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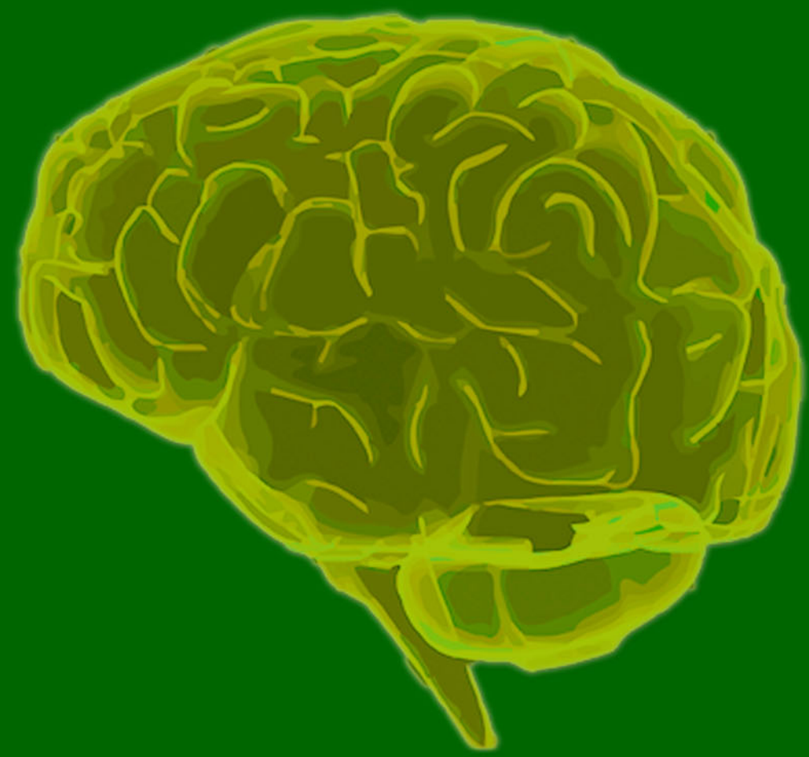

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Iranian Journal of Neurology

INFORMATION FOR AUTHORS

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

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

1. Title page:

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

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

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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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Original Paper

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Effects of early intervention of swallowing therapy on recovery from dysphagia following stroke

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Keywords
Stroke, Dysphagia, Speech Therapy

Abstract

Background: Dysphagia is common after stroke. The onset time of swallowing rehabilitation following stroke has an important role in the recovery of dysphagia and preventing of its complications, but it was either highly variable or was not stated in previous trials. The aim of this study was investigation effects of onset time of swallowing therapy on recovery from dysphagia following stroke.

Methods: Sixty dysphagia patients due to stroke range of age 60-74 (67.1 ± 3.8), participated in this randomized clinical trial study. The patients allocated in Early, Medium and Late groups, on the base of initiation of swallowing therapy after the stroke. After basic clinical and video fluoroscopic swallowing study assessments, traditional swallowing therapy was initiated 3 times per week for 3 months. The outcome measures were North-Western dysphagia patient check sheet, functional oral intake scale, video fluoroscopy, and frequency of pneumonia. Statistical analysis was done by repeated measure ANOVA, Bonferroni and χ^2 tests.

Results: Three groups of patients in terms of demographic and clinical characteristics were similar in the pre-treatment $P > 0.050$. Onset time of swallowing therapy after stroke was effective on swallowing recovery on the main outcome variables. So that in first group patients, recovery was rather than other groups $P < 0.050$. Furthermore, the frequency of pneumonia in the early group was less than other groups and in the early group no patients experienced pneumonia $P = 0.002$.

Conclusion: Our data suggested that early interventions for dysphagia in stroke have an important role in recovery from dysphagia and prevention of complications like aspiration pneumonia.

Introduction

Swallowing, as the first phase of digestion, is one of the most complicated neuromuscular processes of the central nervous system. It involves multiple areas of the brain and a series of voluntary and involuntary muscular contractions.

Oropharyngeal dysphagia is a highly prevalent clinical condition among stroke patients, but the prevalence of dysphagia is different in various studies, because of differences in the definition of dysphagia, the method of assessing swallowing function, the timing of swallowing assessment after stroke, and the number and type of stroke patients studied.[1-3] Overall, swallowing disorders (dysphagia

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with or without aspiration) are seen in about half (55%) of all stroke patients admitted to hospital.[4-7]

The presence of dysphagia can itself cause medical, psychosocial, and economic complications in stroke patients. A medical complication of dysphagia includes aspiration pneumonia, malnutrition, significant weight loss, and dehydration.[8-12] Another complication of dysphagia in stroke patients is psychosocial because eating is a pleasurable and social activity, and inability to eat normally may affect patient morale and quality-of-life.[13,14]

Complications due to dysphagia especially include pneumonia, and managing infection also increases healthcare costs by increasing the length of hospital stay and increasing the need for expensive respiratory and nutritional support.[7]

To prevent and minimize these complications, diagnosis and management of dysphagia must be done as soon as possible by a trained speech-language pathologist.[15]

The current treatment of dysphagia in patients with stroke is the traditional swallowing therapy by a speech therapist. Compensatory approaches and rehabilitative methods are included in this therapy.

Compensatory approaches include: enteral feeding by means of a nasogastric tube or by percutaneous endoscopic gastrostomy, modification of food consistency, postural correction to facilitate bolus transition, reducing rate of eating and ensuring oral hygiene by conventional oral care.[16] Other approaches are rehabilitative methods, including oral motor exercises; airway-protecting maneuver, thermal-tactile stimulation, and Shaker exercise.[16-18] Recently, neuromuscular electrical stimulation, biofeedback, and transcranial magnetic stimulation have been used as techniques for swallowing therapy these techniques are modern swallowing therapy.[19-22]

The onset time of swallowing rehabilitation following stroke was either highly variable or was not stated in the most of investigations. In some studies, interventions have been initiated within 7 days after stroke[23] or 24 h after stroke[24] and between 4 and 6 weeks or even 3-6 months post-stroke.[25,26] In the other hand, some studies have only focused on early intervention, and do not consider the time at which swallowing rehabilitation should be initiated for optimal recovery.[23,24]

The onset time of intervention following stroke is uncertain, and no completed randomized clinical trial (RCT), assessing this question was found. Thus, the aim of this study was to investigate the effect of onset time of traditional swallowing therapy, given by a speech therapist on recovery from dysphagia in stroke patients.

Materials and Methods

Sixty patients, dysphasic due to stroke, in the age range of 60-75 (58.4 ± 7.8), participated in this RCT study. This study was single blind, because all patients included in this study were unaware of their allocation into treatment groups, but the speech pathologist who evaluated and treated the patients was aware of the group and the radiologist who performed video fluoroscopy was unaware of the allocated group.

Totally, 451 acute stroke patients presenting to the emergency neurology ward of our university hospital (Imam Khomeini Hospital) over a 2-year period (February 2012-January 2014) were screened for inclusion criteria of the study. Inclusion criteria in this study were as follows: clinical diagnosis of stroke which was confirmed by a neurologist presence of dysphagia which was assessed clinically by a speech-language pathologist and video fluoroscopically by a radiologist using standardized methods and diagnostic criteria; no history of swallowing treatment, pneumonia or head and neck surgery and other neurological or general disorders that can influence swallowing function. Of 451 stroke patients, 271 patients had dysphagia, and 84 patients were eligible for our study. 24 patients were excluded due to follow-up problems, and finally 60 patients were analyzed (Figure 1).

Randomization was undertaken using a block randomization technique. The patients were allocated into one of three groups according to the time of initiation of swallowing therapy after stroke including: (1) early initiation group (3 days after stroke); (2) medium group (2 weeks after stroke); and (3) late group (1-month after stroke).

The study protocol was approved by the ethics committee of Tehran University of Medical Sciences. Informed consent was obtained from each participant or the next of kin before any examination or intervention was conducted.

This study has been registered in www.irct.ir, number IRCT2013072514161N1.

All patients were screened by the North-western Dysphagia Patient Check Sheet, and dysphagia was diagnosed by a speech pathologist. In all patients after primary diagnosis of dysphagia, swallowing functions were assessed by functional oral intake scale (FOIS), and video fluoroscopy was done by an attending radiologist. For medium and late groups, screening of swallowing function was performed by a speech pathologist weekly before initiation of swallowing therapy. In this period of time, all patients were provided with the usual oral care and advices for feeding such as: precautions for safe swallowing, including positioning and slowed rate of feeding) by the speech pathologist. The swallowing difficulties of some of the patients in these groups resolved spontaneously, and they were excluded from the study.

The diagnosis of pneumonia was based on: fever, a productive cough with purulent sputum and abnormal finding in chest examination and chest X-ray. For all patients, traditional swallowing therapy includes compensatory methods, direct swallowing therapy and swallowing maneuvers were given by the speech pathologist 3 times per week for 3 months. The type of swallowing therapy technique was based on the findings of the clinical examination and video fluoroscopy for all patients. After 2 months, clinical and video fluoroscopy examinations were done for all patients.

Outcome measures in this study included: (1) scores of the North-Western dysphagia patient check sheet; (2) Difficulties in oral or pharyngeal stages swallowing and presence of pharyngeal delay or aspiration according to the North-Western dysphagia patients check sheet (NWDPCS) and video fluoroscopy; (3) FOIS; (4) frequency of pneumonia; and (5) the number of sessions of swallowing therapy needed for improvement.

Statistical analysis of data was done by SPSS software for Windows (version 19.0, SPSS Inc., Chicago, IL, USA), by the use of parametric statistical tests (e.g., repeated measure ANOVA for comparison of normal data between three groups pre and post treatments data) and by non-parametric tests such as χ^2 and Cochran tests.

Results

Three groups of patients in terms of demographic (age, gender, site of lesions, and type of stroke) and clinical characteristics were similar in the pre-treatment $P > 0.050$ (Table 1).

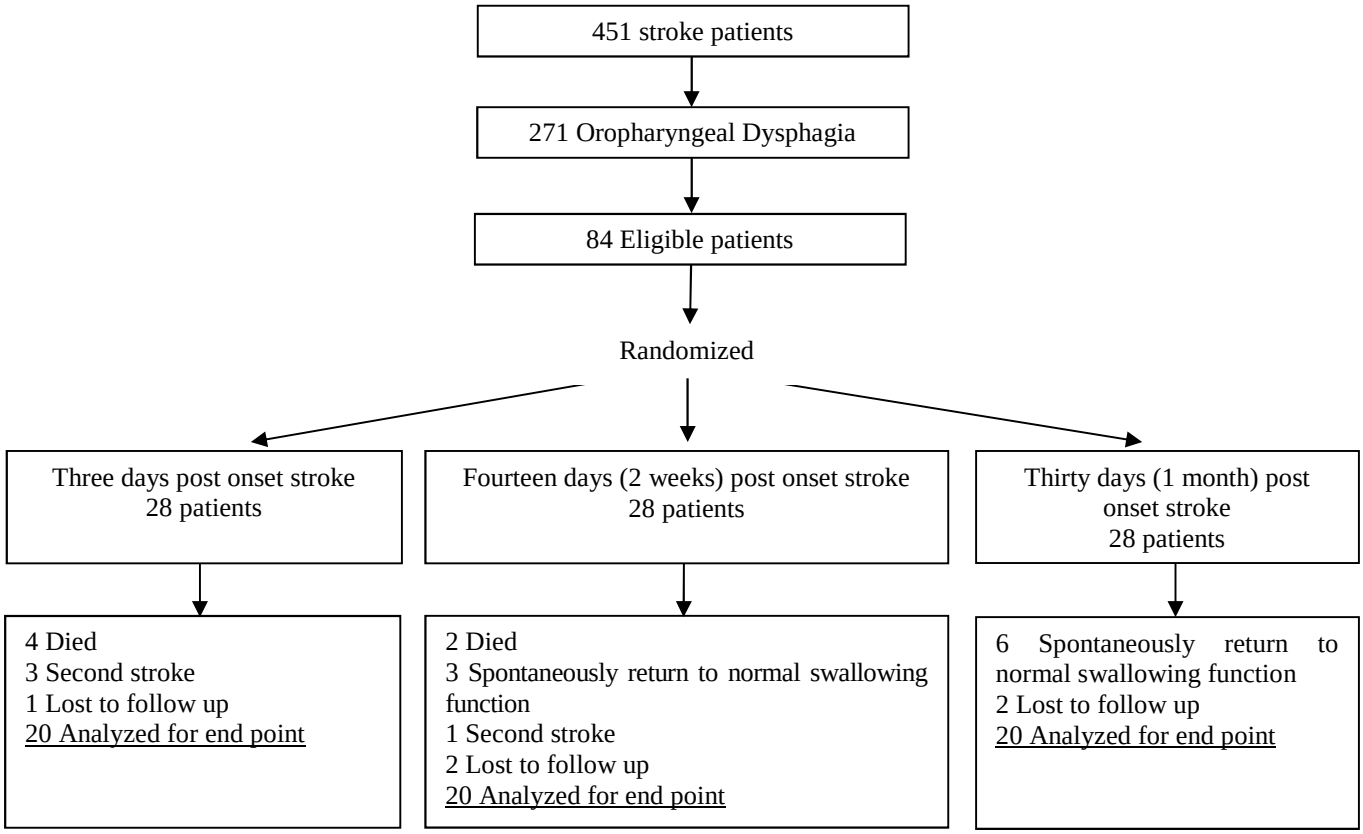

Figure 1. Clinical trial allocation information

Table 1. Comparison of demographic characteristic of participants

Characteristics		Three days post onset (n = 20)	Two weeks post onset (n = 20)	One month post onset (n = 20)	P
Age (mean ± SD)		66.40 ± 4.09	67.15 ± 3.67	67.85 ± 3.97	0.508
Sex (%)	Male	13 (65)	14 (70)	16 (80)	0.247
	Female	7 (35)	6 (30)	4 (20)	
Site of lesion (%)	Right hemisphere	11 (55)	11 (55)	13 (65)	0.957
	Left hemisphere	7 (35)	7 (35)	5 (25)	
	Brain stem	2 (10)	2 (10)	2 (10)	
Type of stroke (%)	Ischemic	14 (70)	16 (80)	18 (90)	0.287
	Hemorrhagic	6 (30)	4 (20)	2 (10)	

