting evidence for vascular MS hypothesis.[17] In another study, no association between chronic cerebrospinal venous insufficiency and lesion burden in MS patients could be found.[18] Results of another investigation were against the significant role of venous congestion in MS pathogenesis.[19]

As noted, this study shows a higher value for the frequency of DVA in subjects without MS. This finding can be justified in part by our study population, which control subjects were not selected from the general population. Another possible explanation for this may be that some DVA cases were not diagnosed in the past years due to the lower magnetic field strength of MRI systems or lower quality of their images. Therefore, we recommend that further research should be undertaken in this area.

A limitation of our research is that controls were not selected from the general population and they consisted of subjects without MS who referred to perform MRI with non-specific reason. However, we excluded subjects with suspicious MS (clinically or radiologically), those with any abnormality in MRI, and those with positive past history (as previously mentioned).

Conclusion

Frequency and anatomical distribution of cerebral DVA in patients with MS do not reveal a significant difference in comparison with subjects without MS. Consequently, our investigation does not provide supporting evidence for the relationship of the etiopathogenesis of MS and DVA, as an example of anomalous venous drainage. Furthermore, it may not be possible to utilize cerebral DVA as ancillary MR finding to make MS diagnosis simpler and more accurate.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Analysis of apolipoprotein E genetic variation in patients with Alzheimer disease referred to Imam Reza Clinic, Rasht, Iran, in 2015

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Keywords
Alzheimer Disease; Apolipoprotein E; Genetic Variation

Abstract

Background: Alzheimer disease (AD) is a progressive neurological degenerative disorder and the most common form of dementia. There are about 100 genes linked to AD including apolipoprotein E (ApoE). This gene exists in the form of three allele polymorphisms of ε_2, ε_3 and ε_4 and six genotypes of $\varepsilon_2\varepsilon_3$, $\varepsilon_2\varepsilon_2$, $\varepsilon_3\varepsilon_3$, $\varepsilon_2\varepsilon_4$, $\varepsilon_3\varepsilon_4$, and $\varepsilon_4\varepsilon_4$. We aimed to study the association of ApoE polymorphism with AD in Guilan province, Iran.

Methods: The study group consisted of 70 AD patients and 100 healthy individuals as a control group. All subjects were recruited from 21 March to 22 September 2015 at Imam Reza Clinic, Rasht, Iran. The genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood leucocytes, and subsequently, subjects were genotyped for ApoE using tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). The association between the risk allele and AD was assessed using the MedCalc software.

Results: The distributions of $\varepsilon_3\varepsilon_3$, $\varepsilon_3\varepsilon_4$, $\varepsilon_2\varepsilon_2$, $\varepsilon_2\varepsilon_4$, $\varepsilon_4\varepsilon_4$ and $\varepsilon_2\varepsilon_3$ Genotypes among patients were 55.7%, 30.0%, 1.4%, 2.9%, 8.6%, 1.4% and in the controls were 79.0%, 8.0%, 0%, 1.0%, 1.0%, 11.0%, respectively. The genotype frequencies were significantly different between cases and the controls ($P < 0.001$). The individuals with the $\varepsilon_4\varepsilon_4$ and $\varepsilon_3\varepsilon_4$ genotypes had a greater risk for AD as compared to others; odds ratio (OR) = 12.15, 95% confidence interval (CI): 1.41-104.50, P = 0.020; OR = 5.32, 95% CI: 2.16-13.08, P = 0.003. In addition, the ε_4 allele is significantly associated with higher AD risk among the studied population (OR = 5.63, 95% CI: 2.74-11.58, $P < 0.001$).

Conclusion: This case-control study suggests that the subjects with $\varepsilon_4\varepsilon_4$ and $\varepsilon_3\varepsilon_4$ genotypes had an increased risk for AD in Iranian population.

Introduction

Alzheimer Disease (AD) is a progressive neurological degenerative disease and the most common form of dementia. It accounts for 50%-60% of dementia cases and affects quality of life in elderly people.[1-3] According to the

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Alzheimer's Disease International, it is estimated that there are currently 30 million people with dementia in the world which will increase to 100 million by 2050.[4] It is also estimated that almost 13% of people over 65 years are affected, and its prevalence increases with age, so that 1% of people with 65 years old and younger, and 40% of persons aged over 90 years suffer from this disease.[5] Less than 1% of all patients with AD experience early onset (before the age of 60-65 years) and 60% of the early AD is familial.[6,7] It is proved that no environmental factors (e.g. head injury, viruses, toxins, lower education level) have a direct role in the pathogenesis of AD. Therefore, it seems that AD late onset results from unknown environmental factors on a predisposed genetic background.[8,9]

There are about 100 genes linked to AD including apolipoprotein E (ApoE), a risk factor for AD that has attracted much attention.[10,11] ApoE gene, located on chromosome 19, is the genetic source of the most common form of AD with late onset. This gene is in the form of three alleles of ε_2, ε_3, and ε_4, and six genotypes of $\varepsilon_2\varepsilon_3$, $\varepsilon_2\varepsilon_2$, $\varepsilon_3\varepsilon_3$, $\varepsilon_2\varepsilon_4$, $\varepsilon_3\varepsilon_4$, and $\varepsilon_4\varepsilon_4$.[12] ApoE protein is expressed by all tissues, and is effective in the regulation of cell function of different tissues and organs in addition to lipid transfer.[13] Human and animal studies clearly have shown that ApoE isoforms differentially affect the assembly and clean-up of β-amyloid. Evidence from genetic, pathologic and functional studies has shown that the imbalanced production and clearance of β-amyloid peptide in the brain leads to its accumulation, and eventually nerve degeneration and dementia.[2,6] Many studies on genome have confirmed that ε_4 allele of ApoE gene is the strongest genetic risk factor for AD. This allele is associated with an increased risk of both early and late AD. β-amyloid deposits in the form of senile plaques in ApoE ε_4 carriers as compared to non-carriers.[14] Therefore, ApoE genotypes strongly influence β-amyloid deposits in the form of senile plaques and lead to cerebral amyloid angiopathy.[15] Clinical autopsy-based meta-analysis studies have shown that the risk of AD in individuals with one copy of ε_4 allele ($\varepsilon_3\varepsilon_4$, $\varepsilon_2\varepsilon_4$) or two copies ($\varepsilon_4\varepsilon_4$) was higher among whites as compared to patients with genotype $\varepsilon_3\varepsilon_3$.[16] Although ε_3 allele is the most common one, various studies have shown that ε_4 allele in people with late family history and sporadic AD, in comparison with control group, has a higher frequency. ε_3 allele has a moderate effect, and its impact on the disease pathology is a basic comparison for ε_4 and ε_2 isoforms due to a very high frequency. ε_2 allele of the ApoE gene has a lower frequency and possesses protective effects against AD.[12]

In the view of the above-mentioned facts, the purpose of conducting this case-control study is to evaluate the association of ApoE polymorphism with the susceptibility to AD in Iranian population.

Materials and Methods

The case-control study was conducted on 70 cases and 100 healthy controls. A questionnaire including information such as age, sex, family history of AD, and the race was used. All subjects were native Iranian living in the north of Iran, Guilan province. Patients' mean age ± standard deviation (SD) was 77.1 ± 9.4, ranging from 65 to 89 years. Patients, diagnosed with AD, were recruited from 21 March to 22 September 2015, at Imam Reza Clinic of Guilan, Rasht. Identification and diagnosis of AD were performed based on National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Patients diagnosed with Parkinson's disease or Parkinsonism at any time before the onset of dementia, patients with a history of stroke, history of alcohol abuse, or conclusive clinical history of schizophrenia or schizoaffective disorder before dementia onset were excluded from the study. Controls with the mean age of 74.7 ± 10.3 years (ranging from 65 to 87 years) were nonrelated and healthy individuals. Cases and controls were matched for age, and there were no significant differences between two groups (case and control) in terms of sex, race and family history of AD ($P > 0.050$). The characteristics of the cases and controls are shown in table 1. Informed consent for the genetic analysis was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki regarding the use of human samples.

For each sample, 1 ml blood was collected by venipuncture and drawn into Ethylenediaminetetraacetic acid (EDTA)-K3 coated tubes. Genomic deoxyribonucleic acid (DNA) was extracted from peripheral leukocytes using extraction kit following standard procedures. Extracted DNAs were frozen at -20 °C until the time of doing the molecular analysis.

Table 1. Characteristics of cases and controls

Characteristics		Case (n = 70)	Control (n = 100)	P*
Sex [n (%)]	Man	32 (45.7)	47 (47.0)	0.990
	Woman	38 (54.3)	53 (53.0)	
Family history of AD [n (%)]	Yes	19 (27.1)	23 (23.0)	0.660
	No	51 (72.9)	77 (77.0)	
Race [n (%)]	Gilak	51 (72.9)	74 (74.0)	0.810
	Talesh	9 (12.8)	14 (14.0)	
	Turk	6 (8.6)	5 (5.0)	
	Tat	4 (5.7)	7 (7.0)	

*Chi-square test
AD: Alzheimer disease

Genomic DNA quality was assessed by electrophoresis with 1% agarose gel. The gel was visualized by the gel documentation system.

The ApoE genotypes were determined by tetra-primer amplification-refractory mutation system-polymerase chain reaction (ARMS-PCR). The extracted DNA was used as a template for PCR. Amplifications were carried out using primers designed by Oligo software (version 7.54, Molecular Biology Insights Inc., Cascade, CO, USA). The reaction was performed for all samples after optimization of PCR conditions for amplification of the desired allele. PCR amplifications were carried out in a total volume of 25 µl containing 30 ng genomic DNA, 1x PCR buffer, 1.5 mM $MgCl_2$, 0.2 mM deoxynucleotide triphosphate (dNTP), 0.5 mM each primer, and 1.5 U of superTaq DNA polymerase. At the end, PCR products were analyzed by agarose gel electrophoresis, and alleles and genotypes were identified based on the length of the used fragments and primers.

The statistical significance of differences between groups was calculated by the chi-square test. A P of less than 0.050 was considered statistically significant. The odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using logistic regression to estimate the strength of the association between ApoE genetic variation and susceptibility to AD. All statistical analyses were conducted using the MedCalc software (version 12.1).

Results

This case-control study included 70 patients with AD and 100 healthy controls. The distributions of $\varepsilon_3\varepsilon_3$, $\varepsilon_3\varepsilon_4$, $\varepsilon_2\varepsilon_2$, $\varepsilon_2\varepsilon_4$, $\varepsilon_4\varepsilon_4$ and $\varepsilon_2\varepsilon_3$ genotypes among patients were 55.7%, 30.0%, 1.4%, 2.9%, 8.6%, 1.4%, and in the controls were 79.0%, 8.0%, 0%, 1.0%, 1.0%, 11.0%, respectively. The genotype frequencies were significantly different between cases and the controls ($P < 0.001$). It was observed that the individuals with $\varepsilon_4\varepsilon_4$ and $\varepsilon_3\varepsilon_4$ genotypes had a greater risk of AD compared to others (OR = 12.15, 95% CI: 1.41-104.50, P = 0.020; OR = 5.32, 95% CI: 2.16-13.08, P = 0.003). The allele frequencies of ApoE were 71.4% ε_3, 3.6% ε_2 and 25.0% ε_4 in the AD cases and 88.5% ε_3, 6.0% ε_2 and 5.5% ε_4 in the controls. We observed a significant difference in allele distribution of ApoE between AD patients and the controls ($P < 0.001$). In addition, the ε_4 allele is significantly associated with higher AD risk among the studied population (OR = 5.63, 95% CI: 2.74-11.58, $P < 0.001$) (Table 2).

Table 2. Genotype and allele frequencies of apolipoprotein E (ApoE) and its association with Alzheimer disease (AD)

Genotype	Case [n (%)]	Control [n (%)]	OR (95% CI)	P*
$\varepsilon_3\varepsilon_3$	39 (55.7)	79 (79.0)	1.00 (Ref)	-
$\varepsilon_4\varepsilon_4$	6 (8.6)	1 (1.0)	12.15 (1.41-104.50)	0.020
$\varepsilon_3\varepsilon_4$	21 (30.0)	8 (8.0)	5.32 (2.16-13.08)	0.003
$\varepsilon_2\varepsilon_2$	1 (1.4)	0 (0)	6.04 (0.24-151.62)	0.270
$\varepsilon_2\varepsilon_4$	2 (2.9)	1 (1.0)	4.05 (0.36-46.06)	0.260
$\varepsilon_2\varepsilon_3$	1 (1.4)	11 (11.0)	0.18 (0.02-1.48)	0.110
Allele				
ε_3	100 (71.4)	177 (88.5)	1.00 (Ref)	-
ε_2	5 (3.6)	12 (6.0)	0.74 (0.25-2.15)	0.580
ε_4	35 (25.0)	11 (5.5)	5.63 (2.74-11.58)	< 0.001

*Chi-square test
OR: Odds ratio; CI: Confidence interval

Discussion

Studies in human and transgenic mice have shown that brain β-amyloid levels and amyloid plaque loads are ApoE isoform-dependent, suggesting an important role of ApoE in modulating β-amyloid metabolism, aggregation, and deposition.[17] ApoE gene, known to mediate the regulation of cholesterol and triglyceride metabolism, is immunochemically localized to the senile plaques, vascular amyloid, and neurofibrillary tangles of AD.[18] Genome-wide association studies confirmed that ε4 allele of APOE is the strongest genetic risk factor for AD.[19] To date, no study has investigated the association between the genotypes of ApoE and the AD risk in the Guilan province. The present study evaluated the effect of ApoE variation on AD in the north of Iran, Guilan. Our findings suggest that individuals with $\varepsilon_4\varepsilon_4$ genotype have the highest risks of developing AD. Moreover, the most frequent genotype was $\varepsilon_3\varepsilon_3$ in patients and controls in Guilan. Our analysis also confirmed a significant association of the ε_4 allele with AD.

To date, many epidemiological studies have suggested a relationship between ApoE genetic variations and AD risk. In 2013, Sabbagh, et al. in their study showed that ApoE ε_4 carriers had a significantly higher percentage of frequentscores for plaques and tangles in comparison with ApoE ε_4 non-carriers for several brain regions.[12] Furthermore, Altmann, et al. showed that APOE ε_4 confers greater AD risk in women.[20] Isbir, et al. in Turkey showed that there was a significantly higher frequency of the ApoE ε_4 allele in the group of Alzheimer's patients than in control subjects.[21] In China, Zhou, et al. studied the relationship between ApoE gene polymorphism and AD in the case group and control group in Uyghurs and Han populations. The distinction was seen in both ethnic groups so that the frequency of $\varepsilon_3\varepsilon_4$ genotype and ε_4 allele in case group of Uyghurs and Han were higher than those in the control group. ApoE ε_4 allele was recognized as a risk factor for AD for both populations.[22]

Another study conducted by Gavett, et al. showed that more ε_2 alleles were associated with less AD pathology and, in turn, with less severe dementia. In contrast, more ε_4 alleles were associated with more pathology and more severe dementia.[23] Mino, et al. showed that there was no statistically significant relationship between case group (with AD and dementia) and control group (without AD and dementia) in terms of sex and family history and distribution of ApoE alleles.[24] A study conducted in 2014 reported that there is a statistically significant relationship between the types of ApoE and patients' age so that risk alleles, such as ε_4, decrease the age of onset as 3-6 months.[5]

ApoE ε_4 allele frequency varies in different ethnic groups, and the mean has been estimated as 6.5 ± 13% in all groups. It has been reported that the lowest frequency was observed among Chinese and Japanese people (7.4 ± 0.8%), and the highest frequency was found among Sudanese (29%),[21] and Finnish people (23-24%).[25] Shahsavar, et al. also found that $\varepsilon_3\varepsilon_3$ genotype with a frequency of 48% was the most common genotype in their study population.[13]

Our study includes a small sample size, and statistically significant results may occur by chance. It is also unwise to ignore other factors like environment and hereditary conditions that may predispose a person to AD, as there are other genes that may affect the susceptibility to AD. Thus, it will be necessary to assess the relationship between the genetic and environmental factors that influence the risks of AD in other studies.

Conclusion

In conclusion, the results of this study provide further evidence that ε_4 increases the risk of AD. However, a larger study that includes more samples may be necessary to confirm the findings.

Conflict of Interests

The authors declare no conflict of interest in this study.

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The effect of swallowing rehabilitation on quality of life of the dysphagic patients with cortical ischemic stroke

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Keywords
Dysphagia; Stroke; Quality of Life

Abstract

Background: Swallowing and swallowing-related quality of life studies following stroke were almost always performed by including both patients with brainstem and cortical involvement. It was aimed in this study to show the presence of dysphagia in patients with only cortical ischemic stroke and to investigate the interaction between dysphagia and quality of life as well as to evaluate the effect of a rehabilitation program in the acute phase.

Methods: Seventy-two patients with cortical stroke (between 0 and 30 days) and dysphagia were included. Swallowing function of patients was assessed by dysphagia screen questionnaire and fiberoptic endoscopic assessment. Also, functional impairment and swallowing quality of life were assessed. The swallowing rehabilitation program for 4 weeks was given to all patients.

Results: All patients demonstrated disorders related to oral phase (n = 69, 95.8%), pharyngeal phase (n = 4, 5.6%) or both phases. The swallowing function, swallowing quality of life and functional impairment were improved at the end of therapy.

Conclusion: Swallowing quality of life is severely affected in cortical hemispheric stroke patients and can be improved with an early rehabilitation program.

Introduction

Dysphagia is defined as disturbance of bolus flow from the mouth to esophagus and it is a severe problem in various neurological diseases and is associated with increased morbidity and mortality.[1]

Stroke is the most common neurological cause of dysphagia. Severe dysphagia is usually observed during the first 2-4 weeks, with a prevalence ranging from 29%-81%.[1-3] However, minor swallowing disorders have been reported as the rate of 91% in stroke.[4]

Dysphagia may cause to important complications such as hydrational and nutritional deficiency, aspiration pneumonia and even death.[1-3] Aspiration pneumonia is seen in patients with dysphagia during the first year, with a mortality rate as up to 45%.[5] Studies have been reported that if it is early diagnosed and treated, the complications may be reduced or even prevented.[6] Moreover, it has been reported that when a person has a dysphagia, the ability to enjoy almost all of life is affected. A minor or intermittent dysphagia can lead to stress in both

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psychological and social situations. Episodes of choking can lead to a fear of eating that can result in malnutrition and social withdrawal.[7,8]

Since central control mechanism of swallowing is located in the brainstem, severe dysphagia is more likely to occur when stroke involves this part.[9] However, unilateral cerebral hemispheric infarction is seen more often than brainstem events.[10] Despite the frequency of dysphagia is typical in the brainstem or bilateral infarct, it is often seen subsequent to one-sided hemispheric infarct in our daily clinical practice. Swallowing studies have been generally concentrated on the brainstem, ischemic and hemorrhagic types of stroke, but patients with brainstem and cortical involvement were evaluated in combination.[11,12] In these studies, most of the hemispheric strokes involve middle cerebral artery (MCA) and perfusion areas. Elaborating more on demographic characteristics of these studied populations indicated that severe dysphagia has been observed in these patients. However, studies have not been performed on ischemic stroke patients with only hemispheric cortical involvement and there is also no study investigating the dysphagia-related quality of life among these patients. Therefore, we aimed to reveal dysphagia in cortical stroke and to demonstrate its impact on quality of life.

Materials and Methods

This study was performed on 72 patients who referred to our Physical Medicine and Rehabilitation (PMR) clinic between 2015 and 2016.

The subjects, ranged from 50 to 75 years and applied for rehabilitation of some problems such as functional impairments in the first 30 days after ischemic hemispheric MCA stroke, approved by magnetic resonance imaging, and had dysphagia which was shown by dysphagia questionnaire, were included. This dysphagia questionnaire that our standard used in clinic includes a neurologic examination test and a water drinking test as well as oxygen saturation measurement by pulse oximetry.

The neurological examination test included some abilities such as head lifting, independent seating balance and cranial nerves related to deglutition. On the basis of this, neurological measure outcome (NMO) was created. Based on monitoring and documentation of the water drinking test, swallowing outcome (SO) was calculated. Dysphagia outcome (DO) was calculated by combining the scores for NMO and SO. Accordingly, patients with a score of 3 and below were evaluated as normal.

Seventy-two patients were included between 4 to 15 scores according to DO score in this study. Patients with a history of tumor, head-neck operation, past stroke, known swallowing disorders, the presence of gastroesophageal reflux disease, dementia (mini-mental test < 15) or psychiatric diseases, brainstem, hemorrhagic, subcortical and/or bilaterality, and smoking were excluded. In addition, exclusion criteria for flexible fiberoptic endoscopic evaluation of swallowing (FEES) method were the severe infective disease, bleeding risk and/or decompensated cardiac disease.

Patients and their caregivers were given information regarding the study and their inscriptive approvals were obtained before starting the study. The confirmation of the Ethics Committee of the hospital was taken. The study was carried out in conformity with the standards of the Helsinki Declaration.

Characteristics of 72 patients including age, gender, education, dominant side, additive diseases and disorders associated with respiratory and dental, infarct area, and passing time following stroke were documented. Educational status was as illiterate, under 5-year, 5-year, 8-year, 11-year and over 11-year education.

The motor available condition was evaluated by Brunnstrom motor level for upper and lower limbs as well as hand, separately and graded between 1 and 6.

The assessment of swallowing function: Swallowing disorders were evaluated using dysphagia screen questionnaire and FEES.

Mann assessment swallowing ability (MASA) test: MASA was applied to a screen test. Twenty-four areas were assessed such as vigilance, communication, hearing, speech and respiration disorders, movement limitation, weakness and incoordination in swallowing muscles, the presence of reflexes associated with swallowing. The score was calculated between 38 and 200 points.

FEES: The test was conducted using a 3.4 mm-diameter fiberoptic nasopharyngoscope. Evaluations were applied in a seated situation or a vertical posture to the utmost. Local anesthetics were not applied to prevent its side effects. To evaluate penetration, aspiration and presence of residue, water was used as the fluid, yogurt and a biscuit as the consistency food. The function of the

pharyngeal stage was assessed with these foods and findings were saved as the video images. Swallowing status was determined between 1 and 6 according to the endoscopic measurement scale generated by Warnecke, et al.[13] According to this, 1 point was defined as normal swallowing, while 2-6 points as dysphagia. The swallowing abnormalities (i.e. oral or pharyngeal stage or both) were detected and noted with respect to results of swallowing assessment procedures.

Other evaluation parameters: The functional status was measured with functional independence measure (FIM), which evaluates two important parts of functions as a motor and cognitive status. This scale includes 18 items and 6 parts comprised of personal care, continence, mobility, transfer, interaction and social cognition; and each item has score between 1 and 7. The total score is between 18 and 126.

Swallowing-related quality of life scale (SWAL-QOL) was used to evaluate the impact of swallowing disorders on quality of life. It was developed by McHorney, et al.[14] to evaluate the quality of life in patients with oropharyngeal dysphagia. SWAL-QOL contains 44 questions on domains of eating disorder, duration of eating, desire to eat, choice of meal, communication, anxiety, mental health, social functioning, fatigue, and sleep. Each question is evaluated by a score ranging between 1 (the worst) and 5 (the best) points. Each domain can be evaluated separately. In our study total scoring was used.

Study evaluation protocol: The study was performed by specialists that composed of swallowing team members in our hospital as blinded to therapy distribution. The dysphagia screen questionnaire, FIM and SWAL-QOL were applied by the 1st PMR expert on the 1st day of hospital admission. Afterwards, patients were evaluated with the endoscopic method by a blinded otolaryngology specialist and were sent to the 2nd PMR specialist.

Rehabilitation methods: Daily care for oral hygiene training and the required swallow maneuvers, head and trunk positioning and diet modification were given according to the condition of swallowing disorder of all patients. Furthermore, oral motor-strengthening exercises for lips, tongue and jaw, cold-tactile stimulation as well as intermittently or alternatively galvanic stimulation to bilateral masseter or submental muscles, according to the presence of an oral or pharyngeal disorder or both, were received by the same physiotherapist. This program was performed for 4 weeks, 20 sessions in total (1 hour a day and 5 hours per week). Apart from these, cognitive, respiratory, sensorial and motor rehabilitation therapies were given to all subjects.

Comparisons: Dysphagia severity level defined by the FEES and MASA, as well as FIM and SWAL-QOL scores were reevaluated after therapy. The results of therapy and changes within the group were compared.

Statistical analysis: SPPS software (version 22, IBM Corporation, Armonk, NY, USA) version for Windows was used for statistical analysis. Shapiro-Wilk test was used to know whether the quantitative data are normally distributed or not. Descriptive statistics were presented as the mean ± standard deviation (SD) or median (minimum-maximum) for quantitative data and frequencies and percentages (%) for qualitative data. Statistically critical differentiations in recurrent evaluations within the group were shown with the Wilcoxon signed-rank test. The Bonferroni correction was performed to avoid potential Type I mistakes in within-group comparison ($P < 0.025$).

Results

A total of 72 patients with hemispheric ischemic patients aged between 50-75 years, who were admitted to hospital as an inpatient, treated in our center during the first 30 days following stroke and were enclosed in the study.

The mean DO which defined the patients as dysphagia was 9.32 ± 2.45. At hospital admission, 8 patients (11.1%) received regimen-3 (normal) diet comprising liquid, semi-solid, and solid foods, 42 patients (58.3%) received regimen-2 diet consisting of semi-solid foods supplemented with intravenous infusion of fluids, 18 patients (25.0%) were fed with nasogastric catheter (n = 18, 25%), and 4 patients (5.6%) received gastrostomy catheter.

The mean age of the 72 patients was 63.32 ± 11.17 years. Among 72 patients, 25 (34.7%) were female, while 47 (65.3%) were male. The patients had right (n = 61, 84.7%), and left (n = 11, 15.3%) hand dominance. In all patients, ischemic stroke involved MCA region (100%). The mean passing time after stroke was 16.51 ± 8.32 days. Demographic and disease characteristics of subjects are presented in table 1.

According to Brunnstrom staging of the motor functions of the patients at admission, median motor function stage of the upper and lower

Table 1. Demographic and disease characteristics of subjects

Feature		Value
Age (year) (mean ± SD)		63.32 ± 11.17
Sex [n (%)]	Female	25 (34.7)
	Male	47 (65.3)
Passing time after stroke (day) (mean ± SD)		16.51 ± 8.32
Educational status [n (%)]	Illiterate	8 (11.1)
	Under 5-year	3 (4.2)
	5-year	48 (66.7)
	8-year	8 (11.1)
	11-year	3 (4.2)
	Over 11-year	2 (2.7)
Dominant side [n (%)]	Right	61 (84.7)
	Left	11 (15.3)
Additive diseases [n (%)]	Hypertension	61 (84.7)
	Coronary artery disease	22 (30.6)
	Diabetes mellitus	11 (15.3)
	Respiratory disease	8 (11.1)
	Hyperlipidemia	29 (40.3)
Additive problem [n (%)]	Dental problems (loss, poor hygiene)	69 (95.8)

SD: Standard deviation

extremities, and hands of the patients were 2.00 (2.19 ± 1.34), 2.00 (2.53 ± 1.42), and 1.00 (2.12 ± 1.09), respectively.

Distribution of bedside screening test and FEES levels results which demonstrated pre-treatment swallowing functions, functional disability and SWAL-QOL scores are shown in table 2. According to bedside screening test and FEES results, the patients demonstrated disorders related to oral phase (n = 69, 95.8%), pharyngeal phase (n = 4, 5.6%) or both phases (n = 21, 30.6%).

Table 2. The distribution of pre-treatment evaluation parameters

Evaluation parameter (score range)	Mean ± SD
MASA (38-200)	118.47 ± 28.31
FEES	
Dysphagia stage (1-6)	3.52 ± 1.65
FIM	
Motor score (13-91)	25.13 ± 9.23
Cognitive score (5-35)	17.46 ± 6.23
Total score (18-126)	42.62 ± 6.57
SWAL-QOL score (44-220)	117.63 ± 26.37

SD: Standard deviation; MASA: Mann assessment swallowing ability; FEES: Flexible fiberoptic endoscopic evaluation; FIM: Functional independence measure; SWAL-QOL: Swallowing quality of life

Distribution of bedside screening test and FEES levels results which demonstrated post-treatment swallowing functions, functional disability and SWAL-QOL scores are shown in table 3. At the end of the treatment nutritional requirement of the patients were met with regimen-3 (n = 65, 90.3%) and regimen-2 (n = 6, 8.3%). One patient (1.4%) was persistently fed via gastrostomy catheter.

Table 3. The distribution of post-treatment evaluation parameters

Evaluation parameter (score range)	Mean ± SD
MASA (38-200)	168.42 ± 21.65
FEES	
Dysphagia stage (1-6)	1.48 ± 0.92
FIM	
Motor score (13-91)	29.42 ± 12.45
Cognitive score (5-35)	28.14 ± 6.87
Total score (18-126)	57.73 ± 11.18
SWAL-QOL score (44-220)	151.63 ± 28.21

SD: Standard deviation; MASA: Mann assessment swallowing ability; FEES: Flexible fiberoptic endoscopic evaluation; FIM: Functional independence measure; SWAL-QOL: Swallowing quality of life

The significant improvement was detected after treatment swallowing functions of the patients (MASA: P = 0.003, and FEES P = 0.004). A significant improvement was detected in cognitive, and total disability scores of functional disability scale using FIM (P = 0.011, and P = 0.023, respectively), while the change in motor function scores was not significant (P = 0.467). Also, a significant improvement was found in SWAL-QOL score (P = 0.001).

Discussion

Dysphagia in patients with stroke commonly occurs after ischemia of the cerebral cortex. In

recent studies, it has been reported that most of these patients had regained their swallowing functions, while in 11-15% of them dysphagia which led to complications as aspiration pneumonia had persisted.[9-11,15-17] In previous studies, it has been shown that brainstem stroke is a primary risk factor for persistent dysphagia. Because, the swallow response is generated in the brainstem swallowing center located in the medulla oblongata which combined knowledge directed from the oral, pharyngeal and suprabulbar areas. These centers were considered to be autonomous central pattern generators largely controlling the synchronization and timing of swallowing. However, a complex array of cortical representation, including motor, premotor, and sensorimotor cortices, appears to be crucial in its effective coordination.[18] These cortical areas provide volitional deglutition and supply primarily to trigger swallowing and control the of swallow motor response.[9,18,19] Normal swallowing is generally divided into four stages. However, this division is not as simple as it is said to be. The normal swallow is a complex, fast, continuous sequence of coordinated muscle movements and there is some overlap between the phases. Cortical stroke has been shown to have impact on the pharyngeal phase of the swallow, with impairment to initiation and duration and increased frequency of penetration and aspiration as well as with impairment in pharyngeal transit and longer oral transit.[20,21]

Brainstem strokes may account for up to 15% of all strokes. In two recently performed studies, in which cortical hemispheric involvement was reported in 90% of the patients who were diagnosed, and followed up with dysphagia at early stroke period, spontaneous return of swallowing functions was indicated in only 9.5% and 37% of the patients, 1 month later in the first, and 3 months later in the second study.[6,22] Moreover, in patients with severe dysphagia who require feeding via a gastrostomy tube, no difference has not been detected between brainstem involvements and cortical hemispheric strokes.[23,24] The other two studies have been demonstrated that the presence of dysphagia is related to MCA involvement in patients with cortical stroke.[25]

Because of these reasons, in our study, we included 72 patients with ischemic stroke involving perfusion area of MCA. We evaluated our patients for a mean period of 16.51 ± 8.32 days after stroke, which was somewhat longer than conventionally reported recovery time, and detected disorders related to oral (n = 69, 95.8%), pharyngeal (n = 3, 4.2%), and oropharyngeal (n = 21, 30.6%) phases. These patients (n = 72) also represented the whole spectrum of mild to very severe dysphagia. Patients' SWAL-QOL scores were nearly half of maximum well-being index scores, and general functional impairment levels were one-third of normal scores. We applied a combination treatment also including electrical stimulation on our patients for 4 weeks.

Generally, spontaneous recovery of swallowing function occurs within the first 2-4 weeks, so in previous studies initiation of a rehabilitation program for dysphagia was postponed after that period. In guidelines for management of dysphagia, treatment of dysphagia is absolutely advised,[26] while in some studies it was advocated that it would provide beneficial effects if applied at an early stage.[6] However according to the guidelines on rehabilitation of stroke lack of adequate data have been stated.[27]

In recent years, the presence of a cortical inhibition in both intact and damaged hemisphere, and functional recovery induced by compensatory cortical re-organization have been indicated.[3,10] Especially early phase was reported as a window of opportunity.[6,28] In a study, in patients who received classical treatment at an early period in stroke within the first 2 weeks 100% improvement was achieved in oral phase problems, and 75-90% recovery in pharyngeal phase disorders with a lesser number of treatment sessions than in patients that same treatment initiated in one month later.

Also, in patients applied treatment after 4 weeks, oral and pharyngeal phase problems were detected which were regressed in 15%, and 45% of the cases, respectively. Aspiration detected video fluoroscopically was persisted in 60% of these patients.[6]

In the light of this information, we also applied combined rehabilitation program for our patients at a considerably early stroke period. Indeed, in studies performed using both traditional methods, and new techniques which involve electrical stimulations, it has been reported that especially combination treatments decreased dysphagic complications and increased rate of oral feeding.[29-32] Similar to our study, Bulow, et al. reported that dysphagia treatment was effective

even in their subacute phase of patients with hemispheric stroke.[32]

The medical complications of dysphagia include aspiration pneumonia and malnutrition. Other complications of dysphagia in stroke patients are psychological and social effects because eating is an enjoyable social activity, and inability to eat usually may affect patient morale and quality-of-life.[33,34]

Swallowing-related quality of life has been evaluated using different scales, and different studies have reported that fear from choking during eating, and inability to control dysphagic symptoms, physical, and social insecurity secondary to anxiety and fear are the most frequently encountered problems. In meta-analyses performed, especially evaluation of the quality of life of dysphagic patients has been indicated.[33,34] These meta-analyses have been reported that fears of these patients, and their reflections on the social environment to be adverse parameters affecting their quality of life. Since they are most frequently seen especially during the acute phase, quality of life is most affected during this early period. However, these studies have been most frequently performed in cases with brainstem strokes.[16,34] We considered that hemispheric strokes are more frequent, and low quality of life may be more prevalent in these patients. Therefore, in our study SWAL-QOL scale was used. The items on the SWAL-QOL address desire for eating, dysphagia symptom frequency, mental health, social concerns related to swallowing problems, food selection, fear related to eating, and the burden of dysphagia. While the quality of life of nearly 50 of our studied patients was deteriorated before treatment, this rate dropped down to 30% after treatment.

Despite lack of similar studies in the literature, our result suggests that dysphagia related to hemispheric strokes is as important as those associated with brainstem strokes with respect to quality of life.

Conclusion

As a result, cortical strokes are frequently encountered in our clinical practice, and contrary to our classical information they can induce dysphagia which will be able to affect the quality of life. We think that rehabilitation programs that applied these patients in early stroke period will decrease both medical and psychosocial complication rates related to dysphagia.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Prognostic value of ictal onset patterns in postsurgical outcome of temporal lobe epilepsy

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Electroencephalography; Temporal Lobe; Epilepsy; Surgery; Outcome

Abstract

Background: To investigate ictal onset patterns (IOP) in scalp electroencephalography (EEG) of patients with temporal lobe epilepsy (TLE) and their prognostic effect on the postoperative outcome.

Methods: We conducted a retrospective cohort study between 2011 and 2015 in our referral Epilepsy Surgery Center enrolling adult patients with refractory TLE and a visible epileptogenic lesion in magnetic resonance imaging (MRI), who underwent epilepsy surgery. Demographic, clinical and MRI findings were collected and ictal findings during video-EEG monitoring were reviewed in detail. The correlation between preoperative findings and the postsurgical outcome was analyzed.

Results: We reviewed 303 seizures in 93 patients. Rhythmic theta and rhythmic spike/sharp and wave were respectively the most common initial ictal pattern and late significant discharges. Engel class I outcome was observed in 88.2% of patients. Female sex, aura, the absence of secondary generalization, rhythmic theta as initial ictal pattern and concordance of ictal-interictal EEG findings were correlated with favorable 1-year postsurgical outcome.

Conclusion: Preoperative clinical and EEG findings can provide valuable information regarding postsurgical prognosis in TLE patients.