SD: Standard deviation

Table 2. Effects of onset time of swallowing therapy on swallowing recovery (North Western dysphagia patients check sheet)

Sources	Sum of squares	df	Mean squares	F	P
Groups (onset time of swallowing therapy)	33.1	2	16.50	8.4	0.0001
Factor (pre/post treatment)	2764.8	1	2764.80	1529.2	< 0.0001
Groups × factor	8.1	2	4.07	2.2	0.1140

df: Degree of freedom

Table 3. Paired comparisons of swallowing recovery (North-Western dysphagia patients check sheet)

Groups	Paired comparisons	Mean difference	P
3 days after stroke	2 weeks after stroke	-1.150	0.002
	1-month after stroke	-1.070	0.003
2 weeks after stroke	3 days after stroke	1.150	0.002
	1-month after stroke	0.075	1.000
1-month after stroke	3 days after stroke	1.075	0.003
	2 weeks after stroke	-0.075	1.000

Table 4. Comparison of swallowing function among three groups after therapy

Variables	Groups of patients			P
	Three days post onset (n = 20) (%)	Two weeks post onset (n = 20) (%)	One month post onset (n = 20) (%)	
Presence of an oral stage swallowing problem				
NWDPCS	0 (0)	0 (0)	3 (15)	0.043
VFSS	0 (0)	0 (0)	3 (15)	0.025
Presence of an, Pharyngeal Stage swallowing problem				
NWDPCS	1 (5)	3 (15)	5 (25)	0.028
VFSS	1 (5)	4 (20)	9 (45)	0.010
Presence of pharyngeal delay	1 (5)	4 (20)	5 (25)	0.045
Presence of aspiration				
NWDPCS	1 (5)	4 (20)	6 (30)	0.043
VFSS	2 (10)	5 (25)	12 (60)	0.002

NWDPCS: North western dysphagia patients check sheet; VFSS: Video fluoroscopic swallowing study

The data analyzed by repeated measure ANOVA and for paired comparisons between groups, we used of post hoc Bonferroni test. The data indicated that onset time of swallowing therapy after stroke was effective on swallowing recovery on the main outcome variable(mean scores of NWDPCS) P = 0.001 (Table 2), so that in first group patients, recovery was rather than other groups P < 0.050, but between medium and late groups swallowing recovery was not differences P > 0.050 (Table 3).Comparison of the frequency of types of swallowing disorders between three groups indicated differences between three groups P < 0.050 (Table 4). Furthermore, the frequency of pneumonia in the early intervention group was less than other groups and in the early group, no patients experienced pneumonia P = 0.002 (Table 5).

The number of swallowing therapy sessions in the early intervention group was (10.25 ± 1.91), in medium group was (17.40 ± 2.60) and in 1-month post stroke group was (32.3 ± 3.2) thus the number of swallowing therapy sessions in the early intervention group significantly lower than in the other two groups and overall the mean of swallowing therapy sessions was significantly different in the three groups P < 0.001.

Discussion

The results of our study indicate that the time of initiation of swallowing therapy after stroke has an important role in the recovery of swallowing function, the presence of aspiration pneumonia and the number of swallowing therapy sessions. As in early intervention group recovery of swallowing function was better than other group, but between medium and late groups was not different on the recovery of swallowing function. These findings are in agreement with those of Takahata et al., which showed that early intervention can improve oral feeding in patients with intracerebral hemorrhage; but the interventions of their study were oral care, changing position, and dietary modifications, compared to ours which included traditional swallowing therapy.[25] The findings of our study are also consistent with those of Carnaby et al., which found that their intervention for dysphagia within the 1st week after stroke improved swallowing function, but they considered the intensity of treatment rather than the time of initiation of it.[24] Some studies in the field of swallowing therapy have investigated a method or approach for dysphagia in stroke patients; these therapeutic methods are initiated in acute, sub-acute or chronic periods post-stroke, and the results indicate the positive effects of swallowing therapy without considering the time of initiation of swallowing therapy.[25-27]

Table 5. Comparison of presence of pneumonia and number in three groups

Pneumonia	Three days post onset (n = 20) (%)	Two weeks post onset (n = 20) (%)	One month post onset (n = 20) (%)	P
Presence of pneumonia (before treatment)	0 (0)	6 (30)	10 (50)	0.002
Presence of pneumonia (after treatment)	0 (0)	1 (5)	3 (15)	0.158

Another issue related to swallowing problems in stroke patients is the spontaneous recovery from dysphagia. Studies have suggested that the recovery from dysphagia spontaneously occurs soon after the stroke, taking between 2 and 4 weeks, and so some clinicians initiate intervention for dysphagia for 2 weeks or more after stroke.[28] However, these studies have relied on bedside clinical examination to diagnose dysphagia and have only assessed swallowing function for short periods, such as 2 weeks after stroke.[29] Meanwhile, long-term follow-up of swallowing disability at 6 months post-stroke clinically and video fluoroscopically showed clinical evidence of a swallowing abnormality in 50% of stroke survivors.[2] Furthermore, nearly half of aspirations in patients with stroke are silent,[1,30] and these have been associated with increased morbidity and mortality in many studies.[31] Thus, intervention for dysphagia management at the proper time can reduce these pulmonary complications. The results of this study showed this positive effect because early detection and management of dysphagia by swallowing techniques can reduce aspiration in stroke patients. The results of this study are consistent with the principles of brain neural plasticity, such as "use it or lose it," and "use it and improve it."[32]

This study is the first RCT that considers onset time of swallowing disorders in stroke patients, but there are some limitations in this study, mainly the awareness of the speech therapist about the group of the allocated patients.

Another limitation of this study was that some patients were not followed up due to repeated stroke within the stage of assessment or treatment period.

Conclusion

The results of this study indicated that early dysphagia detection, using validated screening and assessment tools by a speech therapist and a standard dysphagia program of early swallowing intervention, not only improves swallowing function in stroke patients but also reduces pulmonary complications. The time taken to return to a normal diet was also significantly shorter for patients assigned to early intervention on the base of number of swallowing function.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Original Paper

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Association of Helicobacter pylori antibodies and severity of migraine attack

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Keywords
Helicobacter Pylori, Migraine, Head Pain

Abstract

Background: Recent studies have shown a positive correlation between Helicobacter pylori infection and migraine headache. The aim of this study was to evaluate the role of H. pylori infection in migraine headache with (MA) and without aura (MO).

Methods: This is a case-control study containing information on 84 patients (including MA, MO) and 49 healthy individuals**.** The enzyme-linked immunosorbent assay (ELISA) test was used to measure immunoglobulin G (IgG,) immunoglobulin M (IgM) titer in two groups. Headache severity was evaluated according to Headache Impact Test (HIT6) questionnaire.

Results: Mean ± SD of IgM antibody in Migrainous patients 26.3 (23.1) showed significantly difference with control group 17.5 (11.2) (P = 0.004). In addition, the mean ± SD HIT6 in Migrainous patients differed significantly between MA and MO groups 65.5 (4.7), 54.9 (5.3) respectively, P < 0.001**).** The only significant correlation was found for IgG antibody and HIT6 in MA patients (r = 0.407, P = 0.011) and MO group (r = 0.499, P = 0.002). The risk of migraine occurrence in patients did not significantly associate with the level of IgG and IgM antibodies.

Conclusion: The results give a hope that definite treatment and eradication of this bacterium could be a cure or to reduce the severity and course of migraine headaches.

Introduction

Migraine is a common primary headache disorder with the prevalence of nearly 15% in Western societies.[1]

Migraine is divided into two main categories: migraine with aura (MA), which patients experience transient visual or sensory symptoms (including flickering lights, spots, or pins that develop 5-20 min before attacks), and migraine without aura (MO).[2,3]

Many factors such as genetics, food and nutrients, sleep disorders, environmental factors such as noise, light, and humidity, menstruation, severe trauma, and alcohol even total fat-free mass have been reported as precipitating factors and the possible causes of migraine headaches.[4,5]

In the recent years, the role of infections and also the impact of digestive system disorders on migraine have gained more attention.

Migraine headaches are reported frequently by patients with various gastrointestinal symptoms.[6-8] However, in last few years, researches have focused on the role of Helicobacter pylori activity in the pathogenesis of migraine.

According previous reports, relationship between H. pylori and both MA, MO has been reported.[9-12] It is postulated that recurrent headache secondary to H. pylori infection could be the result of systemic vasospastic effects of pro-inflammatory substances which released by infected gastric mucosa.[10,13]

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It has been also shown that eradication of H. pylori significantly reduces the frequency, intensity, and duration of migraine attacks.[9,14-17]

Since reducing the severity and course of migraine headaches by definite treatment and consequently eradication of the H. pylori infection shows promising results,[12] the current study is designed to evaluate the role of H. pylori infection both in MO or MA patients.

Materials and Methods

The present case-control study contains information of 84 patients of MA and MO that were diagnosed by experienced neurologist, according to the International Headache Society criteria [Headache Classification Committee of the International Headache Society (IHS)][18] referring to an educational hospital in Isfahan, Iran (Al-Zahra).

The inclusion criteria for the patients were age between 15 and 50 years, without gastrointestinal symptoms (such as pyrosis, epigastric pain, belching, bloating) or receiving any nonstandard medication for H. pylori, and physical and mental ability to give written consent form.

Controls were 49 randomly selected companions of non-migrainious patients referring to the Al-Zahra hospital at the about same time as cases.

In the control group, after matching for sex and age with patients group, were included the person should not have any history of migraine headaches. Group matching was done according to educational level, marital status, geographical origin, and socio-economic status. In order to find the appropriate sample size, we used the H. pylori prevalence among cases to be 40%.[10]

The data on age, sex, antibodies including immunoglobulin G (IgG,) immunoglobulin M (IgM) titer (by Enzyme Linked Immunosorbent Assay or ELISA) gathered in all participants in two groups. Furthermore, headache severity was evaluated according to Headache Impact Test (HIT6) questionnaire.[19]

Statistical software SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA) was used for all statistical calculations. The comparison of clinical characteristics of study groups with regarding measured variables was achieved by t-tests. Associations between H. pylori antibodies and severity of headache were estimated using Pearson correlation coefficient. $P \leq 0.050$ was considered in all tests as a significant level.

Results

Table 1 represents the main characteristics of the study groups. Totally, there were included 84 migraine patients in the case group and 49 healthy individuals in the control group. The mean ± SD age is 35.8 ± 11.1 and 33.4 ± 18.9 for case and control group, respectively. Mean ± SD of IgM antibody in Migrainous patients 26.3 (23.1) showed significantly difference with the control group 17.5 ± 11.2 ($P = 0.004$) but such result did not observe in IgG titer antibody. In addition, the mean ± SD HIT6 in Migrainous patients differed significantly between MA and MO groups 65.5 ± 4.7, 54.9 ±5.3, respectively, ($P < 0.001$).

In order to find the possible correlations between MA and MO group with regard to different variables, the Pearson correlation coefficient was utilized. The only significant correlation was found for IgG antibody and HIT6 in MA patients ($r = 0.407$, $P = 0.011$) and MO group ($r = 0.499$, $P = 0.002$).

In the next step based on the laboratory test results (17), H. pylori antibodies divided to "Normal" category (≥ 30 UR/ml for IgG, and ≥ 40 ml/g for IgM), and "High" category (< 30 UR/ml for IgG, and < 40 ml/g for IgM) in migrainous patients.

Table 2 represents the relationship between the aforementioned categories with the severity of headache in the patients group. The results of this table show that a statistically significant difference exist between normal level and high level of IgG antibody with regard to the severity of headache ($P = 0.002$).

Table 3 shows the results of a logistic regression model with the occurrence of MA attacks as the dependent variable response. Based on this table, the risk of migraine occurrence in patients did not significantly associate with the level of IgG and IgM antibodies.