Introduction

The surgical treatment is currently a reasonable approach for patients with focal drug-resistant epilepsy. With the aim of precise determination of epileptogenic zone, presurgical evaluation often consists of careful analysis of seizure semiology, interictal and ictal electroencephalography (EEG), magnetic resonance imaging (MRI), neuropsychological tests and sometimes functional imaging, positron emission tomography (PET) and single photon emission computed tomography (SPECT).[1] However, despite all the investigations, surgical processes have shown variable success rates and many prognostic factors have been proposed.[2-7]

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Prolonged video-EEG monitoring is still the cornerstone of presurgical evaluation. Most studies on EEG, as a prognostic factor of epilepsy surgery, have investigated the ability of interictal and ictal EEG to lateralize and localize the irritative and seizure onset zone and its concordance with clinical and imaging findings.[8-11] There are also studies on correlation of postoperative EEG discharges with postoperative outcome.[12-14] However, few surveys investigated the prognostic value of ictal EEG patterns in epilepsy surgery. Some of them have confirmed the correlation between ictal onset patterns (IOP) and surgery outcome[15-17] and some have failed to find any prognostic value for IOPs.[2,18-20] Sample size in most of these studies is small and the results are controversial. Another problem that makes it difficult to draw a conclusion is the evaluation of one seizure per patient in some studies, which possibly accompanies by the unwanted consequence of selection bias. Therefore, it remains unclear if the detailed analysis of IOP under certain circumstances can help in determining the postsurgical outcome. In this study, we evaluated all recorded seizures for each patient in order to investigate the prognostic value of IOPs in the postsurgical outcome of patients with temporal lobe epilepsy (TLE).

Materials and Methods

This retrospective cohort study was conducted at the referral Epilepsy Surgery Center of Isfahan Medical School University Hospital, Iran, between September 2011 and December 2015. We searched the database and enrolled the adult patients with medically refractory TLE who were admitted for presurgical evaluation. All patients underwent noninvasive long-term video-EEG monitoring until the epileptogenic zone could be definitely determined and it took about 3 to 11 days for different patients. They consequently underwent epilepsy surgery. The inclusion criteria were defined as the age of 18-60 years, MRI evidence of lesion relevant to epileptogenic zone, and one-year follow-up. We excluded patients with prior epilepsy surgery, inadequate data and follow-up evidence of less than 1 year. 93 patients met the criteria. This study was approved by the Ethics Board of Isfahan University of Medical Sciences.

Data including age, sex, handedness, marital status, age at seizure onset, seizure semiology and frequency, risk factors for epilepsy, family history of epilepsy (according to patients' history), irritative zone (based on interictal EEG data), pre-operative MRI findings, type and side of surgery and pathological findings were gathered based on patients' records.

All patients had prolonged scalp EEG monitoring using Nihon Kohden system. Electrodes arranged according to the International 10–20 system with additional temporal electrodes (F9, F10, T9, T10, T1 and T2). The setting was arranged at 200 Hz sampling rate, 0.1 second time constant and 60 Hz notch filter.

We retrospectively reviewed recorded data from 93 patients with 303 seizures. The ictal EEGs that were significantly contaminated by the artifact and rare seizures which occurred when the patient was disconnected from recording set were excluded. We analyzed all registered seizures for each patient. If the patient had more than 10 seizures, we considered the first 10 appropriate ones. At first, ictal rhythms were studied in longitudinal bipolar and referential montages with common filtration [low-frequency filter (LFF) 1 Hz, high-frequency filter (HFF) 70 Hz]. During the evaluation, digital filtering and gain were adjusted to improve the EEG display.

We assessed ictal scalp EEG in four steps. First, we registered the time of onset, awake/asleep state of patient and semiology of each seizure.[21] Then, we noted the interval between clinical manifestations and ictal EEG onset. If there was an aura before other clinical signs, time of clinical presentation was accepted at patient's notification. Duration of artifacts and their time of onset during ictal patterns were also registered. In next step, we described the morphology of ictal discharges during seizure including fast activity (FA), rhythmic alpha activity (RA), rhythmic theta activity, rhythmic delta activity (RD), rhythmic spike/sharp and wave (RS/Sh and W) and background attenuation (BA). We described ictal patterns as a pattern at onset (PAO) and late significant pattern (LSP). The PAO was defined as first definite ictal EEG changes which associated or followed by a clinical seizure. Any changes in morphology or location of PAO was considered as LSP and numbered consecutively. Finally, we noted duration of seizure, occurrence and time of ipsilateral and contralateral propagation of epileptic discharges. We defined ictal-interictal match as ≥ 90% predominance of interictal discharges at the side of the epileptogenic zone.

The ictal EEG findings of all patients were investigated by an epilepsy fellowship assistant and were reviewed by an expert epileptologist.

The electroencephalographers were blinded for interictal EEG findings and MRI results.

We collected 1-year follow-up results from registered post-operative outpatient visits and classified them as favorable and unfavorable. The favorable outcome encompassed class I of Engel outcome scale[22] and the unfavorable outcome was defined as class II-IV.

Statistical analysis was performed using SPSS software (version 23, IBM Corporation, Armonk, NY, USA). Continuous variables were presented as the mean ± standard deviation (SD), median (min-max) as appropriate. Qualitative variables were reported as number (percent). Before the main analysis, Shapiro-Wilk test was performed to check normality. Student's independent t-test, chi-square test, Fisher's exact test, Mann-Whitney test and analysis of variance (ANOVA) were used. We applied Cohen's Kappa statistic to assess inter-observer agreement. All probability tests were two-tailed and the level of significance was defined as $P \leq 0.050$.

Results

We retrospectively reviewed 303 seizures in 93 patients. 303 seizures were analyzed according to defined method. Mean reviewed seizure numbers for each patient was 3.2 ± 1.8. Patients' characteristics are summarized in table 1.

Clinical seizure data: From the semiologic point of view, 79.9% of seizures were categorized in motor type, of which 72.2% were classified as a complex motor seizure (70.9% automotor, 1.3% hypermotor) and 7.7% simple motor seizure. 20.1% of seizures were dialeptic. Aura was detected prior to 14.9% of clinical seizures and 14.2% of seizures were progressed to secondary generalization. 35.1% of seizures occurred during sleep.

Ictal EEG findings: EEG changes were started before and after clinical onset in 88 (29.0%) and 82 (27.1%) seizures, respectively. Simultaneous occurrence of IOPs and clinical signs were detected in 133 (43.9%) seizures. In 10 seizures the exact correlation could not be determined due to artifact at onset. The median interval of EEG changes before and after clinical signs was 4 (1-40) and 6.5 (1-29) seconds. Presence of EEG changes before and simultaneous to clinical signs had a significant correlation with localization ability of PAO ($P = 0.020$), but not the next patterns.

Mean total duration of seizures was 74.7 ± 48.4 seconds (range: 7-464). Propagation to ipsilateral hemisphere occurred in 97.0% of localizing IOPs with a mean time of 6.1 seconds (0.5-38). Lateralization switch was detected in 1.6% of seizures with a mean time of 52.8 seconds (Min-max: 5-100) from seizure onset. Contralateral propagation appeared in 94.9% of primarily lateralized seizures and the mean time of contralateral propagation was 10.2 seconds (0.5-342), although the accurate time of contralateral propagation remained unclear in 33 seizures because of overlapping artifacts.

Table 1. Patients' characteristics

Characteristic		Value
Sex (%)	Man	52.7
	Woman	47.3
Handedness (%)	Right	89.2
	Left	10.8
Marital status (%)	Single	62.4
	Married	37.6
Age at surgery (year) (mean ± SD)		28.9 ± 8.9
Age of onset (year) (mean ± SD)		10.5 ± 8.4
Seizure frequency [n (%)]	Daily	15 (16.1)
	Weekly	58 (62.4)
	Monthly	13 (14)
	Seasonal	7 (7.5)
Epilepsy duration (year) (mean ± SD)		18.5 ± 11.1
Number of AEDs (mean ± SD) (range)		2.6 ± 1 (0-5)
Risk factors [n (%)]	Perinatal complication	9 (9.7)
	Febrile convulsion	24 (25.8)
	CNS infection	4 (4.3)
	Developmental delay	6 (6.5)
	Head trauma	26 (28.0)
Family history (%)	Positive	8.6
	Negative	91.4
Side of epileptogenic zone (%)	Right	47.3
	Left	52.7
Pathological findings [n (%)]	HS	53 (57)
	Tumor	18 (19.4)
	Gliosis	16 (17.2)
	FCD	4 (4.3)
	CA	2 (2.2)
Engel's surgical outcome [n (%)]	Engel I (favorable)	82 (88.2)
	Engel II, III, IV (unfavorable)	11 (11.8)

SD: Standard deviation; AED: Antiepileptic drug; CNS: Central nervous system; HS: Hippocampal sclerosis; FCD: Focal cortical dysplasia; CA: Cavernous angioma

PAO: In patients with more than one reviewed seizures, similar PAO morphology was observed in 41.5%, while 2 to 3 different PAO morphologies were detected in 58.5%. The most common PAO morphology was rhythmic theta. Concerning semiology, rhythmic theta was the most common

PAO morphology in automotor seizures (54.2%) (P = 0.040) and occurred frequently in dialeptic seizures and simple motor seizures as well. However, the most frequent PAO in hypermotor seizures was RD. PAO morphology had no significant correlation with localization ability, but rhythmic theta was significantly relevant to seizure lateralization (P = 0.010).

Presentation of rhythmic theta as PAO was significantly more common in awake state (P = 0.010) and RS/Sh and W was the most frequent PAO at sleep (41.2%). PAO characteristics had no correlation with clinically secondary generalization, the time interval between EEG changes and clinical signs and ipsilateral or contralateral propagation of ictal discharges.

LSP1: LSP1 was detected in 224 (73.9%) seizures. RS/Sh and W was the most common LSP1 morphology in spite of semiology and was associated with the highest lateralization ability (P = 0.030). LSP1 could detect the correct side and location of seizure onset in 60.9% and 24.4% of seizures with unsuccessful lateralization and localization by PAO. No significant correlations were detected between LSP morphology and ipsilateral or contralateral propagation, localization and sleep/waking state.

LSP2: LSP2 occurred in 56 (18.5%) seizures. Lateralization and localization by LSP2 had no significant difference between different semiologies, sleep/wake state and time of seizure onset. More characteristics are summarized in table 2.

Surgery and pathology findings: The surgery types were selective amygdalohippocampectomy (SAH) in 60.9% and lesionectomy in 39.1% of patients. Pathological findings are summarized in table 1.

Surgery outcome: Based on Engel criteria, 1-year follow-up surgery outcome was favorable (class I) in 88.2% of patients and the unfavorable outcome was detected in 11.8% of patients (8.8% class II, 2.2% class III and 2.2% class IV).

Patient characteristics and outcome: Despite the similar distribution of prognostic factors in men and women TLE patients, the outcome was significantly better in females with TLE (P = 0.007). Handedness, marital status, number of AEDs, age at epilepsy onset, age at surgery, duration of epilepsy, seizure frequency, family history and risk factors of epilepsy had no prognostic value for the outcome (Table 3).

Seizure characteristics and outcome: Presence of aura had a significant association with favorable outcome (P = 0.050). The outcome was significantly better in automotor seizures (P = 0.010), while hypermotor seizures had the worst postsurgical outcome (50.0%). Patients who experienced secondarily generalized seizures had a less favorable outcome (P = 0.030). The occurrence of sleep-related seizures had no effect on outcome (P = 0.520).

EEG characteristics and outcome: Rhythmic theta as PAO was associated with significantly better outcome (P = 0.030). To obtain a better knowledge of the effect of rhythmic theta as PAO on the outcome, we more precisely analyzed the characteristics of patients with this PAO and unfavorable outcome. The pathological findings in those patients who had rhythmic theta as PAO, but experienced unfavorable outcome, were hippocampal sclerosis (HS) (87.5% vs. 66.7% in favorable outcome) and focal cortical dysplasia (FCD) (12.5% vs. 1.3% in favorable). The most common seizure semiology in this group was dialeptic (50.0% vs. 17.2% in favorable outcome). There was no considerable difference regarding ipsilateral and contralateral propagation, lateralization and localization by PAO, ictal EEG/clinical seizure interval or clinically secondary generalization.

Table 2. Ictal onset patterns (IOP)

Characteristic		PAO	LSP1	LSP2
Morphology [n (%)]	Rhythmic theta	161 (53.1)	39 (17.4)	6 (10.7)
	RD	45 (14.9)	24 (10.7)	10 (17.9)
	RS/Sh and W	34 (11.2)	145 (64.7)	35 (62.5)
	Other rhythms (RA, FA, BA)	63 (20.8)	16 (7.1)	5 (8.9)
Duration (s) [median (min-max)]		13 (0.5-120)	32 (1-273)	34.5 (3-196)
Lateralization [n (%)]		228 (75.5)	132 (60)	29 (51.8)
Mean lateralization per patient		78.9	58.5	54.8
Localization [n (%)]		129 (56.1)	53 (40.2)	8 (27.6)
Mean localization per patient		49.9	21.1	15.6

PAO: Pattern at onset; LSP: Late significant patterns; RD: Rhythmic delta; RS/Sh and W: Rhythmic spike/sharp and wave; RA: Rhythmic alpha; FA: Fast activity; BA: Background attenuation

Table 3. Predictors of postsurgical outcome

Variable		Outcome		P*
		Engel I	Engel II, III, IV	
Age at onset (year)	≤ 5	28	1	0.080
	> 5	53	10	
Age at surgery (year)	≤ 35	66	8	0.540
	> 35	16	3	
Sex	Man	39	10	0.007
	Woman	43	1	
Epilepsy duration (year)	> 15	44	6	0.950
	≤ 15	38	5	
AED	≤ 3	70	8	0.280
	> 3	12	3	
Frequency	Daily	14	1	0.510
	Weekly	49	9	
	Monthly	12	1	
	Seasonal	7	0	
Seizure semiology (automotor)		196	16	0.010
Aura		44	1	0.050
Secondary generalization		35	8	0.030
EEG vs. clinical onset	Before	77	11	0.460
	Simultaneous	123	10	
	After	74	8	
PAO morphology (rhythmic theta)		153	8	0.030
Lateralization by PAO		205	23	0.610
LSP1 morphology (RD)		23	1	0.400
Lateralization by LSP1		51	2	0.080
Contralateral propagation		199	25	0.760
Ictal-interictal match		64	6	0.010

AED: Antiepileptic drug; EEG: Electroencephalography; PAO: Pattern at onset; LSP: Late significant pattern; RD: Rhythmic delta

Back to the original data for all patients, we realized that LSP1 and LSP2 morphology had no significant correlation with surgery outcome (P = 0.400 and P = 0.780 respectively). Patients with an ictal-interictal match (75.3%) were found to have the significantly better outcome (P = 0.010).

The outcome had no correlation with the intra-individual lateralizing or localizing seizure proportion (P = 0.490 and P = 0.550). We also failed to find any correlation between the ictal EEG/clinical seizure interval, the presence of multiple PAOs per patient, ipsilateral and contralateral propagation of IOPs or their time of onset and outcome (Table 3).

Surgery, pathology and outcome

Pathological findings, surgery side, and type had no significant effect on the outcome.

Inter-observer reliability

Inter-observer reliability for lateralization of IOPs was excellent (κ = 0.92 for PAO and κ = 0.96 for LSP, P < 0.001) and inter-observer agreement for localization was also perfect (κ = 0.89 for PAO and κ = 0.91 for LSP, P < 0.001).

Discussion

This retrospective cohort study was designed to evaluate ictal patterns in patients with refractory TLE who underwent surgery as well as investigating their prognostic value in surgical outcome. Unlike most similar studies, we investigated all recorded seizures for each patient during LTM to prevent neglecting different IOPs and semiologies that could occur in each patient. This approach seems necessary because two or more distinct PAOs have been detected in more than half of our patients and also about one-fifth of them have experienced different seizure semiologies.

Reviewing all enrolled patients, in line with most of the similar studies, we failed to find any correlation between age at onset of epilepsy,[2,20,23,24] age at surgery,[2,20,23,24] duration of epilepsy,[2,20,23-26] preoperative seizure frequency[2,27,28] and risk factors of epilepsy[23,28-30] with the outcome. Despite the few studies reporting man sex as a negative prognostic factor in epilepsy surgery,[31] most of the studies did not find sex as a factor influencing the postsurgical

outcome.[2,18,20,24,32] In contrast to similar studies, we have found the better postsurgical outcome in our female patients. Janszky, et al.[33] have mentioned more secondary generalization in man and more isolated auras and lateralized seizure patterns in woman patients with mesial TLE, which can somehow explain better postoperative outcome in female patients. Nevertheless, we did not find any significant difference between man and woman patients regarding above and other prognostic factors.

In our study, the presence of aura was associated with more favorable outcome. This finding can reflect the fact that most of the reported auras in our study occurred in mesial TLE patients with expected better outcome. Although we could not find any correlation between the contralateral propagation of epileptic discharges and outcome, similar to previous findings,[23,27-30,34] our patients with contralateral propagation which experienced secondarily generalized seizures had significantly unfavorable outcomes. We suggest that contralateral propagation of epileptic discharges, in a way that causes a clinically generalized seizure, is needed to affect the outcome. The underlying mechanism is probably a more diffuse epileptogenic zone or predisposition to secondary epileptogenesis.

According to the results of previous studies,[15,20,35] rhythmic theta was the most frequent initial ictal discharge in our patients. Our review of ictal findings showed that regardless of other factors, rhythmic theta as PAO is significantly associated with favorable outcome in TLE. In line with our results, Sirin, et al.[16] have shown a correlation between rhythmic theta/alpha activity and postsurgical seizure freedom in TLE, although they did not distinct theta and alpha rhythms which make the comparison imprecise. Furthermore, Assaf and Ebersole,[15] in their survey on ictal EEG predictors of postsurgical outcome in TLE, have shown that theta rhythm as ictal onset pattern on visual scalp EEG predicts a significantly better outcome than other rhythms. Also, Lau, et al.[35] in their study on TLE surgery remarked theta rhythm as the most common ictal pattern that carries the best prognosis for TLE particularly in those who have evidence of HS in MRI. In contrast, Malter, et al.[20] in their recent study on the predictive value of scalp EEG for epilepsy surgery did not find any correlation between initial ictal patterns and postoperative outcome in TLE. In a similar study by Monnerat, et al.[2] authors indicated that ictal EEG patterns could not provide any prognostic information regarding the postsurgical outcome, though they did not provide any details about the morphology of IOPs. Although lateralization by PAO and LSP1 was commonly possible in our patients, we found that correct lateralization is more important than the proportion of lateralizing seizures in each patient. The most lateralizing initial pattern in our patients was rhythmic theta and when it presented as PAO, it was considerably correlated to automotor semiology. Our results confirmed previous reports of better postoperative outcome in the case of an ictal-interictal match.[8,9] Since we merely enrolled patients with MRI-visible lesions in this study, our results could only be extended to this group of patients.

Conclusion

Our findings have shown that in TLE patients, woman sex, the presence of aura compatible with mesial temporal lobe origin, the absence of secondary generalization, rhythmic theta as PAO and concordance of ictal-interictal EEG findings are associated with a more favorable outcome.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Molecular changes in obese and depressive patients are similar to neurodegenerative disorders

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Keywords
Obesity; Depression; Neurodegeneration; Forkhead Box Protein; Heavy Metals; Lifestyle

Abstract

Background: Neurodegenerative disorders (NDs) are categorized as multifactorial conditions with different molecular and environmental causes. Disturbance of important signaling pathways, such as energy metabolism and inflammation induced by environmental agents, is involved in the pathophysiology of NDs. It has been proposed that changes in the lifestyle and nutrition (metabolism) during mid-life could trigger and accumulate cellular and molecular damages resulting in NDs during aging.

Methods: In order to test the hypothesis, we investigated the expression level of two energy metabolism-related [forkhead box O1 (FOXO1) and forkhead box O3 (FOXO3A)] and two pro-inflammatory cytokines [interleukin 1β (IL-1β) and IL-6] genes, using quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR). Furthermore, changes in the ionic concentration of three essential heavy metals [iron (Fe), copper (Cu), and zinc (Zn)] by atomic absorption spectroscopy in patients with NDs, depression, obesity, and diabetes type II, were evaluated and compared with the results of normal individuals.

Results: More than half of the participants in obesity, depression, and ND groups had significant up-regulation of FOXO1 and FOXO3A, down-regulation of IL-1β and IL-6, and higher levels of Fe and Cu in their blood. This pattern of gene expression was not repeated in diabetic patients.

Conclusion: It could be concluded that individuals affected with different levels of obesity and depression have increased the risk of developing NDs later in life, probably through changes in energy metabolism, inflammatory pathways, and ionic concentrations.

Introduction

Neurodegenerative disorders (NDs) are a group of diseases resulting from a neuronal loss in different regions of the central nervous system (CNS). It is fully accepted that both environmental and intercellular mechanisms are

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involved in the pathophysiology of NDs.[1,2] Induction of oxidative stress due to increased levels of intercellular metal ions,[3,4,5] mitochondrial dysfunction[6,7] disturbances in energy metabolism and autophagy signaling pathways[8-10] as well as releasing excessive neuroinflammatory factors in the CNS[11] are some of the main intercellular pathways involved in neuronal death. Instead, cellular and molecular dysfunctions in neurons are mostly induced by environmental risk factors such as toxic heavy metals,[12] unregulated homeostasis of essential metal ions[13] and lifestyle habits.[14]

We have recently suggested that changes in the normal concentration of essential metal ions such as Iron (Fe), Copper (Cu) and Zinc (Zn) rather than other factors could initiate neurodegeneration processes.[15] Our proposal was mainly based on increasing/decreasing activity of energy metabolism pathways in neurons due to changes in nutritional habits and lifestyle during mid-life. Basically, changes in our habits have resulted in more energy uptake than its consumption, neurological hormone alterations, and changes in the concentration of essential metal ions. All these conditions, which could be reflected as obesity, diabetes type II, and depression at the clinical level, are directly and indirectly connected to defects in energy metabolism pathways, intracytoplasmic metal ion concentrations, and subsequently cell apoptosis.[15-18] Changes in lifestyle and nutritional habits have also increased the prevalence of multifactorial diseases such as diabetes type II, obesity, and depression along with NDs.[19-22] Moreover, researches have shown that individuals affected by obesity, diabetes type II, and depression have higher risk of developing neurodegeneration during their life.[23-26]

Forkhead box O1 (FOXO1) and forkhead box O3 (FOXO3A) are two important transcription factors that have major roles in promoting autophagy,[27-31] energy metabolism, and stress responses.[32-42] Changes in the expression of these genes in CNS could result in neurodegeneration.[9] Additionally, elevated levels of inflammatory cytokines and alterations in the concentration of essential heavy metals have been reported in affected tissues of NDs, obesity, and diabetes type II.[11,43-50] Although the changes in expression of these two genes have been studied in animal models and are also reported separately in patients suffering from obesity, depression, diabetes type II, and NDs, little is known about the simultaneous pattern of these alterations between all mentioned diseases and healthy individuals.

Therefore, in the present pilot study, we investigated these alterations by measuring the expression of FOXO1 and FOXO3A in combination with two inflammatory genes interleukin 1β (IL-1β) and IL-6 in patients with diabetes type II, obesity, depression, and NDs, and compared them with normal individuals. We also evaluated alterations of the concentration of three metal ions (Fe, Cu, and Zn) in the proposed groups of patients.

Materials and Methods

Totally, 105 blood samples were collected from patients diagnosed with ND [mild cognitive impairment (MCI), non-familial Alzheimer's and Parkinson's diseases, n = 26), depression (n = 17), obesity (n = 20) and diabetes type II (n = 21). Twenty-one normal individuals with normal body mass index (BMI), fast blood sugar (FBS) and without any neurological complications were analyzed as a control. Samples with a positive family history of diabetes type II, obesity, depressive and NDs were excluded from the control group. Informed consent was obtained from all individual participants included in the study. Consent form has been approved by Ethical Committee of Iran National Science Foundation. General information of patients in different groups has been indicated in table 1.

ND and depression samples were obtained from Imam Khomeini hospital, department of neurology, Tehran University of Medical Sciences, Iran. Obesity, diabetes type II and normal samples

Table 1. General information of individuals participated in this study

Group	Sex		Age (year) (mean ± SD)
	Man [n (%)]	Woman [n (%)]	
Normal (n = 21)	11 (52)	10 (48)	35 ± 3
ND (n = 26)	11 (42)	15 (58)	67 ± 7
Depression (n = 17)	2 (12)	15 (88)	42 ± 5
Obesity (n = 20)	8 (40)	12 (60)	48 ± 2
Diabetes type II (n = 21)	8 (38)	13 (62)	54 ± 2

SD: Standard deviation; ND: Neurodegenerative disorders [including Alzheimer's disease, Parkinson's disease and MCI (mild cognitive impairment)]

were collected from the Center of Diabetes Screening, Tehran University of Medical Sciences.

Total RNA was extracted from whole blood using the Trizol-chloroform procedure. Briefly, 600 µl of AccuZol (Bioneer, South Korea) was mixed with 1 ml fresh blood. After shaking, 200 µl chloroform (Merck, Germany) was added to the mix, incubated for 15 minutes on ice and centrifuged at 12000 rpm, 15 minutes at 4 ˚C. The clear supernatant was mixed with 500 µl isopropanol (Merck, Germany), incubated 10 minutes on ice and centrifuged at 11000 rpm, 10 minutes, at 4 ˚C. The RNA pellet was then washed 2 times with 70% ethanol at 7000 rpm, 5 minutes, at 4 ˚C and dissolved in 20 µl RNase free ddH_2O. The quality of RNA was checked on an agarose gel. The quantity and purity of samples were measured using Nano-drop (Thermo scientific, USA) and A260/280 ratio, respectively. High-quality RNA samples were used for cDNA synthesis.

In order to synthesize cDNA, 500 ng of DNase I-treated (Takara, Japan) RNA was mixed with 1 unit AccuPower® CycleScript reverse transcriptase, 1x reaction buffer, 10 mM dNTPs, 0.5 mM oligo dT and 0.5 mM random hexamer primers, RNase inhibitor and up to 20 µl RNase-free ddH_2O. The mix was incubated at 25 ˚C for 30 seconds for 1 round, and 45 ˚C for 4 minutes and 55 ˚C for 30 seconds, for 12 rounds. The reaction was then heat-inactivated at 95 ˚C for 5 minutes.

Quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) was performed to quantify the expression of FOXO1, FOXO3A, IL-1B, and IL-6. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene expression was measured as an internal control of the experiment. Primer sequences have been indicated in table 2.

The qRT-PCR reaction was contained 500 ng of cDNA mixed with 25 µl of SYBR green master mix (GeneON, Germany), 300 nM of each reverse and forward primers and up to 50 µl RNase/DNase-free ddH_2O. PCR reactions were performed in Corbet research instrument (Rotor-Gene™ 6000, Australia) under the following condition: the one-time initial denaturation at 95 ˚C for 10 minutes, and 95 ˚C for 20 seconds, 57 ˚C for 45 seconds, repeated for 40 cycles and followed by melting curve step.

Serums obtained from 3 ml blood samples were used to measure the concentration of free metal ions including Fe, Cu and Zn. Sample dilution for Cu was 1:50 (serum:ddH_2O), for Fe and Zn was 1:10 (serum:ddH_2O). Deionized water was used for dilution of samples and standard preparations were prepared with a resistivity of 18.0 MΩ cm (Elga Labwater, Wycombe, Bucks, UK). Working standard solution was freshly prepared in ddH_2O in 3 dilutions for each metal: Fe standards (0.5, 1, and 2 mg/l), Cu standards (10, 20, and 40 µg/l), and Zn standards (0.1, 0.2 and 0.4 mg/l).

The elemental determination was done by Varian spectra AA-240FS atomic absorption spectrometer (Varian Australia, Pty Ltd, Mulgrave, Victoria, Australia). Flame atomic absorption was used for detecting Fe and Zn. Furnace atomic absorption was applied to measure Cu.

Seronorm leve2 (SERO AS, Norway) was used in each step to control the qualification of the instrument. Hemolyzed samples were excluded for this test.

This research was designed as a pilot study. qRT-PCR and atomic absorption spectroscopy experiments for each sample were done as triplicate and duplicate, respectively. qRT-PCR data were analyzed using the $2^{-\Delta\Delta Ct}$ method. All data were then analyzed by SPSS software (version 11.5, SPSS Inc., Chicago, IL, USA). Analysis of variance (ANOVA) and Tukey's test were used for data analyses. P less than 0.050 was considered as significant.

Table 2. The sequence of primers used in this study

Gene name	Forward 5'-3'	Reverse 5'-3'	Reference
FOXO1	TGGACATGCTCAGCAGACATC	TTGGGTCAGGCGGTTCA	51
FOXO3A	ATGTGACATGGAGTCCATCATCC	TGTCCACTTGCTGAGAGCAGAT	52
IL-1β	ACAGATGAAGTGCTCCTTCCA	GTCGGAGATTCGTAGCTGGAT	53
IL-6	GGTACATCCTCGACGGCATCT	GTGCCTCTTTGCTGCTTTCAC	54
GAPDH	TGCACCACCAACTGCTTAGC	GGCATGGACTGTGGTCATGAG	55

FOXO1: Forkhead box O1; FOXO3A: Forkhead box O3; IL-1β: Interleukin 1β; IL-6: Interleukin 6

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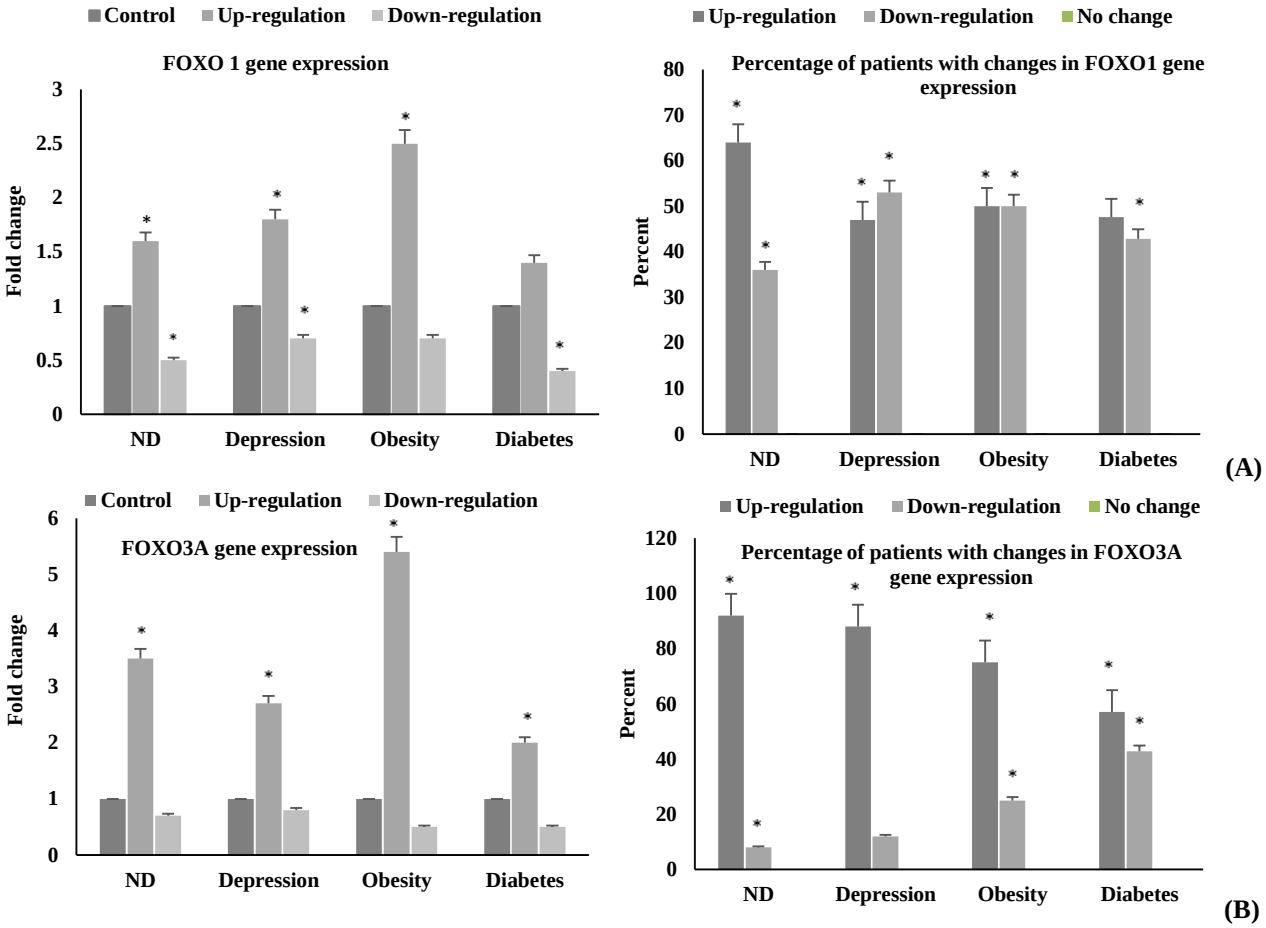

Figure 1. Expression ratio of forkhead genes

The ratio of forkhead box O1 (FOXO1) and forkhead box O3 (FOXO3A) gene expression fold change and percentage of patients in each group of diseases that showed up or down-regulation in these genes are illustrated. Changes in expression of FOXO1 and FOXO3A genes were detected in almost all patients. **A:** More than half of the patients with obesity and depression as well as neurodegenerative diseases (NDs) had significant up-regulation of FOXO1 gene. **B:** The percentage of patients that showed FOXO3A up-regulation is significantly higher in obesity, depression and NDs groups. Patients' data have been normalized with mean C_t values of healthy individuals. The fold change of FOXO1 and FOXO3A for healthy individuals is calculated as 1. The graphs present the fold change and percentage of patients (Y-axis) in each group of diseases (X-axis). Dark gray bars remark expression level in controls, grays bars show up-regulation in patients and light gray bars show down-regulation in patients. In right hand graphs; dark gray bars remark up-regulation and gray bars show down regulation. Standard error of mean (SEM) has been calculated for each bar.

*P < 0.050, ND: Neurodegenerative disorders

Results

Expression of forkhead transcription factors: energy metabolism pathway: In this study, we quantified the expression of FOXO1 and FOXO3A genes in whole blood cells of four groups of patients with NDs, obesity, diabetes type II, and depression and compared them with the normal population. Our data showed that FOXO1 expression was significantly up-regulated (P < 0.050) in more than 50% of obese, depressive, and NDs patients. The number of diabetic patients that showed up-regulation of this gene was not significant. However, the percentage of patients showing down-regulation of FOXO1 was significant (P < 0.011) in all groups of disease (Figure 1A). No significant difference in the pattern of FOXO1 gene expression could be seen between obesity, depression and diabetes type II compared to NDs.

FOXO3A expression was up-regulated in more than 50% of the patients in all four groups of disease. This change was significant for obesity, depression, and NDs (P < 0.050). Down-regulation of this gene which could be seen in less than 42% of the patients was significant (P < 0.003) for obese, diabetic, and neurodegenerative groups (Figure 1B). Similar to FOXO1, the pattern of FOXO3A gene expression was not significantly different between obese, depressive, and diabetic patients versus patients with NDs.