Table 1. Baseline characteristic of migraine patients and healthy individuals according to Helicobacter pylori antibody and Headache Impact Test (HIT6) questionnaire

Variables (mean ± SD)	Healthy control (n = 49)	Migraine patients			P	
		MA (n = 43)	MO (n = 36)	Total (n = 79)	Case versus control	MO versus MA
Age	33.4 ± 18.9	33.5 ± 11.3	37.6 ± 10.4	35.8 ± 11.1	0.375	0.093
HIT6	-	65.9 ± 4.7	59.4 ± 5.3	62.3 ± 6.0	-	< 0.001
IgG (UR/ml)	34.8 ± 40.4	33.1 ± 35.4	29.0 ± 34.2	30.9 ± 34.2	0.570	0.593
IgM (UR/ml)	17.5 ± 11.2	28.1 ± 24.6	25.2 ± 23.3	26.3 ± 23.1	0.004	0.585

HIT: Headache Impact Test Questionnaire; IgG: Immunoglobulin G; IgM: Immunoglobulin M; MO: Migraine without aura; MA: Migraine with aura; SD: Standard deviation

Table 2. The relationship between headache severity and antibody levels in migrainous patients

Antibodies level	HIT6 (mean ± SD)	P
IgG (UR/ml)		
Normal level	61.1 ± 5.5	0.002
High level	65.7 ± 6.0	
IgM (UR/ml)		
Normal level	62.1 ± 6.0	0.364
High level	63.6 ± 5.6	

HIT: Headache impact test questionnaire; IgG: Immunoglobulin G; IgM: Immunoglobulin M; SD: Standard deviation

Table 3. Correlation between antibodies level with occurrence of migraine attacks using logistic regression

Variables	P	OR	B	95% CI for OR	
				Lower	Upper
IgG	0.160	0.37	-0.972	0.098	1.468
IgM	0.458	1.67	0.517	0.428	6.570

OR: Odds ratio; CI: Confidence interval; IgG: Immunoglobulin G; IgM: Immunoglobulin M

Discussion

Based on the literature review, this is the first study attempting to find a correlation between the severity of headache (in terms of HIT6) and H. pylori antibody levels in migraneous patients either with or without aura.

Our results revealed a strong correlation between IgG antibody and the severity of headache between both migraine subgroups. However, no statistically significant difference has been observed in levels of IgG in MA vs. MO groups, as well as in patients versus controls. This finding has been supported by some researches,[20,21] however, some authors argued that compared to the general population, higher IgG antibody titer is seen in migraineous patients.[10,12,14] One reason for seeing such controversial result is that we used matching based factors that may have an effect on H. pylori infection including socio-economic status.[22] Moreover, literature used a variety of control types that differed with our controls in many ways.

However, the significance difference was found (P = 0.004) in IgM antibody titer against H. pylori in our migrainous patients compared to control groups. This finding has shed light to the importance of studying active infection with this bacterium in the etiology of migraine headaches. Previous studies concluded that active H. pylori infection is strongly related to the occurrence and severity of migraine headaches, and H. pylori treatment reduces severity and frequency of the migraine attacks significantly.[19,23] Gasbarrini et al. showed that treatment on patients in whom with the active form of H. pylori, a significant difference was observed in reducing frequency, intensity, and duration of migraine attacks.[24] As a result, the active H. pylori infection is strongly related to the outbreak and severity of migraine headaches, and proper treatment against H. pylori could diminish obviously migraine headaches.

Hosseinzadeh et al. in a case-control study showed that the higher frequency of migraine headaches is observed in patients with gastrointestinal symptoms.[12] Moreover, Gervil et al. performed two studies on 688 patients with gastrointestinal disorders in Italy found that a significant correlation between migraine and digestive disorders exists.[25] This finding was further confirmed by other studies.[26,27]

The pathophysiological mechanism of chronic migraine has not been discovered yet. It is hypothesized that there is a possible involvement of more than one level of the nervous system. The central hypersensitivity of the trigeminal vascular complex increments excitability or decreases pain inhibitory mechanisms.[28,29]

It has been suggested that the pathogenic role of the H. pylori infection in migraine, based on a relationship between the host immune response against the bacterium and the chronic release of vasoactive substances. Postulated factors of the relationship between migraine and H. pylori infection included inflammation, oxidative stress, nitric oxide imbalance, or virulence of CagA-positive H. pylori strains.[10,17,30]

During the infection, the bacterium releases in the infected tissue toxins promoting the special cascade of events related to the host immune response alterations of vascular permeability.[31-33]

Other products included superoxide radicals and nitric oxide.[34] Consequently, the resulting oxidative damage may be assessed as an aggregation of lipid peroxidation by products in the blood stream. Therefore, the prolonged oxidative injury caused by the persistent infection and the release of vasoactive substances might be involved in local cerebral blood circulation changes during migraine attacks.[35] It has been also demonstrated that migraineous patients suffer from elevated plasma Ig levels. However, Ciancarelli et al. showed that H. pylori infection does not potentiate the plasma oxidative status and the

systemic nitric oxide bioavailability of migraineuos patients. Therefore, they concluded that any specific correlation between H. pylori infection and migraine does not exist.[35] In addition, in a case-control study was showed that lower nitrate levels have been found in migraneous patients without aura compared to controls. However, they concluded that the results do not support the role of oxidative stress in patients suffering from H. pylori infection and migraine.[36]

As a result, the infection of bacteria coincides with the severity and progression of the migraine headache; thus, the H. pylori infection can be regarded as one etiology of the migraine headaches.[12]

One of the major limitations of our study was the inability to provide the general inference based on these findings. The reason for this inability comes from the fact that the source population of the cases and controls could not be identified. Hence, drawing any rigid conclusions about these findings should be discouraged.

Conclusion

According to the results of this study and similar researches, the existence of a correlation between IgG against H. pylori and severity changes in migraineous patients has been presented. Since IgG appears in the chronic pattern, association with the severity of migraine attack seems completely logical; but for better conclusion, further investigation should be designed. Furthermore, these results give a hope that definite treatment and eradication of this bacterium could be a cure or to reduce the severity and course of migraine headaches.[37].

Conflict of Interests

The authors declare no conflict of interest in this study.

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Original Paper

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Knowledge and attitudes toward epilepsy among school teachers in West of Iran

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Keywords
Epilepsy, Attitude, Knowledge, Teachers, Students

Abstract

Background: Epilepsy comprised the highest proportion of neurological problem of childhood stage, which observed mostly in the first decade of life. The dramatic effect of having a seizure in the classroom can be very traumatic for any child. The knowledge and attitude of teachers toward epilepsy have a direct impact on the life of students with epilepsy.

Methods: A cross-sectional descriptive survey was conducted in Kermanshah (West of Iran). 305 teachers from 25 public schools were randomly participated in this study. The questionnaire included 39 items and three sections (demographic information, knowledge, and attitude about epilepsy).

Results: In this study, 97% participants had heard or read about epilepsy. Attitude and knowledge about epilepsy was positive in weighted sum of the item responses, but there were deficits in individual items and first-aid management of seizure attacks. There was no meaningful relationship between attitude scores and demographic items, but higher level of education, female gender, and marital status had a positive influence on teachers' knowledge toward children with epilepsy.

Conclusion: The main findings indicated a good knowledge and positive attitude about epilepsy among school's teachers. Nevertheless, there is still a need to improve certain aspects of knowledge and attitude and first aid management of an epileptic attack among teachers.

Introduction

Epilepsy is one of the most common neurological problems which affected about 1% of the world's population.[1] A prevalence rate of 0.7-1.8% has been reported in Iran.[2] It is the one the most prevalent serious brain disorder of societies that involves people in the different age groups, races, and social classes.[3,4] This disorder comprised the highest proportion of neurological problem of childhood stage, which observed mostly in the first decade of life.[5] Globally, there are almost 33 million children with epilepsy, and it is estimated that they have 2-5 times more chances to present behavioral, emotional, and psychiatric problems in comparison with healthy children or children with other chronic diseases.[6] In Iran, in every 1000 school-aged children, there are 4.2 youngsters suffering from epilepsy. Furthermore, 65% of those affected by epilepsy are teenagers and children.[7] The dramatic effect of having a seizure in the classroom can be very traumatic for any child. The children suffering from epilepsy are often stigmatized because of fear of the seizure in public and loss of self-control.[8,9]

Children with epilepsy categorized as students who are at high risk for educational underachievement, learning disability, mental health problem, social isolation, and poor self-steam.[5,10,11] The knowledge and attitude of teachers toward epilepsy have a direct impact on life of those students in several senses, such as: school performance, social skill development, and after school success in the areas of employment, social skills, and social network

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development.[12] Teachers without experience of epilepsy often think that children with epilepsy are victims of bullying and their integration into the school collective is problematic.[13] Several studies indicated that epilepsy has been associated with misconceptions and misbeliefs, which led to stigmatization and discrimination.[14,15] This study aimed to evaluate the knowledge and attitude of teachers toward epilepsy in order to identify the needs and requirements of students with epilepsy in the schools.

Materials and Methods

This cross-sectional study was conducted in surrounding of Kermanshah province, Iran, with a population of 1,945,227 people. This is considered as regional pole for education, which has a several public and private primary and secondary schools and four public universities. 305 teachers from 25 public schools were randomly invited to participate.

The questionnaire included 39 items that were developed after an extensive review of the international literature. These questions were divided into three sections: Demographic information and familiarity with epilepsy (12 items), attitude (15 items), and knowledge about epilepsy (12 items).

We first translated the questionnaire into Persian and then it was localized by consulting three experts in the field of neurology in Iran. A pilot study was conducted in order to test the questionnaire for reliability and validity. Validity of the instrument was tested by Cronbach's alpha test which showed 0.7 consistency between questions. The reliability of questionnaire also was checked by test-retest among 20 teachers. There is no significant difference in teachers' responses in two interviews. These teachers were excluded from final sample of the study. In the subscale of knowledge, 7 items assessed medical-related knowledge about epilepsy (e.g., causes, treatment, seizure triggers), and 5 items were related the social aspects of the disorder (e.g., the individual with epilepsy doesn't possess a normal life expectancy). The attitude subscale consisted ten items assessed respondent's feeling about being in social contact with epilepsy, five items were related to limitations and concealment of epilepsy. Responses to attitude and knowledge items assessed through 5-point Likert-type scale with following options: Strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree.

In addition, familiarity with epilepsy included six items of certain questions i.e. Have you ever heard about epilepsy? Have you ever been student with epilepsy? Did you know the first-aid management of seizure? Have you seen an epileptic fit?

A questionnaire was administered on 305 school teachers from different parts of Kermanshah. Statistical software SPSS for Windows (version 13.0, SPSS Inc., Chicago, IL, USA), the independent sample t-tests and one-way ANOVA were used for analysis of data. Statistical significance considered as ($P < 0.0500$). The regression was performed to determine the effects of demographic and familiarity with epilepsy on knowledge and attitude scales.

Results

Demographics

The sample included 218 women (71.5%) and 87 men (28.5%) aged 22-55 years (mean = 38.4 years, standard deviation = 6.2). Out of 305 teachers, 91.8% of the subjects were married and 8.2% were single. With respect to the level of education, 3.6% had completed high schools, 25.2% had associated diploma, 64.9% had bachelor, and 6.3% were holding master or higher degree. With affect to the years of teaching experiences, 2% taught 1-3 years, 4.9% 3-6 years, 8.5% 6-10 years, and 84.6% 10 years or higher.

Familiarity with epilepsy

Six questions were related to familiarity with epilepsy. The data related to results these questions are presented in table 1. 97% of respondents were heard about epilepsy. 29.8 reported that they have previously taught a student with epilepsy, but only 6.2% reported that were presently teaching a student with epilepsy. There was no significant relationship between these groups.

About 61.3% of teachers had observed an epileptic fit, but only 40% responders explained the first-aid management of seizure. All of them believed that putting an object in the mouth of the students during an epileptic seizure can prevent tongue injuries. This improper knowledge was associated with a higher education ($P = 0.0200$) and years of experience teaching ($P = 0.0010$). 82% of respondents knew symptoms of seizure. There was a significant relationship between understanding of seizure's symptoms and females gender ($P = 0.0300$) and also years of teaching experience ($P = 0.0400$).

Attitude toward Epilepsy

Analysis of scores of attitude part of the questionnaire included evaluation of the weighted sum of the item responses and individual item analysis. Weighted sums of the item responses provide a quantity of the teacher total attitude, with higher scores demonstrating a more agreeable attitude. Scores for the 15 items were ranged from 15 to 75. Analysis of the responses of individual item was showed to calculate teachers' scores on the item. Table 2 lists the attitude items and the mean responses of the participants in this study. To test the possible relationships between demographic variables and familiarity with epilepsy with attitude scale scores, a backward regression analysis was concluded.

According to the statistical analysis, there was no significant association between attitude scores of the teachers and their gender, marital status, level of education, and years of teaching experience with epileptic of students.

Knowledge about Epilepsy

Knowledge scale includes 12 items. Weighted sums of the responses provide measures of the respondents' knowledge about epilepsy with higher scores are demonstrating more good knowledge. Table 3 shows the individual knowledge items and the scores of the participants. To assess the relationships between teacher demographic characters (age, gender, marital, education level, and years of teaching) and familiarity with epilepsy with knowledge scores, a second regression analysis was conducted. The results of the regression analysis were summarized in the table 4. There was a significant association between knowledge score with female gender, marital status, and higher level of education.