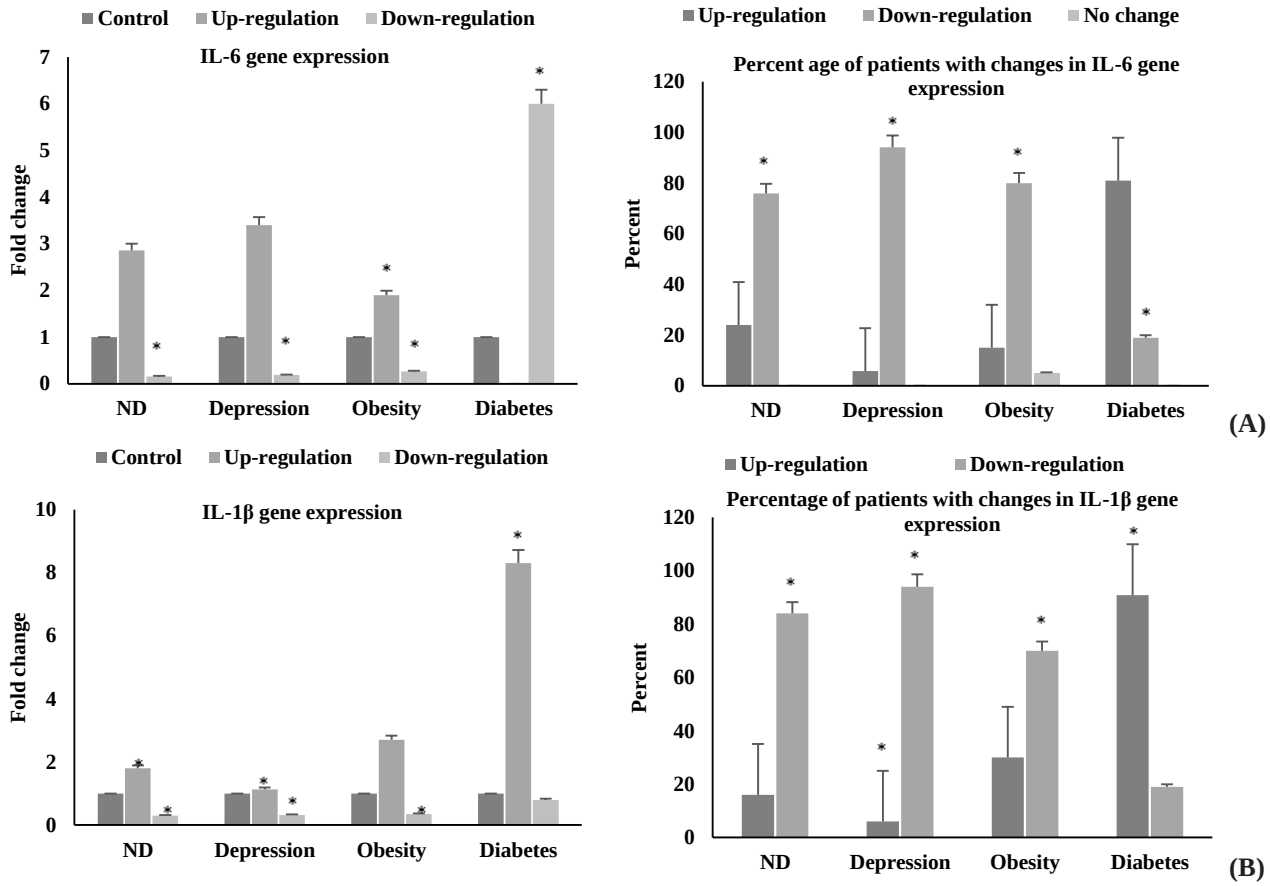

Figure 2. Expression ratio of inflammatory genes

The ratio of interleukin-1β (IL-1β) and interleukin-6 (IL-6) gene expression changes and percentage of patients in each group of diseases that showed up or down-regulation of these genes is illustrated. More than 70% of individuals affected with obesity and depression as well as neurodegenerative diseases (NDs) showed down-regulation of IL-1β (A) and IL-6 (B). Up-regulation of IL-1β and IL-6 in more than 80% of diabetic patients has been detected in this study. Fold change (gene expression) have been normalized with mean C_t values of healthy individuals. The fold change of IL-1β and IL-6 for healthy individuals was calculated as 1. The graphs present the fold change and percentages of patients (Y-axis) in each group of diseases (X-axis). In left hand graphs; Dark gray bars remark expression level in controls, grays bars show up-regulation in patients and light gray bars show down-regulation in patients. In right hand graphs; dark gray bars remark up-regulation, gray bars show down-regulation, and light gray bars show no change. Standard error of the mean (SEM) has been calculated for each bar.

*P < 0.001, ND: Neurodegenerative; IL: Interleukin

There was no significant correlation between changes in the expression of FOXO1 / FOXO3A and clinical data such as BMI, FBS, low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol, and triglyceride in this study.

Expression of inflammatory factors: In order to check the inflammatory status of our patients, we analyzed the RNA expression of IL-1β and IL-6 (two prominent inflammatory cytokines) in whole blood samples. The results revealed that more than 70% of the patients suffering from NDs, depression, and obesity, had decreased expression of both IL-1β and IL-6 ($P < 0.001$). However, more than 80% of the diabetic participants showed overexpression of these genes in their blood (Figure 2, A and B).

There was no significant correlation between changes in the expression of IL-1β / IL-6 and clinical data including BMI, FBS, LDL, HDL, cholesterol, and triglyceride in this study.

Determination of essential heavy metal concentration: Measurement of free Fe, Cu, and Zn ions in the serum of patients, as compared with healthy individuals, revealed that the concentration of Fe and Cu increased significantly ($P < 0.050$) in patients with obesity, depression, and NDs. These changes were not significant between diabetic patients and healthy participants (Figure 3). Changes in the free Zn ion were not significant, as well.

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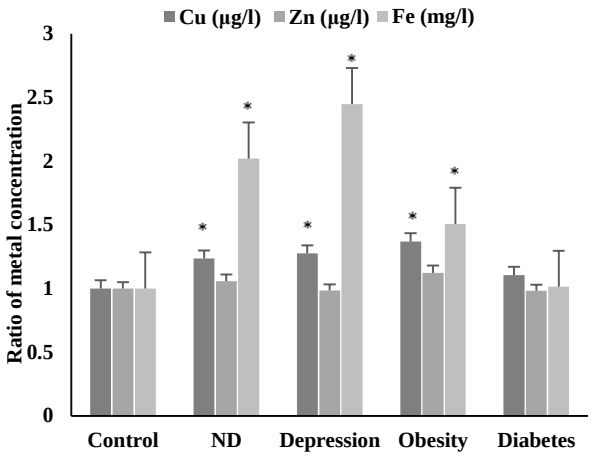

Figure 3. Mean ratio levels of free metal ions in serum of the patients

The mean concentration of free iron (Fe) and copper (Cu) in the serum of patients affected with obesity, depression and neurodegenerative diseases (NDs) is significantly higher than the control group. The concentration of zinc (Zn) ions shows no significant change in patients groups. Diabetic patients do not show any change in concentrations of essential metal ions. The graphs present average of metal iron concentration in patients and controls (Y-axis) in each group of study (X-axis). Dark gray bars remark serum level of Cu (µg/l), gray bars present Zn (µg/l) levels and light gray bars show Fe (mg/l) levels. Standard error of the mean (SEM) has been calculated for each bar.

*P < 0.050, ND: Neurodegenerative disorders

Although Fe and Cu changes in diabetic patients were not significant, we found a significant ($P < 0.001$) positive correlation between changes in Fe/Cu concentration and FOXO3A gene expression (correlation coefficient of 0.704 and 0.613, respectively) in this group.

A positive correlation ($P < 0.050$, correlation coefficient of 0.457) was also found between the concentration of Cu and FOXO3A gene expression in obese patients.

Discussion

In order to test our hypothesis about the relationship between changes in expression of energy metabolism (autophagy) genes and heavy metal concentrations in diabetic, obese, depressive patients and increasing risk of NDs at clinical level, we compared RNA expression of four genes involved in energy metabolism and inflammatory systems as well as determination of essential metal concentrations in blood of two metabolic syndromes (obesity and diabetes type II), an anxiety condition (depression), three NDs (Alzheimer's and Parkinson's diseases and MCI), and normal group. Obesity, diabetes type II and depression are considered as cases with nutritional and lifestyle problems.

Our data showed that more than half of obese and depressed patients had higher levels of FOXO1 and FOXO3A expression (involved in energy metabolism and autophagy signaling pathways),[27-33] lower levels of IL-1β and IL-6 expression (involved in inflammatory responses) and increased concentrations of free Fe and Cu in their serum, as compared to normal individuals. Interestingly, these results were also repeated in cases with NDs. However, the results were not the same for diabetic patients.

Different studies have highlighted the role of FOXO transcription factors in induction of autophagy in various types of cells.[27-31] Up-regulation of FOXO1 and FOXO3A in the blood (mainly lymphocytes) of patients with obesity and depression might reflect similar changes in the expression pattern of these genes in neural cells.[56] Therefore, increasing forkhead gene expression could cause uncontrolled autophagy events, lead to neural death and increase the risk of neurodegeneration in these patients.

Although increased levels of IL-1β and IL-6 in patients with diabetes type II have also been confirmed in different studies,[57,58] down-regulation of these two pro-inflammatory genes in obesity, depression, and ND groups could be controversial because most studies have highlighted higher levels of inflammatory cytokines in all mentioned disorders.[47,59,60] Thus, our results could be explained based on the cells we analyzed in this study and the protective roles of IL-1β and IL-6 in different tissues, especially CNS. Most studies reporting elevated levels of inflammatory cytokines have worked specifically on affected tissues of patients with obesity and neurological problems or have searched for the protein in the serum or cerebrospinal fluid (CSF) of these patients.[61-63] However, in this study, we focused on the expression of cytokine genes in the blood cells that might respond differently to disease conditions as compared to affected tissues. Additionally, some studies have indicated that IL-1β and IL-6 expression have neuroprotective roles,[64-66] and therefore a decrease in their expression below the normal levels could result in neural injury and apoptosis. Because of the multifactorial nature of the diseases studied in this research, it is possible that the same disease in different individuals is resulted from the

impairment of different signaling pathways or environmental factors. That is why we also observed higher levels of inflammatory factors and lower levels of energy metabolism genes in fewer cases of obesity, depression, and NDs.

Another hallmark of our study is the age of our participants. In this research, most of the patients with obesity, depression, and diabetes type II as well as normal individuals were below 50 years old and in the mid-life stage, while the mean age of our ND patients was 67 years. Therefore, the similar pattern of molecular changes in obesity, depressive and NDs group (with different ages) in this study might indicate that disturbance of different signaling pathways and also ionic concentrations during mid-life could increase the rate of NDs during old age.

To the best of our knowledge, this is the first report directly evaluated FOXO1 and FOXO3A expression along with inflammatory gene expression and metal analysis in the serum of obesity, depression, diabetic type II and NDs simultaneously. In conclusion, we propose that people affected with obesity and depression might have a higher risk of developing NDs mostly through changes in the energy metabolism system and essential metal concentrations. Diabetic patients might be at risk of neuronal loss through inflammatory pathways. Another important point is that obesity, depression, and diabetic conditions in early stages or mild forms are mostly ignored either by affected people or clinicians, while changes in the molecular pathways or ionic concentrations and the consequent cellular damages have already started in their body. Thus, informing negligent people could help them to change their lifestyle and start protective measures.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Ten-year trend in stroke incidence and its subtypes in Isfahan, Iran during 2003-2013

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Keywords
Risk Factors; Incidence; Mortality; Stroke; Trend

Abstract

Background: As there was no evidence of long-term studies on stroke trend, stroke subtypes and its relationships to stroke risk factors and demographic characteristics in Iran, we aimed to evaluate the 10-year trend of stroke incidence and stroke subtypes in Isfahan, Iran.

Methods: In a hospital-based retrospective study, 24186 cases with the first-ever stroke were analyzed. We assessed the incidence trend of annual stroke and its subtypes [ischemic stroke (IS) subarachnoid hemorrhage (SAH), and intracranial hemorrhage (ICH)] during the years 2003 to 2013 by sex, and studied the association of demographic and major stroke risk factors with incidence and mortality rate of stroke.

Results: The mean age was 69.46 ± 14.87 years, and 49.29% of patients were women. IS was the most frequent type among all the types of strokes (76.18%). Stroke and its subtypes had decreasing incidence trend during the study period, except for SAH that increased. In addition, stroke and its subtypes had decreasing mortality trend during the study period, except for SAH that did not change anymore. Stroke mortality and incidence rates were lower in urban inhabitants compared to residents of rural areas [odds ratio (OR) = 0.763, P < 0.001].

Conclusion: Despite the relatively high incidence of stroke over the study period, the incidence rate of stroke, especially ICH subtype, had a decreasing trend over the last decade in Isfahan. However, given the current young population in Iran, we can expect that the incidence of stroke would have an escalating trend in future.

Introduction

Stroke is the second most common cause of mortality and disability worldwide.[1] With increasing older population in the world, the increased incidence of stroke is predictable.[2] On the other hand, low and middle-income countries had 100% increase in stroke deaths during the

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past four decades.[3] Furthermore, evidence from the epidemiological trend in stroke and its subtypes worldwide indicates differences in the incidence and mortality rate of stroke by sex,[4] urban/rural area of residence,[5] and its variability trends over time.[6]

According to 2011 national census, over 60-year old population of Iran has increased from 7.22% in 2006 to 8.20%.[7] Apart from demographic change, in the last decade, Iran has been facing profound changes in lifestyle that all of these factors together may be effective in increasing the incidence of stroke and mortality over time. Data from a recent study indicated high stroke incidence and mortality rates in Iran, demonstrating that the crude annual incidence rate of stroke in Iran were 144 and 133 per 100000 in men and in women, respectively.[8]

To our knowledge, there is little information about incidence and trend of stroke in Iranian population taken an explicit systematic approach for long-period studies. Bearing it in mind, we studied stroke incidence, mortality and major types by age in both sexes in Isfahan, Iran, and assessed whether the area of residence (i.e. rural vs. urban) contributed to the variation in stroke incidence and mortality among these populations. Analysis of existing data was necessary to identify a current trend in stroke epidemiology and its subtypes in this part of the world. This could be a basis for later evidence-based prevention programs.

Materials and Methods

This was a hospital-based retrospective cross-sectional study conducted in the Neuroscience Research Center, Isfahan, in collaboration with the Cardiovascular Research Institute, Isfahan University of Medical Sciences. The patients with their first stroke during 2003 until the end of 2013, who were admitted to eight hospitals with departments of neurology, neurosurgery, and intensive care unit (ICU) located in Isfahan, were enrolled in the study. Among these patients, only first ischemic stroke (IS), first hemorrhagic stroke, or first nonspecific stroke for a participant was retained.

Data were collected following the World Health Organization (WHO) stepwise approach to stroke surveillance (STEPS-stroke) protocol.[9] In the first step, we collected information on patients with stroke admitted to health facilities. Strokes, according to WHO definition, were diagnosed[10] and classified into three subtypes, IS, intracranial hemorrhage (ICH), and subarachnoid hemorrhage (SAH) based on neuroimaging reports.[11]

In this study, three nurses who were educated before the study abstracted medical records. A statistician carried out the data entry. This study was reviewed and approved by the Human Ethics Committee, Neuroscience Research Center, Isfahan University of Medical Sciences.

First, the groups of women and men were compared in different aspects using Student's independent t- and chi-square tests. Quantitative and qualitative data were shown as the mean ± standard deviation (SD) and number (percentage), respectively. The incidence rate of stroke was directly standardized to the 5-year age distribution of Segi's world population.[12] Segi's world population was devised in the late 1950s by a cancer epidemiologist, Mitsuo Segi, based on the sum total of men and women populations of 46 countries in the 1950 publications of the WHO.[13] The 95% confidence interval (CI) was calculated for stroke incidence rates. The incidence trend of stroke and its subtypes from 2003 to 2013 were calculated using linear regression. We also used logistic regression models to evaluate the association of sex, age, living area, and stroke subtypes and risk factors for stroke incidence rate and mortality. For all the tests, P less than 0.050 was considered statistically significant. The term, incidence rate, was restricted to only the first stroke. Mortality rate was the number of fatal events that occur within 28 days per a population of 100000 people. All the data were analyzed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA).

Results

During this study from 2003 to 2013, in total, 24186 cases of stroke, including 11922 women (49.29%) and 12264 men (50.71%) were registered in Isfahan from eight hospitals. Patients' demographic characteristics, stroke type, and risk factors are shown in table 1.

It can be seen that the mean age was 69.46 ± 14.87 years and women were significantly older than men (69.99 ± 16.22 vs. 68.94 ± 13.39 years, respectively, $P < 0.001$). The highest percentage of patients was in the age group of above 65 years (66.53%). The frequency of patients aged more than 65 years was significantly higher among women than men [8103 (50.36%) vs. 7987 (49.64%), respectively, $P < 0.001$)]. 20675 (85.48%) and 3370 patients (13.93%) were residents of urban and rural areas, respectively.

Table 1. Characteristics of men and women patients with stroke in Isfahan, Iran, between 2003 and 2013

Characteristic		Total (n = 24186)	Women (n = 11922)	Men (n = 12264)	P*
Age (year) (mean ± SD)		69.46 ± 14.87	69.99 ± 16.22	68.94 ± 13.39	< 0.001
Age group	< 45	1406 (5.81)	710 (50.50)	696 (49.50)	0.780
[n (%)]	45-65	6690 (27.66)	3109 (46.47)	3581 (53.53)	< 0.001
	> 65	16090 (66.53)	8103 (50.36)	7987 (49.64)	< 0.001
Living area	Urban	20675 (85.48)	10233 (49.49)	10442 (50.51)	0.670
[n (%)]	Rural	3370 (13.93)	1630 (48.37)	1740 (51.63)	0.310
	Undetermined	141(0.58)	-	-	-
Stroke type	IS	18425 (76.18)	9047 (49.10)	9378 (50.90)	0.690
[n (%)]	ICH	4334 (17.92)	2143 (49.45)	2191 (50.55)	0.850
	SAH	571 (2.36)	307 (53.77)	264 (46.23)	0.034
	Undetermined	856 (3.54)	-	-	-
Stroke risk	TIA	6160 (16.28)	2900 (47.08)	3260 (52.92)	< 0.001
factor [n (%)]	Diabetes	7417 (19.60)	3964 (53.44)	3453 (46.56)	< 0.001
	Elevated blood pressure	15890 (41.99)	8846 (55.67)	7044 (44.33)	< 0.001
	Hearth attack	8371 (22.12)	4289 (51.24)	4082 (48.78)	< 0.001

*Student's independent t- and chi-square tests (women vs. men)

SD: Standard deviation; IS: Ischemic stroke; ICH: Intracranial hemorrhage; SAH: Subarachnoid hemorrhage; TIA: Transient ischemic attack

There were no statistically significant sex differences between stroke frequency in patients living in urban or rural areas (P = 0.670 and P = 0.310, respectively). IS was the most frequent subtype among all types of stroke, which the frequency of 18425 (76.18%). Moreover, SAH was statistically higher in women than in men [307 (53.77%) vs. 264 (46.23%), P = 0.030]. We did not find any statistically significant difference in the number of other stroke subtypes between sexes. All stroke risk factors examined in this study were observed more frequently in women than in men (P < 0.001 for all), except transient ischemic attack (TIA).

Table 2 shows crude incidence rate (CIR) and age-adjusted incidence rate (AIR) (per 100000) of stroke types in Isfahan during 2003-2013. The occurrence of IS subtypes was highest compared with other subtypes. The age-adjusted occurrence of ICH (β = -3.29, P = 0.001) and IS (β = -5.63, P = 0.007) showed significantly decreasing trend during the study period. However, no significant change was observed in SAH subtype (β = 0.08, P = 0.450).