Table 1. Summarized results of questions regarding understanding of the epilepsy and demographic scores

Result	Q1	Q2		Q3		Q4		Q5		Q6	
	Yes (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
Total	97.0	82.0	18.0	29.8	70.2	6.2	93.8	61.3	38.7	40.0	60.0
Gender											
Male	27.2	21.3	7.2	8.5	20.6	2.6	25.9	18.7	9.9	12.5	16.1
Female	69.8	60.7	10.8	21.3	49.6	3.6	67.9	42.6	28.8	27.5	43.9
Age											
22-33	14.8	11.8	3.6	3,9	11.5	0.7	14.8	9.2	6.2	5.9	9.5
34-44	66.2	56.8	11.1	21,9	46.8	4.9	63.0	43.0	24.9	27.9	40.0
45-55	16.1	13.4	3.3	4,9	11.8	0.7	16.1	9.2	7.5	6.2	10.6
Education level											
Diploma	3.3	2.6	1.0	0.3	3.3	0.3	3.3	1.6	2.0	0.3	3.3
Associated Diploma	24.3	19.0	6.2	6.2	19.0	1.3	23.9	13.8	11.5	8.5	16.7
Bachelor	63.3	55.7	9.2	21.3	43.3	4.3	60.7	41.3	23.6	28.5	36.4
Master and higher	6.2	4.6	1.6	2.0	3.9	0.3	5.9	4.6	1.6	2.6	3.6
Years of teaching experience											
1-3	2.0	1.0	1.0	0.3	1.8	0.3	1.6	1.0	1.0	0.7	1.5
4-6	4.6	4.3	0.7	2.0	3.6	0.3	4.6	3.0	2.0	2.6	2.5
7-10	8.5	6.6	2.0	3.3	5.5	0.7	7.9	4.9	3.6	3.6	4.9
> 10	81.6	70.2	14.1	24.3	59.3	4.9	79.7	52.4	31.8	33.1	51.1

Q1: Have you ever heard or read about epilepsy?; Q2: Did you know symptoms of epilepsy?; Q3: Have you ever been students with epilepsy in your classroom?; Q4: Did you were currently teaching a student with epilepsy?; Q5: Have you ever seen an epileptic fit?; Q6: Did you know how to manage the seizure for the first time?

Table 2. Attitude items and scores of participants

Attitude item	Mean ± SD
Schools should not place children with epilepsy in regular classrooms	2.58 ± 0.99*
Persons with epilepsy have the same rights as all people	4.28 ± 0.69
Persons with epilepsy can safely drive	2.11 ± 0.92*
The onset of an epileptic seizure in a spouse is sufficient reason for divorce	2.14 ±0.81*
Children with epilepsy should attend regular public schools	3.72 ± 0.92
Persons with epilepsy are a danger to the society	1.80 ± 0.74*
Individuals with epilepsy are accident-prone	3.77 ± 0.82
Children of school had to be kept away from classmates who have epilepsy	3.77 ± 0.86
Persons with epilepsy cannot marry with persons without	2.23 ± 0.81*
Epilepsy	3.73 ± 0.78
I allow any child to sit in the same class with a child with epilepsy	3.50 ± 0.93
Equal employment opportunities should be available to individuals with epilepsy	1.62 ± 0.85*
The cause of epilepsy is insanity	3.73 ± 0.84
I allow any child to play with a child with epilepsy	2.33 ± 0.88*
Epilepsy is a kind of incurable disorder	2.48 ± 0.86*
Children with epilepsy have a higher incidence of psychosis than normal children	

Note. Scales ranges from 1 (Strongly disagree) to 5 (Strongly agree); SD: Standard deviation; * Items for which a "disagree" response (scored lower than 3) indicates a positive attitude

Table 3. Items of knowledge and responders scores

Knowledge item	Mean ± SD
The individual with epilepsy does not possess a normal life expectancy	2.45 ± 0.99*
Persons with epilepsy are mentally retarded	2.13 ± 0.80*
Persons with epilepsy can safely participate in strenuous activity	2.61 ± 0.96*
Epilepsy is a disorder of infections	1.63 ± 0.77*
Epilepsy is a disorder of the brain	3.87 ± 0.79
The offspring of parents with epilepsy will also have epilepsy	2.67 ± 0.94*
Persons of epilepsy should not drive	3.56 ± 0.98
Persons of epilepsy should not climb	3.37 ± 0.98
Inadequate steep can cause attacks of seizure in persons with epilepsy	3.66 ± 0.72
Hungry cause attack of seizure in persons with epilepsy	3.45 ± 0.76
Some certain foods or drinks make a seizure	3.60 ± 0.70
Persons with epilepsy need to use drug	3.77 ± 0.82

Note: Scales ranges from 1 (Strongly disagree) to 5 (Strongly agree); SD: Standard deviation; * Item for "disagree" response (scored lower than 3) indicates a good knowledge

Table 4. Results of the regression analysis of variables on knowledge scale scores among teachers

Predator	B	B	T	P
Gender	0.091	0.121	2.015	0.0145
Marital status	-0.150	-0.124	-2.106	0.0360
Education	-0.036	-0.066	-1.103	0.0266
Years teaching	-0.018	-0.034	0.574	0.5670
Teach now	0.014	0.032	0.547	0.5840
Have taught	0.051	0.021	0.342	0.7320
Know epilepsy	0.051	0.058	0.908	0.3650
Epileptic fit	0.023	0.036	-0.550	0.5830
First aid	0.004	0.006	0.094	0.9250
Heard epilepsy	0.012	0.006	0.0102	0.9190

Note. Teach now: Currently teaching a student with epilepsy; Have taught: Have previously taught a student with epilepsy; Know epilepsy: Know the symptom of epilepsy; Seen epileptic fit: Has seen an epileptic fit; First aid: Knows the first aids in the management of epileptic fit; Heard epilepsy: Has ever heard or read about epilepsy

Discussion

In this study, the most of teachers heard or read about epilepsy. Awareness about epilepsy is shown to be high in several studied.[16-21] In contrast, the awareness about epilepsy among school teachers in Thailand was limited to 57.8%.[22] The reason for this difference is not clear, but it may be due to close relationship population and public health education and also experience teaching a student with epilepsy. The present study showed female teachers and who had higher years of teaching, knew symptoms of epilepsy better than other teachers. It could be the result of higher level of communication between the teachers, especially female teachers, and epileptic students. In our study, participants have shown a positive attitude toward epilepsy similar to finding in other literatures.[4,5,9,16,23] On the other hand, they had a better attitude than subjects in previous studies.[1,7,24] This result is promising and encouraging. There was no significant relationship between attitude scale and demographic items and familiarity with epilepsy. Bishop showed that there was a relationship between higher levels of education and years of teaching experiences with higher scores in the attitude scale.[5] In Turkish study found young teachers age and male gender predictive of positive attitude.[25] However, the attitude score was positive, but individual item analysis showed different issues. For example 1/3 of respondents accepted as true that children with epilepsy have a higher incidence of psychosis in comparison to the normal children and also some teachers believed that epilepsy could be enough reason to prevent marriage or for divorce. Mustapha et al. Reported similar findings in their study among school teachers in Osogbo.[16]

This is believed that children with epilepsy should be separated from normal students and they are making distressing in social learning. 3.3% responders agreed that epilepsy is a form of in the insanity, which is more positive than the results of previous studies performed in Iran[1] and other Asia countries.[4,12,18,20,21] Furthermore, negative association between insanity and epilepsy has been reported by developed countries such as, USA, Denmark, and Italian.[26-28] Relation of insanity to epilepsy has been considered true from ancient times despite of scientific evidence in the countries to reject this. Regarding treatment the most of teachers believed that epilepsy is a kind of

curable disorder similar to results reported in the previous studies.[18,21,22,29] This belief made the children refer to physicians and ability to present their selves in the society.

The teacher combination scores on the knowledge scale also showed a positive drift in all items. The most of the participants knew that hungry, some foods and also inadequate sleep may lead to seizure attacks. These results are very encouraging because having awareness about these topics caused that they cared more for nutrition of the children. In the study of Akpan, poor knowledge of seizure disorder with respect to the cause, diagnosis, and treatment is noted among school teachers.[30] Regarding the knowledge about the cause of epilepsy, the most of teachers acknowledged that epilepsy is a disorder of the brain and persons with epilepsy need to use the drug for control their seizure. These acquaintances caused that teachers stimulated students for following-up of their treatment. There was a significant association between knowledge scores with female gender, marital status, and higher level of education. Ghanean et al. reported similar findings in their study among public in Tehran.[31]

In terms of the first time management, the majority of teachers were not familiarized with the initial procedures management of seizure attack. Contrary to standard first- aid management of epileptic fit,[32] all of the teachers who answered this question would be somehow inappropriate, similar to other studies.[5,9,16,24,33] Our study found a correlation between this misconception and higher level of education and teaching experience. This finding may be reflected to several reasons, containing attained from unreliable resources, and poor educative programs about epilepsy. This result suggested poor educative programs about epilepsy. This unfamiliarity can be a source of a serious problem for children with epilepsy when seizure fit occurred in schools.

Sufficient information about epilepsy caused that children were able to existing in society properly and lived likely other children. Increase awareness of teachers about epilepsy is necessary due to the role of teachers in the psychosocial development and quality of life of students with epilepsy. Mass media and physicians have an important role in the teachers' knowledge about epilepsy.

Limitation

Present study was performed in an urban population. Therefore, these results cannot be generalized countrywide due to extensive cultural differences between urban and rural areas.

Conclusion

This study showed overall good knowledge of epilepsy and positive attitudes toward epilepsy among school's teachers. Although there were deficits in some of the items and first - aids management of seizure. In general, the participants with a higher level of education showed better answers about knowledge of epilepsy.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Original Paper

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Injury-related characteristics and quality-of-life among Iranian individuals with spinal cord injury

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Keywords
Quality-of-Life, Spinal Cord Injury, Health Survey, Iran

Abstract

Background: Health-related quality-of-life (HR-QOL) may be affected by various factors including injury-related characteristics among individuals with spinal cord injury (SCI). However, the impact of the influence of these variables has not yet been fully described in Iranian population. Here, we assessed the relationships between injury-related characteristics and HR-QOL among Iranian people with SCI.

Methods: HR-QOL was assessed using short-form health survey (SF-36). Referred patients to Brain and Spinal Injury Research Center between 2010 and 2012 were invited to participate in this investigation. Injury-related characteristics including injury level and completeness, time since injury, plegia type, and American Spinal Injury Association (ASIA) Impairment Scale were evaluated.

Results: Total of 104 patients (85 men and 19 women) entered the study. The majority of patients had a complete injury (77.9%). The most frequent ASIA score was A (75%), and the most common level of injury was at thoracic sections (61.5%). Lower injury levels were associated with higher scores in physical component summary (P = 0.040), mental component summary (P = 0.010) and subsequently total score (P = 0.006). Mean age and time since injury were 52.58 ± 12.69 and 10.88 ± 16.68 years, respectively, and were not related with HR-QOL (P = 0.70 and 0.220, respectively). There was no difference in terms of HR-QOL between patients with complete and incomplete injury. Paraplegic individuals had significantly higher scores in the domain of physical functioning compared to patients with tetraplegia (P = 0.007).

Conclusion: lower injury level is a significant predictor of better QOL among individuals with SCI whereas other injury-related characteristics including completeness, time since injury and plegia type may not influence HR-QOL.

Introduction

Spinal cord injury (SCI) influences the life of affected individuals due to sensory and motor impairments along with increased risk of related secondary complications.[1-3] By considering the increased incidence of SCI in developing countries,[4] implementation of strategies to improve health-related quality-of-life (HR-QOL) among these people is essential.[5] People with SCI tend to have lower level of physical, mental and social health and they also report lower level of well-being feeling.[6,7] Many investigations have tried to identify determinants of quality-of-life (QOL) among people with SCI.[8,9] Improving QOL is a major clinical goal and has become a key outcome measure in this population.[10]

HR-QOL presents self-perceived health status. HR-QOL contains two main domains: the physical and the mental.[11,12] HR-QOL is dependent to many factors including self-esteem,[13] marital status,[14] post injury duration[15] and injury level.[16] Since both injury-related characteristics and environmental conditions

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can affect HR-QOL, levels of QOL may vary among people with SCI in different countries. However, many studies in different nations such as USA,[17] Norway,[18] Canada,[19] and Sweden[20] have shown lower levels of QOL in comparison with the general population. To our knowledge, limited investigations have assessed HR-QOL, and its related factors among Iranian individuals with SCI and most of these studies have focused on evaluating QOL in veterans.[16,21,22] Here we tried to assess HR-QOL and its related variables among the Iranian population with SCI.

The aim of this study was to evaluate injury-related characteristics including injury level, completeness, time since injury and American Spinal Injury Association (ASIA) score on HR-QOL assessed by using a 36-item short-form (SF-36). SF-36 is a validated standard tool for assessment of QOL, and the Persian version of this measure has approved validity and reliability.[23]

Materials and Methods

This is a cross-sectional investigation to evaluate HR-QOL in Iranian people with SCI. Participants were individuals with SCI, who were referred to Brain and Spinal Injury Research Center between November 2010 to April 2012. Exclusion criteria were: pregnancy, lactation, amputation, and non-traumatic SCI etiology. Patients with history of diabetes, cancer, endocrinology disease, acute infection, use of special medications such as glucocorticoid, hormones, thyroid hormones, anticonvulsive agents, heparin, aluminum-containing antacids, lithium, omega-3 fatty acids or other nutrients supplements, and smoking or alcohol consumption were also excluded. Patients with a history of addiction to illegal drugs were excluded as well. Written consent was obtained from each participant before enrollment. The study was approved by the ethics committee of Tehran University of Medical Sciences, Iran.

Patients' age, gender, and time since injury were asked directly during interviews and were indexed in pre-prepared forms. Completeness of injury was defined as complete (no preserved sensory or motor function) or incomplete (variable motor function preserved below the neurological level of injury).[24] Level of injury was assessed with clinical examinations and magnetic resonance Images and was confirmed by a neurologist. Classification of participants according to ASIA Impairment Scale was as follows: ASIA-A indicates complete injury with no preserved motor or sensory function below the neurological level. ASIA-B describes incomplete injury in which only sensory function is preserved below the neurological level. ASIA-C illustrates preserved motor function in which more than half of key muscles below the neurological level have a muscle grade < 3. ASIA-D indicates preserved motor function in which at least half of key muscles below the neurological level have a muscle grade of 3 or more. Only ASIA-A represents complete injury.[25,26]

HR-QOL was assessed using the SF-36 questionnaire. This instrument is a standard measurement tool for assessment of QOL and has been used for a long time among people with SCI. The psychometric properties of the Iranian version of the SF-36 questionnaire along with its validity and reliability are well-documented.[23] This measurement tool includes 36 items which assess QOL in eight domains: physical functioning (PF), role limitation due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitation due to emotional problems (RE), and mental health (MH). These scales provide two component summary scores: physical component summary (PCS) and mental component summary (MCS). Scores range from 0 to 100, and higher scores are representative of better QOL.[27,28] PCS includes domains of PF, RP, BP, and GH. MCS includes domains of VT, SF, role limitation due to RE, and MH.

All statistical analyses were performed using SPSS for Windows (version 21.0, SPSS Inc., Chicago, IL, USA). The chi-square test (Fisher's exact test) was used to compare categorical variables in the univariate analysis. The comparison of SF-36 scores between groups was performed using one-way analysis of variance. Pearson correlation analysis was used to evaluate the relationship between continuous variables. Descriptive analysis with an expression of frequency and percentages for categorical variables and mean ± standard deviation (SD) for continuous values was presented. Age, time since injury, injury level, and completeness, ASIA score and plegia type (tetraplegia vs. paraplegia) were considered as independent variables. $P < 0.050$ was considered to be statistically significant.

Results

Eighty-five men and 19 women with SCI participated in this study. The majority of patients were men (81.7%). Mean age was 51.86 ± 13.44 years in male participants and 56.05 ± 7.89 years in females which showed no significant difference between genders ($P = 0.180$). Seventy-eight (75.0%) had a complete injury and subsequently, the most common ASIA score was A (75.0%). The majority of participants were paraplegic (87.5%). The most frequent injury level was thoracic (61.5%) whereas 21 patients (20.2%) had an injury at the lumbar level, and only 19 subjects (18.3%) had an injury at the cervical level. Table 1 shows the baseline demographic characteristics among participants.

Figure 1 illustrates the obtained mean scores in domains of the SF-36 questionnaire. Females had significantly higher scores in BP domain (P = 0.018). However the PCS, MCS, and the total score did not differ between men and women. Injury level was a determinant of HR-QOL. Scores in PF and VT were significantly higher among patients with injury at lumbar level (P < 0.0001 and 0.020, respectively) (Tables 2 and 3). PCS (P = 0.040), MCS (P = 0.010), and total scores (P = 0.006) were higher in patients with injury at lumbar level. However, completeness of injury was not associated with better HR-QOL. The mean total scores were 66.66 ± 14.9 and 61.20 ± 17.21 in patients with complete and incomplete injury, respectively (P = 0.18). On the other hand, ASIA-C was associated with lower total score. Mean total scores in ASIA-A, B, C, and D were 67.22 ± 14.3, 57.87 ± 18.4, 47.55 ± 16.9, and 69.41 ± 14.3, respectively (P: 0.04). However, there are some concerns about the reliability of this outcome since there were only 4 patients with ASIA-C. Moreover, patients with ASIA-D showed higher scores in VT (P = 0.020), BP (P = 0.001), and SF (P = 0.030) domains. Further analysis with grouping patients into two groups of paraplegics and tetraplegics revealed no association between type of plegia and scores of the SF-36 questionnaire (P = 0.34). However, paraplegic individuals had significantly better scores in the domain of physical functioning (P = 0.007) (Table 3).

Correlation analysis detected no significant association between age and scores of PCS (P = 0.25) and MCS (P = 0.55) and the effect of age on total score of SF-36 questionnaire was also insignificant (P = 0.70). Mean time since injury was 9.26 ± 6.32. Time since injury had no influence on HR-QOL and the relationships between time since injury and PCS (P = 0.430), MCS (P = 0.180), and total scores (P = 0.220).

Table 1. Baseline characteristics in participants with spinal cord injury

Category	Frequency (%)	Mean ± SD
Gender		
Male	85 (81.7)	-
Female	19 (18.3)	-
Age (year)		52.58 ± 12.69
Completeness		
Complete	78 (75.0)	-
Incomplete	26 (25.0)	-
ASIA score		
A	78 (75.0)	-
B	12 (11.5)	-
C	4 (3.8)	-
D	10 (9.6)	-
Plegia		
Paraplegia	91 (87.5)	-
Tetraplegia	13 (12.5)	-
Time since injury (years)	-	9.26 ± 6.32

ASIA: American Spinal Injury Association; SD: Standard deviation

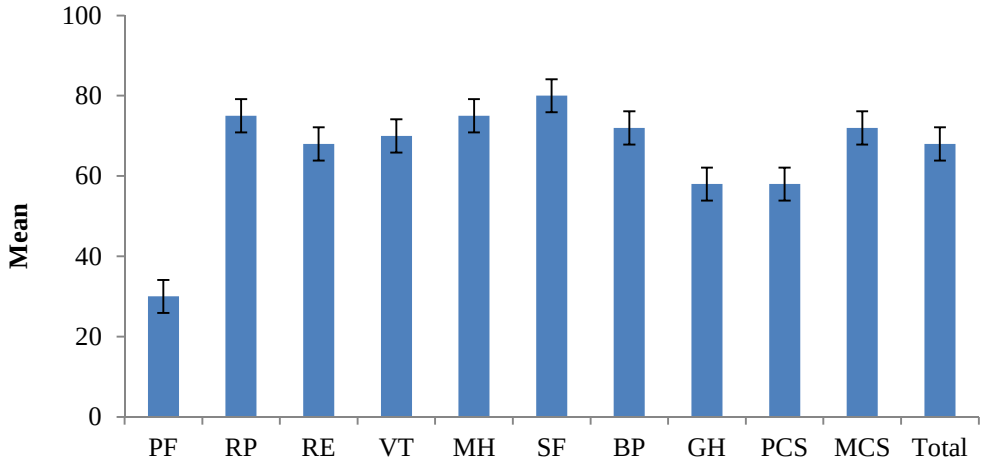

Figure 1. The obtained mean scores in domains of Short-Form-36 questionnaire
PF: Physical functioning; RP: Role limitation due to physical problems; RE: Role limitation due to emotional problems; VT: Vitality; MH: Mental health; SF Social functioning; BP: Bodily pail; GH: General health; PCS: physical component summary; MCS: mental component summary

Table 2. Scores of short-form-36 (SF-36) questionnaire domains in patients with spinal cord injury classified according to injury characteristics

Category	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS	Total
Gender											
Male	29.35 (22.6)	71.64 (39.8)	75.12 (24.7)	58.25 (22.2)	70.0 (15.7)	82.07 (22.5)	67.48 (42.1)	76.0 (17.2)	58.18 (15.8)	73.9 (18.5)	66.40 (14.7)
Female	18.82 (12.1)	69.44 (40.7)	58.75 (25.6)	54.11 (27.1)	61.76 (18.3)	69.85 (23.4)	62.22 (48.5)	68.70 (19.7)	54.19 (19.6)	66.65 (21.7)	60.14 (18.8)
Injury level											
Cervical	11.57 (15.0)	71.25 (40.8)	68.25 (31.3)	51.31 (26.3)	65.25 (14.1)	74.40 (25.4)	54.38 (48.7)	71.57 (15.6)	50.36 (18.8)	65.53 (19.8)	58.30 (16.9)
Thoracic	29.47 (20.2)	67.74 (40.8)	72.2 (23.2)	59.58 (22.2)	70.60 (17.5)	80.32 (22.7)	68.36 (41.7)	74.98 (19.8)	57.63 (13.7)	74.36 (19.3)	66.31 (14.0)
Lumbar	37.77 (23.1)	83.34 (34.3)	78.05 (26.2)	57.22 (22.4)	85.29 (14.8)	85.41 (20.6)	74.07 (40.5)	77.11 (12.5)	74.09 (19.4)	84.95 (17.2)	89.60 (16.9)
Completeness of injury											
Complete	26.38 (18.3)	72.11 (39.3)	73.83 (23.2)	59.07 (22.4)	70.34 (16.2)	80.68 (22.9)	69.77 (41.8)	75.14 (18.3)	58.04 (14.5)	74.48 (18.6)	66.66 (14.9)
Incomplete	30.90 (29.8)	68.18 (42.4)	67.72 (32.2)	51.09 (25.1)	62.50 (16.1)	77.71 (23.5)	55.55 (46.3)	73.14 (15.9)	55.87 (22.1)	66.53 (20.4)	61.20 (17.2)
ASIA score											
A	27.07 (18.8)	74.0 (38.6)	75.40 (22.4)	60.75 (22.1)	70.21 (16.8)	70.74 (23.2)	69.44 (42.1)	74.94 (18.7)	59.50 (13.8)	74.33 (19.1)	67.22 (14.3)
B	21.66 (11.5)	60.41 (45.8)	47.29 (31.2)	54.58 (20.5)	63.33 (16.5)	82.29 (23.5)	52.77 (45.9)	80.66 (11.7)	45.98 (19.8)	69.76 (19.7)	57.87 (18.4)
C	22.50 (38.6)	67.50 (43.3)	64.37 (37.4)	35.0 (8.66)	67.50 (10.4)	88.87 (21.3)	58.33 (50.0)	69.33 (10.0)	35.20 (24.3)	59.90 (13.5)	47.55 (16.9)
D	31.87 (20.8)	77.78 (36.3)	85.56 (15.6)	42.77 (28.9)	85.78 (24.1)	90.01 (23.8)	66.67 (47.1)	66.80 (17.3)	68.30 (15.8)	68.32 (20.8)	69.41 (14.2)
Plegia											
Paraplegia	29.69 (21.3)	70.40 (39.9)	72.12 (24.6)	58.70 (21.8)	68.59 (16.8)	81.17 (21.9)	67.06 (42.5)	75.38 (17.4)	58.06 (15.9)	73.48 (18.9)	65.95 (15.3)
Tetraplegia	12.08 (16.3)	76.92 (40.1)	75.0 (32.5)	49.16 (30.4)	68.07 (14.3)	72.11 (28.9)	63.88 (48.1)	70.0 (18.3)	53.50 (20.4)	67.03 (20.9)	60.93 (17.5)

ASIA: American Spinal Injury Association; PF: Physical functioning; RP: Role limitation due to physical problems; BP: Bodily pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role limitation due to emotional problems; MH: Mental Health

Table 3. P values in the relationships between injury characteristics and health-related quality of life assessed by short-form-36 (SF-36) questionnaire

Category	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS	Total
Gender	0.0670	0.83	0.018	0.50	0.610	0.05	0.66	0.12	0.400	0.180	0.170
Injury Level	< 0.0001**	0.35	0.490	0.40	0.021*	0.32	0.34	0.63	0.045*	0.011*	0.006**
Injury completeness	0.3900	0.68	0.320	0.20	0.760	0.59	0.18	0.65	0.600	0.100	0.180
ASIA score	0.1900	0.22	0.001**	0.05	0.027*	0.038*	0.64	0.32	0.140	0.013*	0.040*
Plegia	0.0070**	0.58	0.710	0.18	0.810	0.33	0.81	0.83	0.410	0.300	0.340

ASIA: American Spinal Injury Association; PF: Physical functioning; RP: Role limitation due to physical problems; BP: Bodily pain; GH: General Health; VT: Vitality; SF: Social functioning; RE: Role limitation due to emotional problems; MH: Mental health; PCS: Physical component summary; MCS: Metal Component Summary

* Statistically significant at the 0.05 level; ** Statistically significant at the 0.01 level

Discussion

The findings of this study illustrate that level of the injury is the major determinant of QOL in patients with SCI. It is well-described that higher level of injury is associated with more severe muscle loss and decreased muscle strength and performance which may contribute to lower HR-QOL.[29] Jain et al.[29] demonstrated that higher injury level and complete injuries are associated with poorer QOL. Although our investigation has shown similar results on the effect of injury level, no relationship between injury completeness and HR-QOL could be detected in our study. In line with our results, several studies have illustrated the insignificant influence of injury completeness on QOL.[30,31] Some investigations have described that complete motor lesions may lead to increased likelihood of occurrence of pressure ulcers and other related complications by limiting the

patients to wheelchair[32] which may contribute to poorer QOL in comparison with patients with incomplete injury.[33] However, patients with incomplete injuries may be limited to wheelchairs as well, and thus completeness of injury may not be the single factor affecting QOL. Existence of various factors which influence QOL may play a role in these conflicting outcomes. However, it seems that completeness of injury is not a major determinant of QOL among individuals with SCI whereas the level of injury plays an important role in determining the level of QOL among these people.