Table 2. Age-adjusted incidence rate (AIR) (per 100000) of stroke types in Isfahan, Iran, during 2003-2013

Year	Type of stroke					
	SAH [OR (95% CI)]		ICH [OR (95% CI)]		IS [OR (95% CI)]	
	CIR	AIR	CIR	AIR	CIR	AIR
2003	3.7 (1.3-7.3)	4.9 (2.7-9.0)	37.3 (25.7-48.9)	53.8 (40.1-67.5)	108.6 (88.8-128.4)	157.0 (133.6-180.4)
2004	2.5 (0.5-5.5)	3.2 (0.2-6.6)	35.9 (24.5-47.3)	51.1 (37.7-64.5)	106.2 (86.6-125.8)	150.5 (127.5-173.5)
2005	3.0 (0.3-6.3)	3.7 (0.1-7.3)	27.3 (17.4-37.2)	38.4 (26.8-50.0)	118.6 (97.9-139.3)	165.3 (141.2-189.4)
2006	2.1 (0.7-4.9)	2.6 (0.4-5.8)	25.4 (15.8-35.0)	34.7 (23.6-45.8)	108.7 (88.9-128.5)	149.5 (126.5-172.5)
2007	2.0 (0.7-4.7)	2.5 (0.5-5.5)	20.5 (11.9-29.1)	27.7 (17.8-37.6)	86.2 (68.5-103.9)	115.2 (95.0-135.4)
2008	1.9 (0.7-4.5)	2.2 (0.6-5.0)	17.0 (9.2-24.8)	22.1 (13.2-31.0)	84.5 (67.0-102)	111.0 (91.1-130.9)
2009	2.5 (0.5-5.5)	2.8 (0.4-6.0)	13.6 (6.6-20.6)	17.4 (9.5-25.3)	69.1 (53.3-84.9)	89.6 (71.7-107.5)
2010	2.4 (0.6-5.4)	2.9 (0.3-6.1)	20.1 (11.6-28.6)	25.1 (15.6-34.6)	103.8 (84.4-123.2)	132.4 (110.7-154.1)
2011	4.1 (0.2-8.0)	4.8 (0.6-9.0)	18.6 (10.4-26.8)	23.0 (13.9-32.1)	90.5 (72.4-108.6)	112.9 (92.8-133.0)
2012	3.7 (0.1-7.4)	4.1 (0.3-7.9)	20.4 (11.8-29.0)	24.0 (14.7-33.3)	89.5 (71.5-107.5)	107.8 (88.1-127.5)
2013	4.7 (0.6-8.8)	5.1 (0.8-9.4)	15.7 (8.1-23.3)	18.3 (10.2-26.4)	94.2 (75.7-112.7)	110.7 (90.7-130.7)
Average	3.0 (0.3-6.3)	3.5 (0.2-7.0)	22.9 (13.8-32)	30.5 (20.1-40.9)	96.4 (77.7-115.1)	127.4 (106.1-148.7)
β*	0.13	0.08	-1.94	-3.29	-2.27	-5.63
P**	0.162	0.450	0.002	0.001	0.093	0.007

*Regression coefficient; **Chi-square test (AIR values are adjusted by the Segi's world population[12])

OR: Odds ratio; CI: Confidence interval; SAH: Subarachnoid hemorrhage; ICH: Intracranial hemorrhage; IS: Ischemic stroke; CIR: Crude incidence rate; AIR: Age-adjusted incidence rate; β: Regression coefficient

Table 3. Crude incidence rate (CIR) (per 100000) and age-adjusted incidence (AIR) (per 100000) of stroke in men, women, and total population in Isfahan, Iran, during 2003-2013

Year	Men [OR (95% CI)]			Women [OR (95% CI)]			Total [OR (95% CI)]		
	n	CIR	AIR	n	CIR	AIR	n	CIR	AIR
2003	1253	152.6 (129.9-175.3)	298.0 (268.5-327.6)	1303	167.4 (143.7-191.1)	167.4 (143.7-191.1)	2556	159.8 (135.8-183.8)	229.8 (201.5-258.2)
2004	1190	142.4 (120.5-164.3)	275.6 (247.1-304.2)	1263	159.2 (136.1-182.4)	226.6 (199.9-253.4)	2453	150.6 (127.3-173.9)	213.0 (185.7-240.4)
2005	1225	144.0 (121.9-166.1)	198.9 (173.6-224.2)	1310	162.1 (138.8-185.5)	227.7 (200.8-254.6)	2535	152.8 (129.3-176.3)	212.8 (185.4-240.2)
2006	1127	130.2 (109.2-151.2)	224.6 (198.3-250.8)	1218	148.0 (125.7-170.4)	202.7 (177.2-228.2)	2345	138.9 (116.5-161.3)	190.3 (164.4-216.2)
2007	988	111.8 (92.3-131.3)	183.1 (159.1-207.0)	908	108.4 (89.3-127.6)	145.7 (124.0-167.4)	1896	110.2 (90.2-130.1)	147.3 (124.4-170.1)
2008	920	102.9 (84.2-121.6)	170.8 (147.6-193.9)	904	106.1 (87.2-125.1)	137.4 (116.2-158.5)	1824	104.5 (85.0-123.9)	136.5 (114.5-158.5)
2009	807	86.8 (69.5-104.1)	138.2 (117.2-159.1)	726	77.8 (61.4-94.1)	101.7 (83.4-120.1)	1533	86.4 (68.7-104.1)	111.3 (91.4-131.2)
2010	1231	127.2 (106.3-148.1)	211.0 (185.1-236.9)	1115	110.4 (90.8-129.9)	142.1 (120.2-163.9)	2346	130.3 (108.6-152.1)	165.2 (140.9-189.5)
2011	1127	136.2 (114.8-157.6)	213.9 (188.1-239.7)	1037	116.3 (96.4-136.2)	142.9 (121.1-164.6)	2164	126.5 (105.1-147.8)	157.2 (133.5-180.9)
2012	1201	127.1 (106.2-148.0)	195.1 (170.1-220.2)	1050	116.2 (96.3-136.1)	138.5 (117.0-160.0)	2251	121.8 (100.7-142.8)	145.6 (122.8-168.5)
2013	1195	125.0 (104.3-145.7)	187.3 (162.7-212.0)	1088	118.9 (98.7-139.1)	138.8 (117.2-160.4)	2283	122.0 (101.0- 143.1)	142.9 (120.2-165.6)
Average		126.0 (105.4-146.7)	208.8 (183.4-234.1)	-	126.4 (105.9-147.0)	161.0 (138.3- 183.8)	-	127.6 (106.2-149.0)	168.4 (144.1-192.7)
β^{*}		-2.3	-8.2	-	-5.9	-8.3	-	-3.8	-8.7
P^{**}		0.210	0.050	-	0.021	0.019	-	0.058	< 0.009

*Regression coefficient; **Chi-square test (AIR values are adjusted by the Segi's world population[12])
OR: Odds ratio; CI: Confidence interval; CIR: Crude incidence rate; AIR: Age-adjusted incidence rate; β: Regression coefficient

Table 3 shows stroke CIR and AIR (per 100000 population) during 2003 to 2013. The mean CIR and AIR of stroke in both sexes over the study period were 127.6/100000 (95% CI: 106.2-149.0) and 168.4/100000 (95% CI: 144.1-192.7), respectively. Men had a higher AIR rate of stroke compared to women (208.8/100000, 95% CI: 183.4-234.1 vs. 161.0/100000, 95% CI: 138.3-183.8, respectively), but this was not observed in CIR, with 126.0/100000 (95% CI: 105.4-146.7) for men and 126.4/100000 (95% CI: 105.9-147.0) for women. Overall, the CIR and AIR rate of stroke decreased from 2003 to 2013 (CIR, β = -3.8 and AIR rate, β = -8.7), but this trend was significant only in crude incidence (P = 0.009). Similarly, there was a decreasing trend in the CIR and AIR of stroke in both sexes from 2003 to 2013; however, this trend was significant only for women (Table 3). Figures 1-4 show the trends of CIR and AIR (per 100000 population) of stroke and its subtypes among the total population, men, and women, respectively. As can be seen, decreasing trend was seen in incidence rates during the study period, except for SAH.

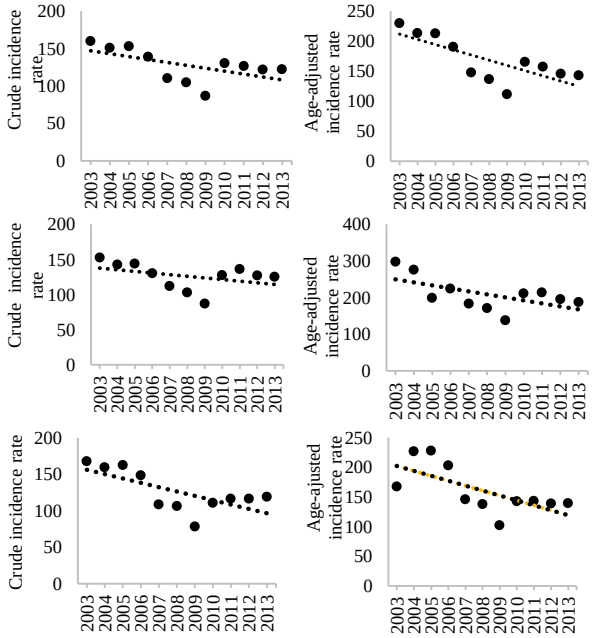

Figure 1. Crude incidence rate (CIR) and age-adjusted incidence rate (AIR) (per 100000) of all stroke types among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

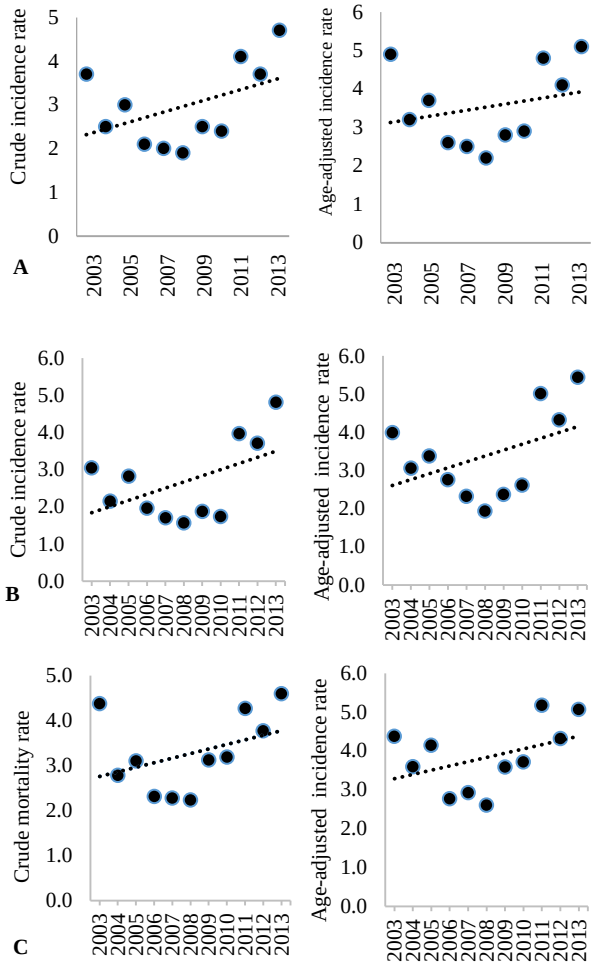

Figure 2. Crude incidence rate (CIR) and age-adjusted incidence (AIR) (per 100000) of subarachnoid hemorrhage (SAH) among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

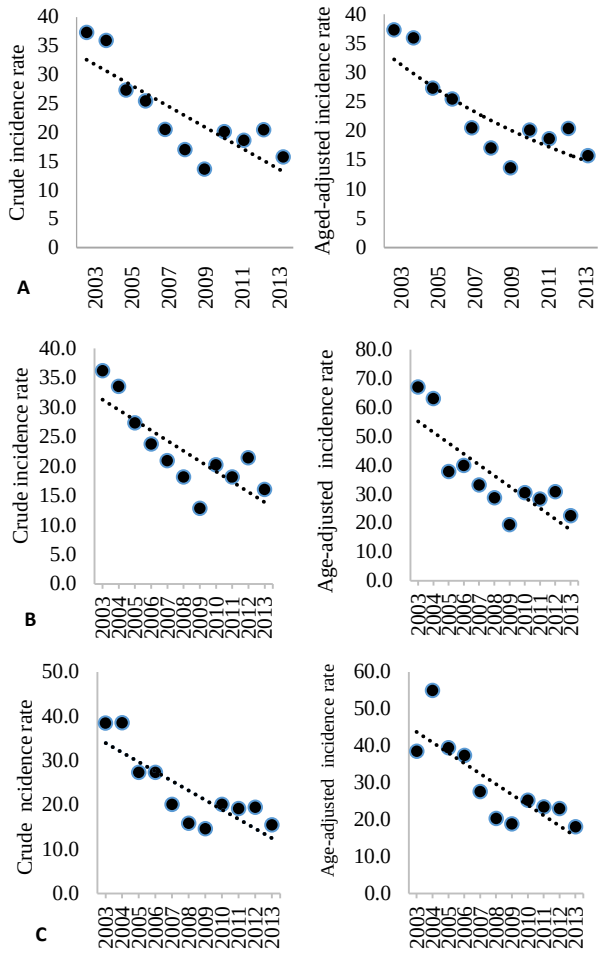

Figure 3. Crude incidence rate (CIR) and age-adjusted incidence (AIR) (per 100000) of intracranial hemorrhage (ICH) among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

Figures 5-8 show the trend of crude and age-adjusted mortality rates (per 100000 population) of stroke and its subtypes among the total population, men, and women, respectively. Decreasing trend was visible in mortality rates among the total population, men, and women in Isfahan, during the study period.

As shown in table 4, men were less likely to die due to stroke compared to women (OR = 0.81, 95% CI: 0.75-0.87, P < 0.001). With increased age in patients with stroke, the mortality OR increased (OR = 1.04, 95% CI: 1.03-1.05, P < 0.001). Stroke mortality rate was lower in individuals from urban areas than rural areas (OR = 0.76, 95% CI: 0.69-0.85, P < 0.001).

The odds ratios (OR) of 28-day mortality due to ICH (OR = 4.04, 95% CI: 3.71-4.41, P < 0.001) and SAH (OR = 3.94, 95% CI 3.20-4.86, P < 0.001) were higher than IS (as reference).

The stroke mortality risk in patients with TIA was higher than the patients without it (OR = 1.31, 95% CI: 1.20-1.41, P < 0.001). The stroke mortality and risk in patients with a history of heart attack were higher than in patients without a history of heart attack (OR = 1.46, 95% CI: 1.35-1.57, P < 0.001 and: OR = 1.29, 95% CI: 1.14-1.45, P < 0.001, respectively).

Discussion

This was a retrospective, non-community epidemiologic study on stroke and its subtypes in Isfahan. Overall, over the 10-year period of 2003-2013, a decreasing trend in stroke incidence was observed among both sexes. Indeed, AIR decreased from 229.8/100000 in 2003 to 168.4/100000 in 2013. In recent decades, several studies have reported a decline in stroke incidence rate[14-16] which agrees with our results.

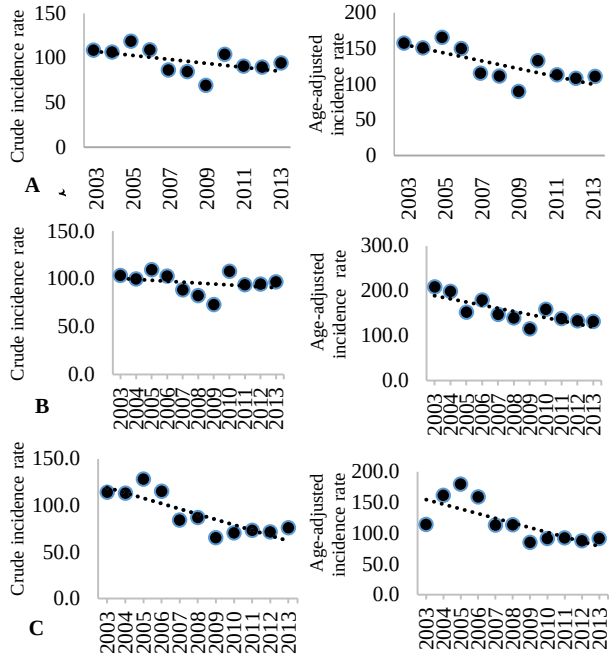

Figure 4. Crude incidence rate (CIR) and age-adjusted incidence (AIR) (per 100000) of ischemic stroke (IS) among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

On the other hand, this finding is not consistent with previous studies in some cities of Iran that have reported an increasing trend of stroke in recent years.[8,17]

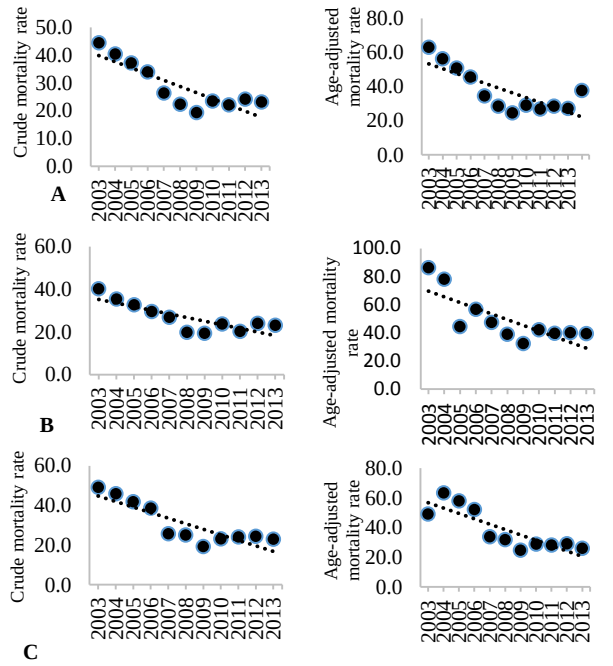

Figure 5. Crude incidence rate (CIR) and age-adjusted incidence (AIR) (per 100000) of all stroke types among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

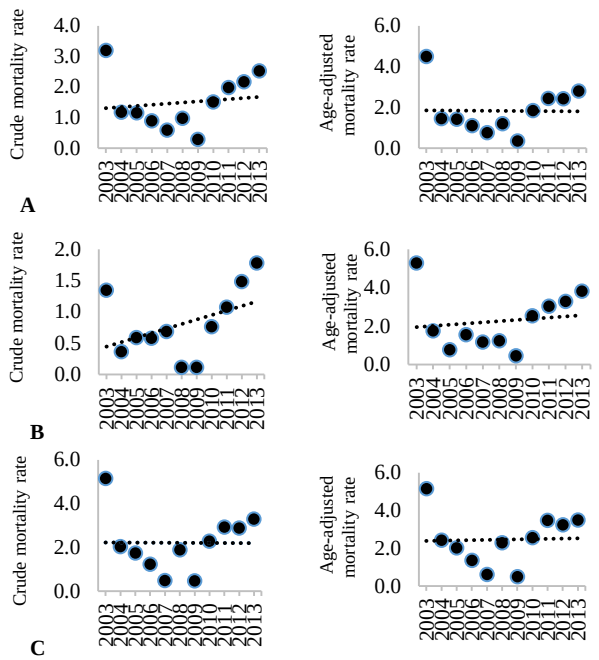

Figure 6. Crude incidence rate (CIR) and age-adjusted incidence (AIR) (per 100000) of subarachnoid hemorrhage (SAH) among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

It is worth noting that the duration of previous studies conducted in this regard in Iran was between one to six years.

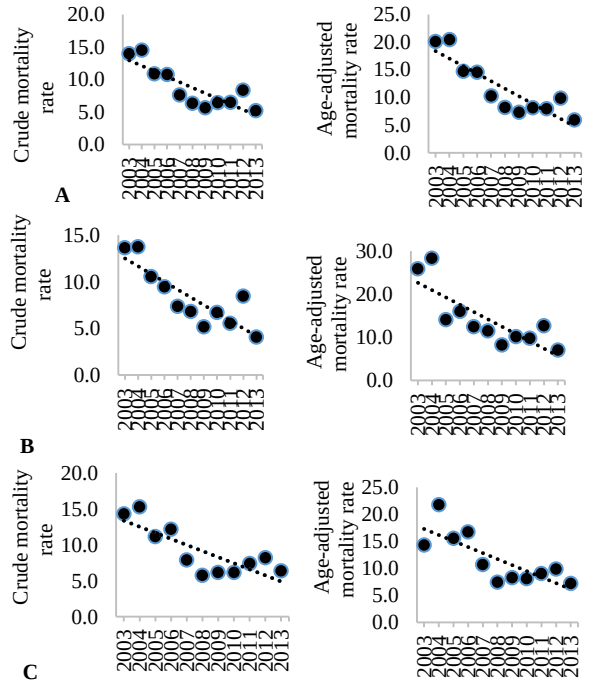

Figure 7. Crude incidence rate (CIR) and age-adjusted incidence (AIR) (per 100000) of intracranial hemorrhage (ICH) among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

Table 4. Logistic regression analysis for the association of sex, age, living area and stroke risk factors for stroke incidence and mortality

Variable		28-day mortality		
		OR	95% CI	P*
Sex	Woman	1	-	
	Man	0.81	0.75-0.87	< 0.001
Age		1.04	1.04-1.05	< 0.001
Living area	Rural	1	-	
	Urban	0.76	0.69-0.85	< 0.001
Stroke subtypes	IS	1		
	SAH	3.94	3.20-4.86	< 0.001
	ICH	4.04	3.71-4.41	< 0.001
TIA	Yes	1.31	1.20-1.42	< 0.001
	No	1	-	
Diabetes	Yes	1.02	0.94-1.11	0.590
	No	1	-	
High blood pressure	Yes	0.92	0.85-0.99	0.040
	No	1	-	
Hearth attack	Yes	1.46	1.35-1.57	< 0.001
	No	1	-	

*Logistic regression; OR: Odds ratio; CI: Confidence interval; IS: Ischemic stroke; SAH: Subarachnoid hemorrhage; ICH: Intracranial hemorrhage; TIA: Transient ischemic attack

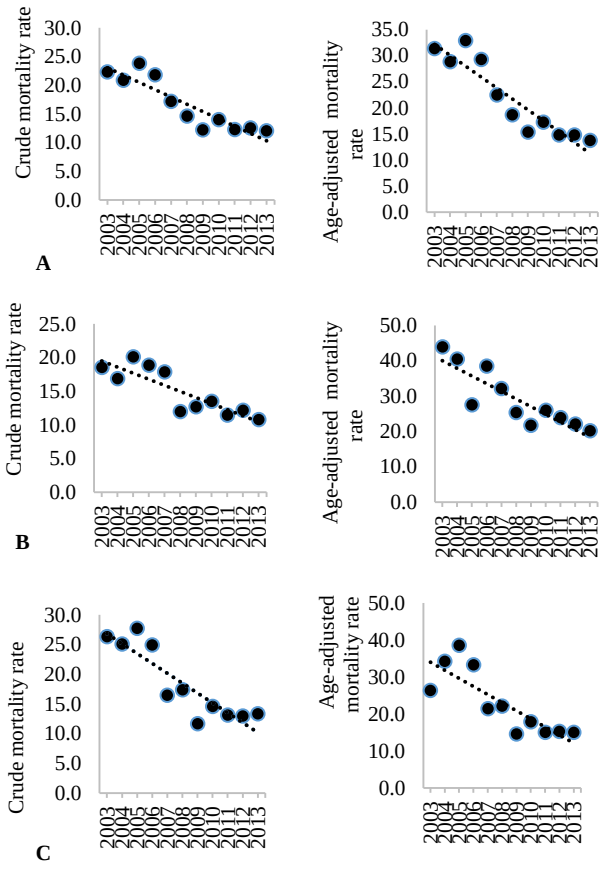

Figure 8. Crude incidence rate (CIR) and age-adjusted incidence (AIR) (per 100000) of ischemic stroke (IS) among the total (A), men (B), and women (C) in Isfahan, Iran, from 2003 to 2013

Nevertheless, the mean age-adjusted stroke incidence observed between 2003-2013 in Isfahan (168.4/100000) was high in comparison with previous studies in Iran and some developing countries.[8,11,18] The reason for this large difference with most other countries in the world and region is not clear.

In this study, the crude stroke incidence in each sex, separately and in combination, increased after adjusting for age. The low CIR of stroke indicated that our study population is young.[8] The CIR of stroke in women (126.4/100000) was slightly higher than men (126.0/100000), whereas this was reversed after adjusting for age. This indicates a higher incidence of stroke among older women than men. As was observed in this study, overall, women were older than men, which is consistent with the findings of Di Carlo, et al.[19] in a study involving 7 European countries.

In this study, among all types of stroke, IS was predominant stroke subtype, which was in line with previous studies from Iran.[8,17] In addition, high blood pressure had the highest frequency among other stroke risk factors which is in line with previous studies.[20,21]

Despite the decreasing trend of IS and ICH incidence during 2003-2013 in Isfahan, there was a significant increasing trend in SAH subtype incidence. It seems that SAH subtype is more common in younger populations[11,22] that may explain the increasing trend in this study.

In line with the other studies, results of this study showed the higher mortality risk among women.[23]

The reason for high mortality risk could be explained by the higher mean age of female patients as well as higher proportion of all risk factors among them. Furthermore, some studies pointed out that women have worse recovery than men after stroke.[23,24]

We found higher stroke mortality risk in rural areas compared to urban areas. Individuals from urban areas are more likely to have access to healthcare services before the stroke, such as continuous monitoring of blood pressure, than those from rural areas. On the other hand, after the occurrence of stroke, urban residents are more likely to receive stroke care than rural residents.[5]

In the current study, patients with ICH had a higher risk of stroke mortality followed by SAH and then, IS. These results were consistent with previous studies that identified ICH as deadliest form of stroke.[25,26]

Overall, the risk factors examined in this study showed a significant effect on stroke mortality and incidence risk. Among the risk factors, blood pressure with greater proportion than other risk factors appears to play an important role in stroke incidence.[27] Nevertheless, the result obtained in the present study, showing high blood pressure reduced the risk of stroke mortality, was somewhat unexpected and indicated a need for further investigation.

Based on our findings, diabetes mellitus, and history of a heart attack can be suggested predictors of risk of stroke and mortality.

Conclusion

The present study provided a comparative and longitudinal study of stroke incidence in Isfahan. Overall, despite the relatively high incidence of stroke over the study period, the stroke incidence rate had a decreasing trend over the past decades in Isfahan, especially in ICH subtype. However, given the young population of Iran, there will be a larger elderly population than expected in the coming years. On the other hand, due to the lack of appropriate control of risk factors in our elderly population, it could be expected that the stroke incidence would be rising in the future. Because of the high frequency of stroke, policy should focus on developing stroke care interventions as well as raising awareness about the risk factors.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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Review Article

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Molecular mechanisms of omega-3 fatty acids in the migraine headache

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Keywords
Omega-3 Fatty Acids; Migraine; Neuroinflammation; Headache

Abstract
Migraine is a common chronic inflammatory neurological disease with the progressive and episodic course. Much evidence have shown a role of inflammation in the pathogenesis of migraine. Omega-3 fatty acids are an important components of cell membranes phospholipids. The intake of these fatty acids is related to decrease concentration of C-reactive protein (CRP), proinflammatory eicosanoids, cytokines, chemokines and other inflammation biomarkers. Many of clinical trials have shown the beneficial effect of dietary supplementation with omega-3 fatty acids in inflammatory and autoimmune diseases in human, including Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), multiple sclerosis (MS) and migraine headaches. Therefore, omega-3 fatty acids as an alternative therapy can be potentially important. This review focuses on the pathogenesis of a migraine, with an emphasis on the role of omega-3 fatty acid and its molecular mechanisms.

Introduction

Migraine is a common chronic disease with nerve inflammation and dysfunction of the vascular endothelial cell.[1] The prevalence of a migraine in women and in men has been reported as 17% and 6%, respectively. In America, almost one out of four people has some degree of a migraine and a third of women under 45 years are affected by migraine headache.[2-4] Although the cause of migraine is still unknown, many factors involved in its pathogenesis include genetic factors, cerebral vasoconstriction, increased levels of glutamate in the attack phase, magnesium deficiency, monoaminergic pathway disorders, mitochondrial disorders, calcitonin gene-related peptide (CGRP) and neurogenic inflammation.[5] During the active phase of the disease, neuronal activity is increased which leads to the release of proinflammatory peptides from nerve terminals. So far, several studies confirm the role of inflammation in the development and progression of a migraine.[6,7]

The main fatty acids used in the brain and

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nerve system are long chain polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[8] A large number of studies have proved the effects of anti-inflammatory and neuroprotective effects of some nutrients such as omega-3 fatty acids.[9,10] EPA and DHA are able to inhibit the production of inflammatory proteins such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8 in various cell types including endothelial cells, monocytes, macrophages and dendritic cells. Thus, PUFAs with similar mechanism of anti-inflammatory drugs are important to determine the severity of inflammatory diseases and reduce the neurogenic pain.[11,12] Considering this findings, in this review article, the role of omega-3 in a neuroinflammatory disease like migraine will be studied.

Neuroinflammation

The immune system plays important roles in maintaining the homeostasis of tissue and responding to infection and injury.[13-15] Activation of immune cells lead to the release of leukocytes into tissues, but in the brain, this does not occur unless there has been damage or destruction of blood-brain barrier.[16] The term neuroinflammation is used for chronic inflammation of central nervous system (CNS) and defined as a reaction that is caused by infectious diseases, and malicious damage. Two groups of nerve cells inflammatory are involved in the immune response. The first group consists of lymphocytes, monocytes, and macrophages and the second group is microglia and astrocytes in the CNS. Microglia is responsible for the safety and innate response to inflammatory signals and is able to get warning signals.[15,17] Microglial activation is involved in the pathogenesis of several neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD).[18-20]

Astrocytes accomplish many housekeeping functions, consisting of maintaining the extracellular environment and stabilization of cell-cell communications in the CNS.[21] The other important metabolic links between neurons and astrocytes is the glutamate-glutamine shuttle that maintains the homeostasis of glutamate in the CNS.[22,23] Therefore, potential astrocyte dysfunction in neurodegenerative diseases lead to Impairment of glutamate transporters and neurons surrounded and cause cell susceptibility to death in some neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), AD and Huntington's disease.[8,24,25]

Nerve inflammation breaks down the blood-brain barrier and allows the blood cells to exit the bloodstream and penetrate to damaged tissues.[26] Immune cells produce active complement, cytokine, chemokines, IL, nitric oxide (NO), reactive oxygen species (ROS) and growth factors. These releasing substances have devastating effects on cells and cause of more damage.[27]

Neuroinflammatory disorders

Neuroinflammation in the pathogenesis of degenerative diseases is a known factor in diseases like depression, AD, PD, Huntington's disease and multiple sclerosis (MS). Pro-inflammatory cytokines attract leucocytes and increase their proliferation at the site of inflammation.

AD is neurodegenerative and debilitating chronic disease leading to loss of memory and cognitive deficit. Several factors are involved in the pathogenesis of AD including genetic predisposition, decreased synthesis of acetylcholine neurotransmitter, extracellular accumulation of amyloid beta (Aβ) in the brain, and abnormalities in tau protein and oxidative stress.[26] Cleavage of amyloid precursor protein (APP) can produce Aβ peptide which activates microglia through toll-like receptors (TLRs). These receptors, in turn, can activate the transcription factors, named nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and activate protein factor (AP-1). These factors induce the production of ROS;[28,29] therefore, the expression of inflammatory mediators like cytokines happens. These inflammatory factors stimulate astrocytes and cholinergic neurons, which reinforce proinflammatory signals to induce neurotoxic effects.[30-32]

In the case of a patient with MS, who is genetically predisposed to the disease, some forms of infection may upregulate expression of adhesion molecules on the surface of brain vascular endothelium and allow leukocytes to enter the normal immunological CNS and lead to the formation of an acute inflammatory and demyelinating lesion.[33] Viruses or bacteria or other environmental stimuli infection cause microglia and astrocytes activation in MS, by producing NFKB-activating pro-inflammatory cytokines.[34,35] Activated microglia and astrocytes secrete TNF-α, ROS, (NO) and IL-23, leading to the damages in the myelin of nerve axons.[36-38]

In PD, degeneration of dopaminergic neurons happened. some factors like oxidative stress and cytokine receptor-mediated apoptosis cause dopaminergic cell death.[39,40] Losing of dopaminergic neurons in the substantia nigra of the midbrain and accumulation of Lewy bodies are the main neuropathological hallmarks of PD.[41,42] Forming Lewy bodies can activate microglia which produces proinflammatory mediators and ROS, which eventually activates NFkB pathway.[43] NFkB directly affects both dopaminergic neurons of the substantia nigra, and microglia that increases the inflammatory response.[43-45]

The pathology of ALS, like other neurodegenerative diseases, is degeneration of motor neurons.[46] Mutations in the superoxide dismutase-1 (SOD1) gene lead to familial ALS. In ALS, the accumulation of mutant SOD1 protein cause degeneration of motor neurons.[47] This phenomenon induces inflammatory responses by microglia through TLR2 and cluster of differentiation 14 (CD14). Then, microglia produces cytokines and induces astrocyte activation, which in turn they can damage motor neurons by activating NFkB and apoptosis-triggering molecules like TNF-α.[48]

Migraine pathogenesis

Migraine is a common chronic inflammatory neurological disease with the progressive and episodic course. The etiology of migraine is still unclear. However, much evidence have shown a role of inflammation in the pathogenesis of migraine. Other factors involved in the pathogenesis of migraine include genetic factors, increased levels of glutamate during phases of attack, magnesium deficiency disorders, monoaminergic pathway disorders, mitochondrial disorders, CGRP and neurogenic inflammation.[5,49,50] Some psychological factors like menstrual cycle, pregnancy, lifestyle, diet, anxiety, and chronic stress can also contribute to the pathogenesis of migraine.[50,51]

Genetic factors

Genetic component has been considered as a strong factor in migraine.[52] It has been hypothesized that genetic abnormalities lead to a lowered threshold of response to particular trigger factors in a patient with migraine, while in normal people lacking migraine-related genetic deficits, exposure to the same trigger factors would not affect the migraine threshold; therefore, an attack would not happen.[53] Mutations in some genes like calcium voltage-gated channel subunit alpha 1A (CACNA1A) are responsible for familial hemiplegic migraine (FHM).[54] Dysfunction of Ion channels, regulating neuronal excitability, may result in abnormal hyper-responsively of the brain of migraine patients. The theory claims that this migraine-specific channelopathy triggers provoking the CNS dysfunction that eventually initiates the early stages of a migraine attack.[55]

Magnesium deficiency and glutamate

The Mg^{2+} levels of serum and salvia have been shown to be decreased during attacks in migraine.[56] Reduction of magnesium concentration in the cell might lower the threshold for a migraine headache.[57] Magnesium is related to the control of N-methyl-D-aspartate (NMDA) glutamate receptors, that has an important role in pain transmission and cerebral blood flow regulation within the nervous system.[58] Magnesium ion suppresses the NMDA receptor and it also prevents calcium ions to enter the cell.[59,60] Since the activation of the NMDA receptor is required to trigger cortical spreading depression (CSD) in human neocortical tissues. Therefore Magnesium, as an antagonist of the NMDA receptor complex, can play an important role in migraine attack.[59]

Disorders of monoaminergic pathway

Serotonin (5-HT) and dopamine (DA) metabolism disorders have been observed in the patients with migraine.[61] Low doses of the DA agonist induce yawning in migraineurs. Treatment with dopaminergic antagonists may decrease migraine-related nausea and vomiting. Thus, these findings recommend a dopamine deficiency as the pathophysiology of migraine.[62] During migraine attack, the amount of serotonin in blood platelets decreases. This discharge of platelet serotonin may reflect serotonin depletion at central synapses, in raphe-cortical pathways, and may induce a migraine headache.[61,63]

CGRP and neurogenic inflammation

Secretion of CGRP leads to increase in the activity of NO synthase induction (iNOs) and production of NO, expression and activity of the cyclooxygenase-2 (COX-2) enzyme, and cytokine

secretion of inflammatory factors such as IL-6, TNF-α, IL-1β.[64] Cytokines, by increasing the permeability and cell-to-cell interaction, play an important role in the pathogenesis of inflammation and pain in migraine disease.[49] In patients with migraine, vascular disorder causes endothelial activation and increased production of factors such as an inflammatory cytokine, adhesion molecules and intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule-1 (VCAM). Pro-inflammatory cytokines such as TNF-α are vasodilators and induce expression of ICAM and VCAM. Increased expression of these factors is associated with microglia, which activates inflammation and neuropathic pain in the brain.[2,6,65]

Omega-3 fatty acids metabolism

PUFAs are classified as omega-3 and omega-6.[66] Omega-3 fatty acids are a very important component of cell membrane phospholipids. Dietary intake of fish oil, that is rich in EPA and DHA, leads to increase the content of long-chain fatty acids in phospholipids of blood cells membrane, particularly those involved in the inflammatory response such as neutrophils, lymphocytes and monocytes.[27,66]

Some of the effects of omega-3 PUFA are related to modulation of the amount and types of eicosanoids which are made from omega-3 fatty acids. Other effects are associated with eicosanoid-independent mechanisms, including intracellular signaling pathways, transcription factor activity, and gene expression. Some inflammatory diseases such as depression, aging, and cancer are characterized by increasing the level of IL-1 as a proinflammatory cytokine.[11,27] Many of clinical trials have shown the beneficial effect of dietary supplementation with fish oil in inflammatory and autoimmune diseases in human, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, lupus erythematosus, MS and migraine headache. Supplementation with fish oil, as well as anti-inflammatory drugs, in chronic inflammatory diseases have shown a significant benefit.[27,67]