No significant relationship could be found between age and HR-QOL, which contradicts with some of the previous investigations which had shown a negative effect of older ages on QOL.[19,29] In line with our results, Cushman and Hassett[34] and Barker et al.[35] reported no association between age and QOL. Since QOL is affected by various factors such as educational level, employment status, income, social activities and familial support,[36] the relationships between these variables may vary among nations due to existence of different environmental conditions. In fact, the association between age and HR-QOL can be affected due to the existence of these confounders, and it is emphasized to perform multivariate analysis with control for confounders in each population. In this regard, Ebrahimzadeh et al.[22] showed that age was not related with HR-QOL in Iranian population with SCI, which approves our results.

This study shows no association between time since injury and HR-QOL as well. These results are in line with previous reports in Ebrahimzadeh et al.,[22] Cushman and Hassett[34] and Barker et al.[35] studies. On the other hand, Geyh et al.[37] demonstrated that shorter time since the injury is a significant predictor of lower QOL which contradicts with our results. According to Wijesuriya et al. study,[38] shorter time since injury was significantly associated with higher levels of fatigue among individuals with SCI. It seems that the association between time since injury and QOL can be affected by other factors such as fatigue which may explain the significant contribution of shorter time since injury in lower QOL in Geyh et al.'s findings. More investigations with control for these confounders should be performed to understand the association between time since injury and QOL.[37]

Previously, Lin et al.[39] reported that tetrapegics have poorer QOL in comparison with people with paraplegia. However our results difference HR-QOL between patients with tetraplegia vs. paraplegia which is in line with Lidal et al.[18] and Ebrahimzadeh et al.[22] studies. One probable reason, which has also been described by Ebrahimzadeh et al., may be the existence of accessible facilities and recreational programs for patients with tetraplegia which enables them to participate in social contributions and improves their degree of dependency.[22] According to our study, paraplegic individuals had significantly better physical functioning compared with patients with tetraplegia. It seems that although recreational and rehabilitation programs may compensate the higher level of dependency in patients with tetraplegia to some extent, still paraplegic individuals have significantly better QOL in the domain of physical functioning.

Lidal et al.[18] found no significant difference in the HR-QOL between patients with ASIA Impairment Scale A-C versus D-E. However, Kivisild et al.[40] showed that ASIA scale can be a significant predictor of PF domain in the acute phase of the injury. In this study, people with ASIA-B showed higher scores in domains of BP, VT, and SF in comparison with ASIA-A. People with ASIA-A have a complete injury with no preserved sensory and motor functions whereas in ASIA-B, the sensory function is preserved to some extent. It seems that this preserved sensory function contribute to better QOL in patients with ASIA B in comparison with ASIA-A. However, a conflicting outcome which was detected in our analysis was the lower total scores of SF-36 questionnaire among patients with ASIA-C. It is noticeable that there may be some concerns about the reliability of analysis in patients with ASIA-C since only four patients with ASIA-C participated in our investigation. Altogether, it can be concluded from our results that ASIA-B is accompanied with better QOL in comparison with ASIA-A. However, further investigation with larger sample size may be required to clarify the association between ASIA impairment Scale and HR-QOL.

Conclusion

This investigation shows that lower injury level is a significant predictor of better QOL among individuals with SCI whereas other injury-related characteristics including completeness, time since injury and plegia type may not influence HR-QOL. Age and gender were not determinants of QOL as well.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Emotional stress recognition using a new fusion link between electroencephalogram and peripheral signals

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Keywords
Electroencephalogram, Emotional Stress, Signal Processing, Recognition, Support Vector Machine

Abstract

Background: This paper proposes a new emotional stress assessment system using multi-modal bio-signals. Electroencephalogram (EEG) is the reflection of brain activity and is widely used in clinical diagnosis and biomedical research.

Methods: We design an efficient acquisition protocol to acquire the EEG signals in five channels (FP1, FP2, T3, T4 and Pz) and peripheral signals such as blood volume pulse, skin conductance (SC) and respiration, under images induction (calm-neutral and negatively excited) for the participants. The visual stimuli images are selected from the subset International Affective Picture System database. The qualitative and quantitative evaluation of peripheral signals are used to select suitable segments of EEG signals for improving the accuracy of signal labeling according to emotional stress states. After pre-processing, wavelet coefficients, fractal dimension, and Lempel-Ziv complexity are used to extract the features of the EEG signals. The vast number of features leads to the problem of dimensionality, which is solved using the genetic algorithm as a feature selection method.

Results: The results show that the average classification accuracy is 89.6% for two categories of emotional stress states using the support vector machine (SVM).

Conclusion: This is a great improvement in results compared to other similar researches. We achieve a noticeable improvement of 11.3% in accuracy using SVM classifier, in compared to previous studies. Therefore, a new fusion between EEG and peripheral signals are more robust in comparison to the separate signals.

Introduction

Emotions are complex phenomena that play a significant role in the quality of human life.[1] Emotions are part of any natural communication among humans, generally considered as non-verbal cues.[2] When thinking about emotional stress recognition systems, one of the applications that generally come to mind is the lie detector, but this is just the top of the iceberg and that many more applications can be targeted by research on emotional stress assessment.[3] Emotional stress is psychology condition, which affects the central nervous system.[1] In assessment of emotions, brain activity plays a central role. Emotion plays a major role in motivation, perception, cognition, creativity, attention, learning, and decision-making.[1,4,5] Electroencephalogram (EEG) is the reflection of brain activity and is widely used in clinical diagnosis and

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biomedical researches. Researchers have found that the following frequency bands of EEG signals are interesting to be interpreted such as delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (> 30 Hz).[1,6] EEG signals inherently associated with perceptible characteristics that change in different situations will change. Thus, by extracting these features and analyzing them, it is possible to get a right perception about the nervous system.

A lot of research has been undertaken in the assessment of stress and emotion over the last years. The main reason is the fact that those feelings are present in many situations where humans are involved. Stress is often defined as the body's reaction to a perceived mental, emotional or physical distress. Psychologists don't agree on what is considered an emotion and how many types of emotions exist.[7] Kleinginna gathered 92 definitions of emotion from literature present that day. He concluded that emotion is a complex set of interactions among subjective and objective factors, mediated by neural/hormonal systems.[8] There are two main approaches to the definition of basic emotions: The biological view that is strongly anchored in the Darwinian and the Jamesian theories, and the psychological view.[9] The most well-known theory represents emotions in two or three dimensional spaces, originating from cognitive theories, where valence-arousal space in emotions is expressed as a combination of two continuous variables: valence ranging from negative to positive (or unpleasant to pleasant) and arousal extending from calm to excited.[10]

In recent years, higher order spectra, wavelet coefficients, and chaotic invariants have received increasing interest in some of the applications.[1,11-14] Most of researches in the domain of stress use peripheral signals such as respiratory rate, skin conductance (SC), blood volume pulse (BVP),[15] and temperature.[16] Previous studies have investigated the use of peripheral and brain signals separately, but little attention has been paid so far to the fusion between brain and peripheral signals.[1,3,11,17]

An important issue in every cognitive system is the correct labeling of the data. Here, labeling means the assessment of the data using a series of visual criteria used by psychologists and a proposed cognitive system for peripheral signals in order to verify the existence of a close correlation of the data and the psychological state of the subject. In this kind of research, putting the subject in the desired psychological state is very important. Most of the previous research performed in this field would expect the desired state only based on the assumption that the correct stimulus would bring it about. However, one needs to consider a lot of interfering parameters that can affect the mental and cognitive state of the subject individual, which will possibly result in not being in the desired state. As a result, many of the errors in emotional state recognition systems can be related to the lack of substantiating the existence of a close correlation of the data and the psychological state of the subject.

In this research, in addition to the stimulus, the output responses of the autonomic nervous system (ANS) or in other word the peripheral signals are used as the confirming characteristics to improve the labeling process. In other words, the desired psychological state of the subject is validated by qualitative and quantitative analysis of the peripheral signals.

This part provides a list of relevant studies concerning emotion assessment from bio-signals. In one study, Aftanas et al.[18] showed significant differentiation of arousal based on EEG data collected from participants watching high, intermediate, and low arousal images. Chanel et al.[10] asked the participants to remember past emotional events, and obtained the result of 79% using EEG signals and 53% using peripheral signals for three categories, 76% using EEG signals, and 73% using peripheral signals for two categories. In another study, Chanel[3] asked the participants to remember past emotional episodes, and obtained the result of 88% using EEG for three categories with support vector machine (SVM) classifier. Furthermore, their results showed that, the importance of EEG signals for emotion assessment by classification as they had better accuracy than peripheral signals on the 8 s of recorded signal. Hosseini et al.[5] used the induction visual images for recording the bio-signals in stimulate participants with two different emotions, resulting in 70% of correctly identified patterns, using EEG signals for two categories of emotional stress states. Their results showed that the EEG signals performed equally well as the peripheral signals, but a combination of both improved the results. In another study, Hosseini et al.[19] used the induction visual images based acquisition protocol for recording the EEG and peripheral signals under two categories of emotional stress states of participants, and obtained the result of 78.3% using EEG signals with SVM classifier. Kim et al.[20] used the combination of music and story as stimuli and there were 50 participants, to introduce a user independent system, the results were 78.4%, 61% for three and four categories of different emotions respectively. Takahashi[21] used film clips to stimulate participants with five different emotions, resulting in 42% of correctly identified patterns. Schaaff et al.[22] used pictures from the International Affective Picture System (IAPS) to induce three emotional states: pleasant, neutral, and unpleasant. They obtained the

result of 66.7% for three classes of emotion, solely based on EEG signals.

The main goal of this research is to produce a new fusion link between peripheral and EEG signals for emotional stress states recognition in terms of quality and quantity. We investigated the recognition of two emotional stress states (calm-neutral and negatively excited) using SVM classifier.

The layout of the paper is as follows: Section 2 presents briefly the data acquisition protocol and labeling process of EEG signals. The methods and materials are given in Section 3. The results are covered in Section 4. The discussion is presented in Section 5. Finally, the conclusion is provided in Section 6.

Acquisition protocol

Stimuli

Every standard test in stress and emotion recognition has its own advantages and disadvantages.[1] Most experiments that measure emotion from EEG signals use pictures from the IAPS.[23] The IAPS evaluated by several American participants on two dimensions of nine points each (1-9). In this study, we chose the picture presentation test, based on the closeness of valence and arousal scores. The stimuli to elicit the target emotions (calm-neutral and negatively excited) are some of the pictures. The valence dimension ranging from negative to positive and the arousal dimension, ranging from calm to excited. The images in these classes are picked according to the rules in (1). Particular images, for example, erotic images duo to ethical considerations are removed from the selection.

$$\begin{array}{ll} \text{Calm} & \text{Arousal} < 4 \\ & 4 < \text{valence} < 6 \\ \text{Negative exciting} & \text{Arousal} > 5 \\ & \text{valence} < 3 \end{array} \quad (1)$$

The participant sits in front of a portable computer screen in a bare room relatively, the images to inform him about the specific emotional event he has to think of. Each experiment consists of 8 trials. Each stimulus consists of a block of four pictures, which ensures the stability of the emotion over time. In addition, each picture is displayed for 3 s leading to a total 12 s per block. Prior to displaying images, a dark screen with an asterisk in the middle is shown for 10 s to separate each trial and to attract the participant's attention. The detail of each trial is shown in figure 1.

This epoch duration is chosen because to avoid participant fatigue. In figure 2, each presentation cycle started with a black fixation cross, which is shown for 10 s. After that pictures are presented for 12 s.

Subjects

Fifteen healthy volunteered subjects are right-handed males between the age of 20 and 24 years. Most subjects are students from Islamic Azad University in Mashhad Branch. Each participant is examined by a dichotic listening test to identify the dominant hemisphere.[1,24] All subjects have normal or corrected vision; none of them have neurological disorders. These are performed to eliminate any differences in subjects. All participants gave written informed consent.[1] Then each participant is given a particulars questionnaire.[1] During the pre-test, several questionnaires have been evaluated in order to check the best psychological input to start the protocol phase; this test is state-trait anxiety inventory.[1] At the end of the experiment, participants are asked to fill in a questionnaire about the experiment and give their opinions. Because, it is possible that the emotion that a participant experiences differs from the expected value. For that reason, the participant is asked to rate his emotion on a self-assessment.