Anti-neuroinflammatory and neuroprotective mechanisms of omega-3 fatty acids

Omega-3 fatty acids with different mechanisms affect the inflammatory process. Non-esterified fatty acid can directly act through fatty acid receptors, located on the cell surface or intracellular, and also by inducing transcription factors like peroxisome proliferator-activated receptor (PPAR).[11] DHA and EPA, through the cyclooxygenase and lipoxygenase enzymatic pathway, cause production of Resolvins and related compounds with anti-inflammatory effects such as Protectine. Resolvin E1 (RvE1), Resolvin D1 (RvD1) and Protectin D1 inhibit migration of neutrophils from endothelial membrane.[68] EPA and DHA are able to inhibit production of inflammatory proteins such as TNF-α, IL-1, IL-6, IL-8 and IL-12 in various cell types including endothelial cells, monocytes, macrophages and dendritic cells by phosphorylating inhibitor of kappa B (IkB) (less NFkB activity) and reducing the activity of mitogen-activated protein kinases (MAPKs). Another mechanism of PUFA anti-inflammatory performance is through PPAR-ϒ. The PPAR-Y is a transcription factor that has anti-inflammatory function and can directly regulate the expression of inflammatory genes. It interferes with the activation of NFkB. PUFA and their derivatives are known ligands for these receptors. Some G protein-coupled receptors (GPCRs), like GPR120, are localized in the cell membrane and can bind to omega-3 fatty acids. This binding results in the activation of cell signaling pathways responsible for reducing the response of macrophages, decreasing phosphorylation of IkB (more NFkB activity) and production of TNF-α and IL-6.[11,69] Therefore, omega-3 fatty acids are remarkably effective in the treatment of inflammation and can be considered in the treatment of inflammatory pain.[67]

Omega-3 fatty acids effects in neuroinflammatory and neurodegenerative disease

AD is a progressive neurodegenerative disorder, in which extracellular Aβ plaque deposition is its major pathological hallmark.[70,71] Cellular pathways that regulate brain fatty acids are involved in both inflammatory and oxidative stress cascades which have effect in the pathogenesis of AD.[66] DHA is changed to docosanoid, neuroprotectin 1 (NPD1) by phospholipase A2 and lipoxygenase.[72,73] NPD1 upregulated the B-cell lymphoma 2 (Bcl-2) family of anti-apoptotic proteins and it also inhibit pro-apoptotic signaling pathways, and production of eicosanoids from arachidonic acid (AA), which can cause neuronal injury.[74] The formation of NPD1 from DHA is tightly regulated by the redox state of neurons. The other

inflammatory disease of the CNS is MS.[75] Several studies have shown a decrease in inflammatory cytokines levels such as, TNF-α, interferon-g (IFN-γ), IL-1, IL-2, and vascular cell adhesion protein 1 (VCAM-1) by immune modulatory effects of omega-3 fatty acids.[76] It has been hypothesized that supplementation omega-3 fatty acid family may improve learning and behavioral symptoms of attention deficit hyperactivity disorder (ADHD).[77] Furthermore, more evidence has reported improvement in positive and negative syndrome scale in schizophrenic individuals who have supplemented for 12 weeks.[78,79] Finally in some studies, decreased DHA and total omega-3 fatty acids have been reported in autistic children.[80] Therefore, various mechanisms may be involved in neuroprotective effects of EPA and DHA including a reduction in oxidative stress, excitotoxicity, and neuroinflammation, and activation of anti-apoptotic pathways. Omega-3 has turned into an effective additive to improve neurological diseases[81,82]

Migraine and omega-3 fatty acids

Several studies have shown that omega-3 fatty acids in vitro, inhibit the production of proinflammatory cytokines from macrophages and it shows a beneficial inhibitory effect in autoimmune diseases in vivo. DHA, with targeting lipopolysaccharides (LPS) surface receptor, suppresses NFkB activity and the production of inflammatory cytokines in microglia. Some anti-inflammatory effects of DHA is due to its metabolite, named NeuroprotectinD1, which inhibits the expression of cytokines induced by Aβ peptides in microglia. Omega-3 fatty acids produce Resolvin, that inhibits the production of inflammatory cytokines in microglial cells and has anti-inflammatory effects.[83] RvE1 and RvD1, derived from EPA and DHA, inhibit expression of inflammatory cytokines like TNF-α, IL-6, and IL-1β which results reduction of inflammation and pain in rat. Moreover, RvE1 and RvD1 can inhibit pain through transient receptor potential cation channel subfamily V member 1 (TrpV1) that play a major role in the production of inflammatory pain.[67]

The effects of omega-3 fatty acids on oxidative stress and NO in microglial cells have been studied in rats. It has been reported that PUFA reduces significantly the production of ROS and NO in active microglia and has neuroprotective effects.[69] Many studies have shown beneficial effects of omega-3 fatty acids on neuroinflammation and neurodegenerative disease; however, few studies have examined the effects of omega-3 fatty acids in migraine. Indeed, a study that survey inflammatory and endothelial factors involved in the pathogenesis of this disease in genome is proposed.[83] The effects of sodium valproate and fish oil when they are given to patients with migraine, in combination or alone, have been studied and the results showed that the duration, frequency, and severity of a headache were significantly increased as compared to baseline. The significant reduction of duration, frequency, and severity of a headache has been observed in the group receiving the synergistic effect of fish oil and sodium valproate, as compared to the group receiving medication alone. Therefore, receiving sodium valproate with fish oil can control the severity of migraine disease more effectively than receiving sodium valproate alone.[84] In a study conducted on patients with migraine, it has been shown that 2 months supplementation with 1 g of omega-3 fatty acids significantly decreased the frequency of headaches and also patients reported 74% reduction in the duration of their headache.[85]

Conclusion

The omega-3 fatty acids, especially EPA, have anti-inflammatory properties that compete with AA as a substrate for cyclooxygenases and 5-lipoxygenase. The eicosanoids are considered to link PUFA with inflammation and the immunity. Because of their effects on prostaglandins, thromboxane, and leukotrienes, omega-3 fatty acids not only can inhibit the production of IL-1β by suppressing the IL-1 mRNA, but also they decrease the expression of Cox-2 mRNA which is induced by IL-1β. The Experimental studies have shown that omega-3 fatty acids can modify inflammatory and immune reactions. Thus, these fatty asides have a potential therapeutic effect on inflammatory and autoimmune diseases. In numerous studies on animals and human, the ability of dietary omega-3 to limit inflammation has been demonstrated under the different situations and doses. Omega-3 intake is associated with decreased concentrations of CRP, proinflammatory eicosanoids, cytokines, chemokines and other inflammation biomarkers. Therefore, nutritional supplementations with omega-3 fatty acids, as an alternative therapy, can be potentially important because the diseases are

heterogeneous and also the current therapies are drug-based with many side effects.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Short Communication

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Height, shape and anterior-posterior diameter of pituitary gland on magnetic resonance imaging among patients with multiple sclerosis compared to normal individuals

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Keywords
Multiple Sclerosis; Pituitary; Height; Shape; Magnetic Resonance Imaging

Abstract

Background: Several studies indicate contribution of hypothalamus-pituitary-adrenal (HPA) axis in multiple sclerosis (MS) disease. This study was designed to determine whether there is an effective difference in pituitary height, shape, and anterior-posterior diameter (APD) between patients with MS and the control group.

Methods: In this study, sagittal pituitary height and APD of 134 men and women (64 patients with MS and 70 healthy subjects as control group) were measured by T1 sequence magnetic resonance imaging (MRI). All the subjects were free of sellar or parasellar pathology without a history of surgical intervention or prolactin affecting drugs like bromocriptine and cabergoline or corticosteroid consumption.

Results: Mean height of pituitary gland was 6.62 ± 1.43 and 5.78 ± 1.15 mm for patients and the control group, respectively, and the difference between the two groups was statistically significant (P = 0.001). Mean APD was 10.40 ± 1.29 mm for the group of patients and 10.25 ± 1.41 mm for the control group, respectively, without significant differences. 46.9%, 37.5%, and 15.6% of patients had flat, convex, and concave hypophyseal surfaces, respectively. This rate was 50%, 30%, and 20% among the control group, respectively. There was no significant difference between our measurements among patients on whom imaging study was performed at time of disease onset with others.

Conclusion: Mean height of pituitary gland among patients with MS was significantly greater than the control group (P = 0.001). So can we consider the same etiology for pituitary hypertrophy among patients with MS as a hypothesis?

Introduction

Multiple Sclerosis (MS) is known as the most

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common demyelinating disease of human central nervous system. It's a complex neurological condition with demyelination and axonal loss.[1,2]

MS incidence rate has been estimated as 2.5 million individuals worldwide. The incidence of MS in Iran is estimated to be 54.51 per 100000 population,[3] and 31.5 individuals per 100000 in Kerman Province, Iran.[4]

The stress system has peripheral and central parts: the hypothalamus-pituitary-adrenal (HPA) axis, and the sympathetic and adrenomedullary systems are the peripheral limbs, however, central components are in the hypothalamus and the brain stem; the main function of this system is to maintain basal and stress-related homeostasis.[5]

Several studies indicate the contribution of HPA axis among patients with MS, increasing activity of HPA.[6] This study was designed in order to evaluate these responses on anatomy of pituitary gland and to determine whether there are differences in height, shape and anterior-posterior diameter (APD) of pituitary between patients with MS and the control group.

Materials and Methods

In this case-control study, 64 definite patients with MS (57 women and 7 men) with the age range of 15-40 years old and 70 healthy, age and sex–matched controls were selected according to revised Mc-Donald's criteria. All the patients and control group had no history of sellar or parasellar pathology or cranial surgical intervention. During last 3 months prior to study, they had no history of consumption of drugs like bromocriptine, corticosteroids, and cabergoline, which may affect HPA.

Pregnancy and lactation were considered as criteria of excluding from the study. Imaging was performed using GE Signa Excite, 1.5 Tesla Scanner.

For 28 patients (43.75%), imaging was performed at disease onset (before MS treatment).

Results

The mean age was 27.06 and 27.54 years for patients and the control group, respectively, without statistically significant difference (P = 0.580).

The mean height of pituitary gland was respectively 6.62 ± 1.43 and 5.78 ± 1.15 mm among patients with MS and among the control group, being higher for patients than the control group (P = 0.001).

The mean APD diameter was 10.40 ± 1.29 mm for the group of patients and 10.25 ± 1.40 mm for the control group, respectively (P = 0.520).

46.9%, 37.5%, and 15.6% of patients had flat, convex, and concave hypophyseal surfaces, respectively. These rates were respectively 50%, 30%, and 20% among the control group. There was no difference in shape distribution percentage between the two groups (P = 0.610). It can be observed that the convex shape has increased among the patients with MS, however the concave shape has decreased among them.

There is no significant difference between the patient individuals and control group members in our measurements (height: 6.88 ± 1.52, APD: 10.45 ± 1.32) versus (height 6.42 ± 1.34, APD: 10.37 ± 1.12). The imaging study among the patients was performed at the time of disease onset (P < 0.050).

All the patients and controls were divided into 3 groups according to their ages.

The mean height of pituitary gland for men in the group of patients was respectively 6.60 ± 1.66 mm in the age range of 15 to 20 years old, 7.06 ± 1.19 mm in the age range of 21 to 30 years old, and 6.16 ± 1.60 mm in the age range of 31 to 40 years old. There was no significant difference with P value equal to 0.11. Mean AP diameter of hypophysis in above mentioned groups was 9.98 ± 1.30, 9.99 ± 1.36 and 10.37 ± 1.52 mm respectively.

Discussion

Our results showed higher pituitary gland height among patients with MS compared to healthy controls. The height and AP diameter values of hypophysis among normal individuals in Kerman Province are 5.78 and 10.25 mm, respectively.[7] These findings are in agreement with other studies.[8]

To our knowledge, we didn't find any report about measurements of pituitary gland among patients with MS in the researches published in English language.

Clinical and experimental studies show that HPA axis has abnormality among patients with MS undergoing severe levels of MS. It might be associated with the pathogenesis of the disease. Hyperactivity of HPA axis is seen among 50% of patients with MS.[8]

Pituitary height was significantly more among 15- to 20-year-old controls. We know that pituitary height is significantly greater among women than men, especially among the adolescent and young individuals; this problem is known as physiologic hypertrophy.[9] MS disease is more frequent among women in almost the same age group.

Table 1. Mean of height and anterior-posterior diameter (APD) among patients and control group

Variable	Group	n	Mean ± SD	P
Height (mm)	Patients	64	6.62 ± 1.43	0.001
	Controls	70	5.78 ± 1.15	
APD (mm)	Patients	64	10.40 ± 1.29	0.520
	Controls	70	10.25 ± 1.41	
Age (year)	Patients	64	27.06 ± 5.03	0.580
	Controls	70	27.54 ± 5.07	

SD: Standard deviation; APD: Anterior-posterior diameter

Among individuals undergoing MS with fatigue, HPA axis is more active compared to patients without fatigue. Adrenocorticotropic hormone (ACTH) concentration is significantly high in patients with fatigue. Proinflammatory cytokines are increased among patients with MS, which might be the reason for fatigue and changes of HPA axis.[10]

In this study, 28 cases (43.75%) of patients with MS did not receive interferon-beta (IFN-β), however, 36 cases (56.25%) received IFN-β. There is no significant difference in height and AP diameter of hypophysis (Table 1). Acute IFN-β administration transiently activates the hypothalamic-pituitary-adrenal (HPA) axis, however, long-term treatment reduced the responsiveness of the HPA axis to the injection.[11]

Conclusion

The mean height of pituitary gland among patients with MS was significantly greater than that of the control group (P = 0.001). So can we consider the same etiology for pituitary hypertrophy among patients with MS as a hypothesis?

Conflict of Interests

The authors declare no conflict of interest in this study.

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Clinical Note

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Vertebral artery occlusion after anterior cervical discectomy with fusion

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Anterior cervical discectomy with fusion (ACDF) is an established intervention for cervical degenerative disease. However, on rare occasions, complications, including dural tear, esophageal injury, and dysphagia, may occur.[1] Here, we report a case of cerebellar infarction due to vertebral artery (VA) occlusion that was diagnosed 2 days after ACDF.

A 50-year-old woman presented with 3 months history of bilateral arm and neck pain with shoulder radiation and clumsy hand. Cervical magnetic resonance image (MRI) demonstrated cord compression by osteophyte at the level of C5-C6 and C6-C7 (Figure 1, a). She had no medical history of heart valve disease or arrhythmias that could have caused a cerebral embolism. She underwent a 2-level ACDF according to a standard anterior cervical approach. A microscope was used during most of the procedure and the vertebral bodies were separated by the repeated use of a spreader during osteophyte removal. For the interbody spaces of C5-C6 and C6-C7, titanium cages (SynCage-C: Depuy Synthes) with a 7-degree lordotic angle and anterior heights of 7.0 and 5.0 mm were used, respectively (Figure 1, b and c). The patient's recovery from general anesthesia was normal and her symptoms were alleviated. However, 36 hours after surgery, she complained of mild nausea and vertigo. As these symptoms gradually deteriorated MR angiography and MRI were performed 48 hours postoperatively, which revealed right cerebellar infarction and right VA occlusion (Figure 1, d and e). She responded well to argatroban and was discharged 21 days after surgery without neurological symptoms. During the following 2 years, she has lived a normal life. MR angiography performed 2 years after discharge revealed complete recanalization of the right VA (Figure 1, f and g).

The VA is particularly susceptible to injury, and VA occlusion following cervical fracture,[2] chiropractic manipulation,[3] or even after abrupt head movement[3] has been reported. A potential mechanism of VA occlusion in such cases is intimal disruption followed by thrombus formation and thus, clot occlusion of the vessel lumen.[3,4] The reason why VA occlusion occurred in this case is unknown, however repeated use of a spreader in two consecutive intervertebral space may have triggered this sequence of events.

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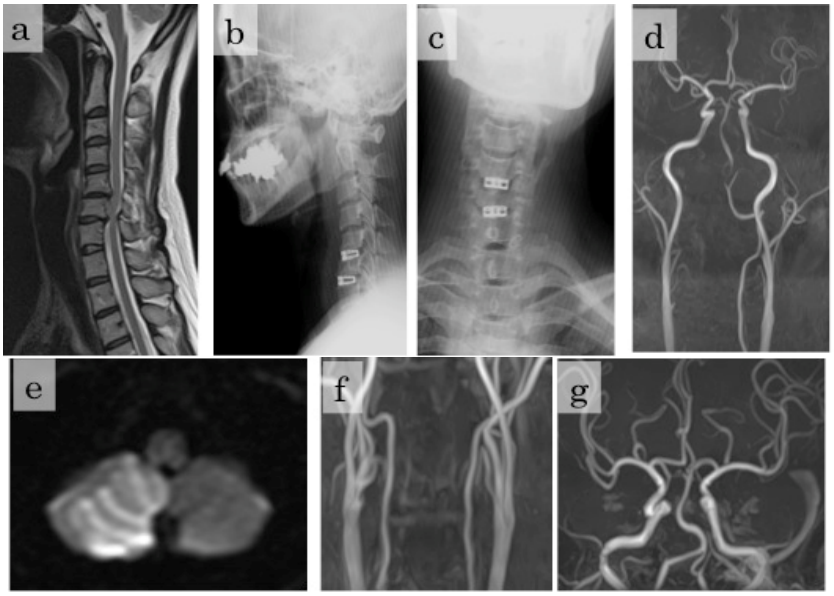

Figure 1. Preoperative cervical MRI (magnetic resonance imaging) demonstrating spondylotic changes at the level of C5-C6 and C6-C7 (a), Lateral and (b), Anteroposterior (A-P) view of immediate postoperative cervical radiography demonstrating titanium cages appropriately placed at C5-C6 and C6-C7 (c), Cervical and cranial MR angiography 2 days after surgery demonstrated right vertebral artery occlusion (d), Diffusion-weighted MRI 2 days after surgery demonstrated cerebellar infarction in the right cerebellar lobe (e), Cervical (f) and Cranial MR angiography 2 two years after discharge revealed complete recanalization of right vertebral artery (g).

Our experience demonstrates the need for surgeons performing ADCF procedures to be aware of this potential complication. There are many other prophylactic treatments of this complication such as maintaining appropriate cervical positioning during surgery or prevention of postoperative dehydration; however, care should be taken to avoid intimal disruption of the VA by overly dilating the intervertebral space.

Conflict of Interests

The authors declare no conflict of interest in this study.

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