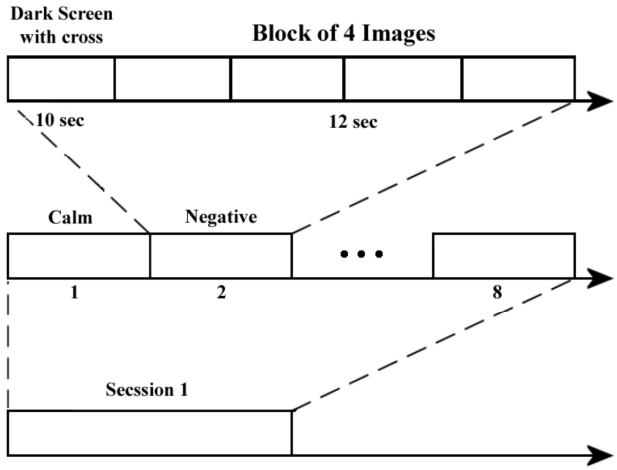

Figure 1. The protocol of data acquisition

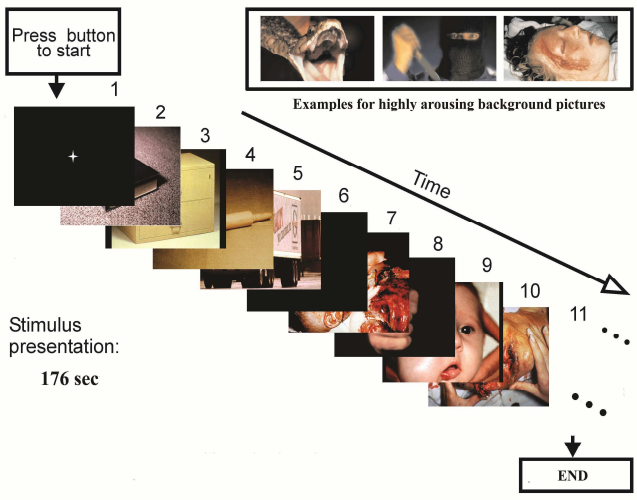

Figure 2. Process of picture presentation test

We used a 10 channel Flexcom Infiniti device, with 14-bit resolution for data acquisition.[25] It is connected to a PC using the USB port. An optical cable connects to device, to prevent any electrical charge from

reaching the participant. The Flexcom Infiniti hardware only worked well with the accompanying software. Two programs are available, Biograph Infiniti Acquisition and ezscan. The central activity is monitored by recording EEGs. The peripheral activity is assessed using the following sensors: A SC sensor to measure sudation; a respiration belt to measure abdomen expansion; a plethysmograph to record BVP. We recorded SC by positioning two dedicated electrodes on the top of left index and middle fingers. The sample rate of the BVP and SC signals acquisition is 2048 Hz and respiration signal acquisition is 256 Hz. For reduce of calculation volume, are implemented the downsampling on BVP and SC signals. EEG is recorded using electrodes placed at five positions. The scalp EEG is obtained at location FP1, FP2, T3, T4, and Pz, as defined by the international 10-20 system. In order to measure a reference signal that is (as much as possible) free from brain activity, we have two electrodes to attach to the participants earlobes. The sample rate of the EEG signal acquisition is 256 Hz. Each recording lasted about 3 min. More details of the data acquisition protocol can be found in Hosseini.[1]

Labeling process of EEG signals

In order to choose the best emotional stress related to EEG signals, we implemented a new emotion-related signal recognition system, which has not been studied so far.[1,11] We recorded peripheral signals concomitantly in order to firstly recognize the related to emotional stress state and then label the correlated EEG signals. In other words, we used the peripheral signals as a tutor for labeling system.

The process of labeling EEG signals consists of three stages: First self-assessment, second the qualitative analysis of peripheral signals, and third the quantitative analysis of peripheral signals. Figure 3 shows the different stages of the process. After the experiment, there is also a self-assessment stage, which is a good way to have an idea about the emotional stimulation "level" of the subject, because emotions are known to be very subjective and dependent on previous experience.[26] In this research, we will be able to get a general idea of the quality of the data, i.e. if the data are good or bad.

One kind of this data is respiration. Emotional stress processes influence respiration.[27,28] Slow respiration, for example, is linked to relaxation while irregular rhythm, quick variations, and cessation of respiration correspond to more aroused emotions like anger or fear.[10] Another one is SC, which measures the conductivity of the skin. Since sweat gland activity is known to be controlled by the sympathetic nervous system, electrodermal activity has become a common source of information to measure the ANS. SC increases if the skin is sweaty, for example, when one is experimenting emotions such as stress. Moreover, blood pressure and heart rate variability (HRV) are variables that correlate with defensive reactions, pleasantness of a stimulus, and basic emotions.[10] We obtained HR signal using BVP signal recorded by a plethysmograph. A method to determine HR from a BVP signal is proposed in Wan and Woo.[29] Analysis of HRV provides an effective way to investigate the different activities of ANS, an increase of HR can be due to an increase of the sympathetic activity or a decrease of the parasympathetic activity. Two frequency bands (HR spectrum) are generally considered for HR signal, a low frequency band ranging from 0.05 Hz to 0.15 Hz and a high frequency band including frequencies between 0.15 Hz and 1 Hz.[1] In order to analyze the peripheral signals quantitatively, we need to pre-process them, to remove environmental noises by applying filters. The peripheral signals are filtered by moving average filters to remove noise.

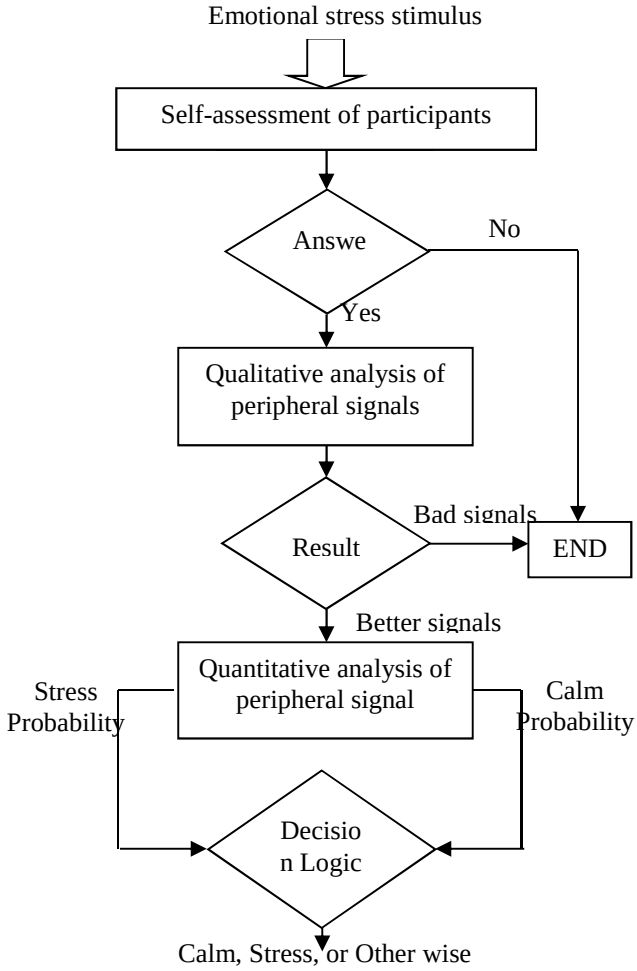

Figure 3. Labeling process of electroencephalogram signals

We used a common set of feature values for analysis of the peripheral signals (Table 1).[1,17] The

respiration features are from time and frequency domains, the SC features and the BVP features are from time domain, and the HRV features are from time, frequency domains, and fractal dimension.

After extracting the features, we need to classify them using a classifier. There are several approaches to apply the SVM for multiclass classification.[30] The LibSVM toolbox is used for implementation of the SVM by one-versus-all method.[31] Two SVMs that correspond to each of the two emotions are used. The i_{th} SVM is trained with all of the training data in the i_{th} class with calm labels, and the other training data with negative labels.

In the emotional stress recognition process, the feature vector is simultaneously fed into all SVMs and the output from each SVM is investigated in the decision logic algorithm to select the best emotional stress states (Figure 4). In the SVM classifier, is used a radial basis function (RBF) as a kernel function. RBF projects the data to a higher dimension.

A confusion matrix will also be used to determine how the samples are classified in the different classes. A confusion matrix gives the percentage of samples belonging to class ω_i and classified as class ω_j. The accuracy can be retrieved from the confusion matrix by summing its diagonal elements $P_{i,j}$ weighted by the prior probability P (ω_i) of occurrence of the class ω_i. The confusion matrices results of the SVM used for the classification of the peripheral signals under two emotional stress states is given in table 2.

The results show that, the classification accuracy with peripheral signals is 76.95% for the two categories, using SVM classifier with RBF kernel. The numbers of rejected trials that are badly classified that is lower than the number of correctly classified. The percentage of rejected trials is 11%. Method at this stage it has been used to select suitable segments of EEG signal for improving the accuracy of signal labeling according to emotional stress state. More details of the labeling process can be found in Hosseini.[1]

Table 1. Features extracted from peripheral signals

Signal	Extracted features
Respiration	Mean, variance, SD, Kurtosis, Skewness, maximum minus minimum value, power in the 0 to 2 Hz (Δf = 0.5 Hz) bands
SC	Mean, variance, SD, Kurtosis, Skewness, maximum, mean of derivative, energy response and proportion of negative samples in the derivative versus all samples
BVP	Mean, variance, SD, Kurtosis, Skewness, mean of trough variability, variance of trough variability, mean of peak variability, variance of peak variability, mean of amplitude variability, variance of amplitude variability, mean value variability, variance of mean value variability, mean of baseline variability, variance of baseline variability
HRV	Mean, variance, SD, low power frequency of 0.05-0.15 Hz, proportion low power frequency versus all power frequency, fractal dimension

SD: Standard deviation; SC: Skin conductance; BVP: Blood volume pulse; HRV: Heart rate variability

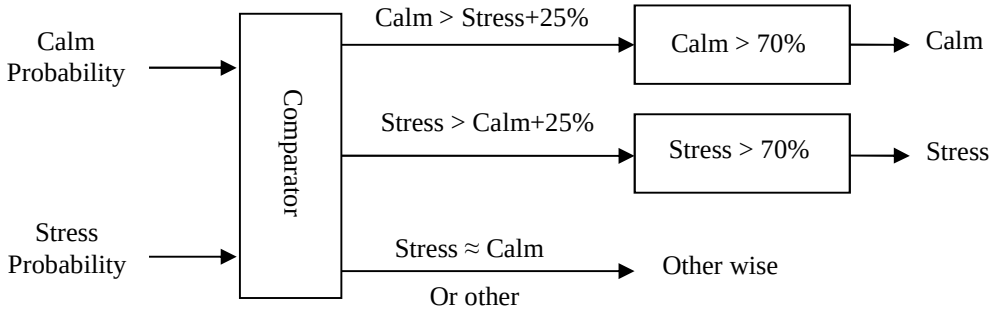

Figure 4. Decision logic algorithm to select the best emotional stress states

Table 2. The confusion matrices across participants using peripheral signals using radial basis function (RBF) kernel of support vector machine (SVM)

Truth	Classified with SVM	
	Calm-neutral (%)	Negative excited (%)
Calm-neutral	65.4	34.6
Negative excited	11.5	88.5

SVM: Support vector machine

Materials and Methods

Before analysis, we first remove the data segment, which contains eye blinking, environmental noises, and drifts. The data are filtered using a band pass filter in the frequency band of 0.5~40 Hz.

Feature extraction is the process of extracting useful information from the signal. Features are extracted for each channel of EEG signals using wavelet coefficients, fractal dimension, and Lempel-Ziv complexity.

Petrosian fractal dimension (PFD) is generally used due to its quick estimation.[32] In this method, a signal is produced by subtracting consecutive samples from the waveform record. From this sequence of subtractions, a binary sequence is created assigning +1 or −1 if the result of the subtraction is positive or negative, respectively. In short, PFD is defined as follows,

$$PFD = \frac{\log_{10} N}{\log_{10} N + \log_{10}(\frac{N}{N+0.4\times N_{\Delta}})} \quad (2)$$

Where N and N_{Δ} are the number of points of the sequence and the number of sign changes (number of dissimilar pairs) in the binary sequence generated, respectively. In this research, the best results are obtained for estimating the fractal dimension of the EEG; N = 512 samples (2 s) and window overlap = 0%.

Lempel and Ziv proposed a measure of the complexity of EEG recordings in 1976.[33] Lempel-Ziv complexity counts the number of different patterns in a sequence, starting from short patterns to longer ones. In this study, Lempel-Ziv complexity is used for EEG analysis, since it can effectively characterize the development of spatiotemporal activity patterns in non-linear systems of high-dimensionality,[34] such as the brain. Moreover, the concept of C(n) is simple to understand and its computation is easy. Before calculating Lempel-Ziv complexity, the signal must be transformed into a finite symbol sequence P. Here, a signal is transformed into a binary sequence (i.e. a 0-1 sequence) as follows,

$$P = s(1), s(2),\ldots,s(n) \quad (3)$$

Where,

$$s(i) = \begin{cases} 0, \text{if } x(i) < T_d \\ 1, \text{otherwise} \end{cases} \quad (4)$$

Usually, the median is used as the threshold T_d because of its robustness to outliers. A value which is below or equal to the mean of the data is represented by "0" and a value which is above the mean of the data is represented by "1." The complexity of a random sequence with length n, b(n), for a sequence which consists of different binary codes with equal probability can be calculated as:

$$b(n) = \frac{n}{\log_2(n)} \quad (5)$$

The normalized Lempel-Ziv complexity that reflects the arising rate of new patterns in the sequence, C(n), is obtained as:

$$C(n) = \frac{c(n)}{b(n)} \quad (6)$$

Discrete wavelet transform (DWT) based feature extraction has been successfully applied with promising results in physiological pattern recognition applications.[13] Choice of suitable wavelet and the number of levels of decomposition is very important in the analysis of signals using DWT. In this study, we used Daubechies wavelet function with order db4 for extracting the statistical feature from the EEG signal. The number of levels of decomposition is chosen based on the dominant frequency components of the signal. The levels are chosen such that those parts of the signal that correlate well with the frequencies required for classification of the signal are retained in the wavelet coefficients. Since the EEG signals do not have any useful frequency components above 32Hz, the number of levels is chosen to be five. Thus, the signal is decomposed into the details D1-D5 and one final approximation, A5. The range of various frequency bands are shown in table 3.

Table 3. Frequencies corresponding to different levels of decomposition for "db4" wavelet with a sampling frequency of 256 Hz

Decomposition levels	Frequency bandwidth (Hz)	Frequency bands
D1	64-128	Noises
D2	32-64	Noises (gamma)
D3	16-32	Beta
D4	8-16	Alpha
D5	4-8	Theta
A5	0-4	Delta

The extracted wavelet coefficients provide a compact representation that shows the energy distribution of the EEG signal in time and frequency. Table 2 presents frequencies corresponding to different levels of decomposition for db4 wavelets with a sampling frequency of 256 Hz. It can be seen from table 2 that the components A5 are within the delta (0-4 Hz), D5 are within the theta (4-8 Hz), D4 are within the alpha (8-13 Hz), and D3 are within the beta (13-30 Hz). Lower level decompositions related to higher frequencies have negligible magnitudes in a normal EEG. In order to further diminish the dimensionality of the extracted feature vectors; statistics over the set of the wavelet coefficients is used.

• Mean of the absolute values of the wavelet coefficients in each sub-band

• Average power of the wavelet coefficients in each sub-band

• Standard deviation of the wavelet coefficients in each sub-band.

These features are extracted for each channel, so the total number of features by this method is: [3×4] = 12.

In order to normalize the features in the limits of [−11] we used (7).

$$Y_{norm} = \frac{-2Y'_s + Y'_{smax} + Y'_{smin}}{Y'_{smin} - Y'_{smax}} \quad (7)$$

Here Y_{norm} is the relative amplitude.

Genetic algorithm (GA) is one of the methods described for selecting appropriate features.[35] The emphasis on using the GA for feature selection is to reduce the computational load on the training system while still allowing near optimal results to be found relatively quickly. The GA uses populations of 100 sizes, starting with randomly generated genomes. The probability of mutation is set to 0.01 and the probability of crossover is set to 0.4. The classification performance of the trained network using the whole dataset is returned to the GA as the value of the fitness function (Figure 5). We attempted to detect the feature sets related to negative/calm emotion response from EEG signal.

We used GA in assessment of all the features because a perfect feature group is not necessarily achievable by simply putting a few superior features since the data characteristics and features may have overlapping.

After extracting the desired features, we still have to find the related emotional stress states in the EEG. A classifier will do this process. SVM are maximum margin classifiers that try to maximize the distance between the decision surface and the nearest point to this surface. Non-linear SVM, maps the input space to a high dimensional feature space, and then constructs a linear optimal hyperplane in the feature space, which relates to a non-linear hyper-plane in the input space. The major problem of training machine is to find a kernel function that can not only capture the essential properties of the data distribution, but also prevent the over-fitting problem. We used three kernel functions including linear, polynomial, and RBF. The C parameter that regulates the tradeoff between training error minimization and margin maximization is empirically set to1 in this study.

Results

In this research, we used a 2 s time intervals rectangular window without overlap, corresponding to blocks of 512 samples of EEG signals for data segmentation. In classification is important that the training set contain enough instances. On the other hand, it also important that the test set contains enough samples to avoid a noisy estimate of the model performance. We used around 75% of the EEG signals for the training, and 15% of the data for testing whether the learned relationship between the data and emotional stress is correct and the last 10% is used for validating the data. The results show that, the average classification accuracy with EEG signals is 89.6% for the two categories using the SVM classifier with RBF kernel. This is particularly true in our case since the number of emotional stimulations is limited by the duration of the protocols, which should not be too long to avoid participant fatigue, as well as elicitation of undesired emotions.

Discussion

Each standard test in stress assessment has its own advantages and disadvantages. We chose the picture presentation test, based on its valence and arousal scores in different psychological states. We have chosen the brain signals over the pure peripheral signals since that brain signals represent behavior directly from their source, but the peripheral signals are secondary manifestations of the ANS in response to emotional stress. Comparing the results of peripheral signals analysis, we notice that the breathing and SC signals are less reliable in accuracy compared to BVP and HRV signals. The results show that the classification accuracy with peripheral signals is 76.95% for two categories by SVM classifier with RBF kernel.

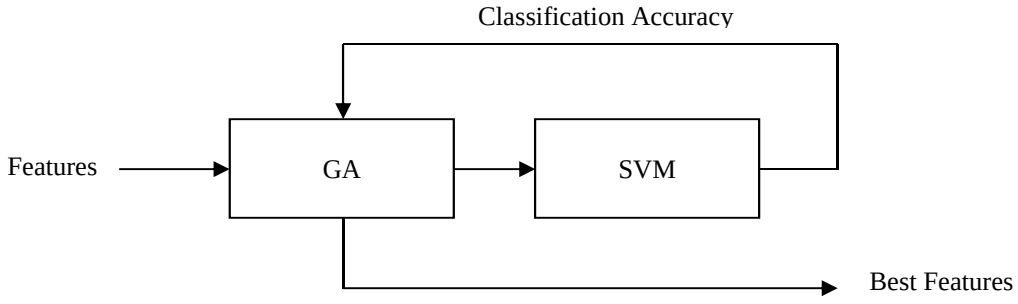

Figure 5. Combination of Genetic Algorithm and support vector machine to achieve the best features
GA: Genetic algorithm; SVM: Support vector machine

The process of labeling EEG signals consists of three stages: first self-assessment, second the qualitative analysis of peripheral signals and third the quantitative analysis of peripheral signals. After the experiment, there is also a self-assessment stage, which is a good way to have an idea about the emotional stimulation "level" of the subject, because emotions are known to be very subjective and dependent on previous experience. The only use of the personal moods and the subject's self-assessment to confirm the quality of the registered brain signals can cause many errors. As a result, we need to use peripheral signals as a secondary trainer. In order to choose the best emotional stress state related to EEG signals, we implemented a new emotion-related signal recognition system, which has not been studied so far.[1,11] Furthermore, we recorded peripheral signals continuously in order to first recognize the related to emotional stress state and then preferred label to EEG signal. Recent researches on the EEG signals, revealed the chaotic nature of this signal.[1,14] It is logical not to use conventional methods that assume emotion can be analyzed by linear models. Because brain signals essentially have a chaotic non-linear behavior. We performed emotional stress assessment using both linear and non-linear features. Wavelet coefficients and chaotic invariants like fractal dimension and Lempel-Ziv complexity are used to extract the characteristics of the EEG signals. For most non-linear measures, a dimension should be defined to visualize the attractor in phase space. However, a problem associated with all of them is that defined dimension for the phase space is not constant either for all channels of recorded EEG signals or for different subjects. Depending on the conditions, the chosen dimension can be different. On the other hand, the performance of each measure can be depending on the values of dimension. Hence, using some equations and trial and error the optimum dimension for getting the best results can be discovered.

The results obtained of the fractal method indicate that a similar trend of reduction in fractal dimension value for the negative state compared to the calm state. The reduction in fractal dimension values characterizes the reduction in brain system complexity for participants with negative emotional stress state. Therefore, the number of the necessary dynamic equations for the description of the brain state in the negative emotional stress state experienced a decrease. A new approach to emotional stress states analysis using Lempel-Ziv complexity is described in this research. The results of analysis of the non-linear characteristics show that, if the parameters and the length of data are determined appropriately, the results can be a good representation of the brain behavior in emotional stress states.[1] Hence, the application of non-linear time series analysis to EEG signals offers insight into the dynamical nature and variability of the brain signals. Therefore, it seems that non-linear features would lead to better understanding of how emotional activities work.

In this research, two of the advantages confirm the credibility of our results. We use dichotic hearing test and peripheral signals to label the brain signals correctly. Therefore, we can deduce that in short term data acquisition there is no specific dynamicity, which can be attributed to the short time intervals of 2 s. It is possible that by performing longer tests and using bigger intervals there is hope to identify some dynamics.

The results show that, the analysis of EEG signals for emotional stress assessment is better than peripheral signals.[10] We used 2 s time intervals with rectangular window without overlap to analyze the brain signals, which resulted in a time resolution of 2 s in emotional stress states recognition. If we had used shorter time intervals with overlap, we could have achieved a greater but virtual time resolution. For example, it can be useful in biofeedback applications. The problem of high dimensionality is solved using GA as a feature selection method. The results show that the average classification accuracy is 89.6% for two categories of emotional stress states using the SVM classifier. In addition, it is shown that the new fusion link, between EEG and peripheral signals are more robust in comparison to the separate signals.[1,11,19] This is a great improvement in results compared to other similar previous researches. Using proposed hybrid approach, we achieved a noticeable improvement of 11.3% in accuracy in comparison to previous studies.[19]

As a side result, many of the errors in emotional state recognition systems can be related to the lack of substantiating the existence of a close correlation of the data and the psychological state of the subject. Analyzing and comparing the results of previous researches is a complicated task, because the number of participants, the type of data, the method which is used and the time interval for analysis are different. Due to these differences, we cannot exactly compare our results with previous studies.

Conclusion

In this research, we proposed a new approach to classify emotional stress in two main areas of the valance-arousal space using multi-modal bio-signals. EEG signals are the reflection of brain activity and are

widely used in clinical diagnosis and biomedical research. These signals are used as a main signal. The visual stimuli images are selected from the subset IAPS database. The qualitative and quantitative evaluation of peripheral signals are used to select suitable segments of EEG signals for improving the accuracy of signal labeling according to emotional stress states. This is a great improvement in results compared to other similar researches. We achieve a noticeable improvement of 11.3% in accuracy using SVM classifier, in compared to previous studies. Therefore, a new fusion between EEG and peripheral signals are more robust in comparison to the separate signals.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Observation of c.260A > G mutation in superoxide dismutase 1 that causes p.Asn86Ser in Iranian amyotrophic lateral sclerosis patient and absence of genotype/phenotype correlation

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Amyotrophic Lateral Sclerosis, Genotype-Phenotype Correlation, Mutation, p.Asn86Ser, Superoxide Dismutase 1

Abstract

Background: Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disorder in European populations. ALS can be sporadic ALS (SALS) or familial ALS (FALS). Among 20 known ALS genes, mutations in C9orf72 and superoxide dismutase 1 (SOD1) are the most common genetic causes of the disease. Whereas C9orf72 mutations are more common in Western populations, the contribution of SOD1 to ALS in Iran is more than C9orf72. At present, a clear genotype/phenotype correlation for ALS has not been identified. We aimed to perform mutation screening of SOD1 in a newly identified Iranian FALS patient and to assess whether a genotype/phenotype correlation for the identified mutation exists.

Methods: The five exons of SOD1 and flanking intronic sequences of a FALS proband were screened for mutations by direct sequencing. The clinical features of the proband were assessed by a neuromuscular specialist (SN). The phenotypic presentations were compared to previously reported patients with the same mutation.

Results: Heterozygous c.260A > G mutation in SOD1 that causes Asn86Ser was identified in the proband. Age at onset was 34 years and site of the first presentation was in the lower extremities. Comparisons of clinical features of different ALS patients with the same mutation evidenced variable presentations.

Conclusion: The c.260A > G mutation in SOD1 that causes Asn86Ser appears to cause ALS with variable clinical presentations.

Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder characterized by wasting and weakness of limbs, bulbar, and respiratory muscles. ALS is accompanied by degeneration of motor neurons in the spinal cord, brainstem, and cortex. This progressive motor neuron degeneration usually leads to death 3-5 years after onset of the disease.[1-3] ALS is the third most common neurodegenerative disease in countries of European descent.[4,5] Incidence and prevalence of the disease in these countries are, respectively, 1-2 per 100,000 and 4-13 per 100,000.[6,7] Although most cases of ALS appear

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sporadic (SALS), approximately 1-13% of cases are familial ALS (FALS). The familial cases most often show autosomal dominant inheritance.[8] The clinical features of ALS are variable among patients. Age at onset of symptoms from 1 to 94 years has been reported,[9,10] and the site of onset can be either bulbar or in the limbs.[11] The rate of progression, and thus survival in the patients also varies significantly, from a few months to more than 10 years.[6,11-13] Cause of death is usually respiratory failure.

To date, at least 20 ALS causing genes have been identified (http://alsod.iop.kcl.ac.uk/).[14-16] Based on the functions of the genes, oxidative stress, axonal transport, vesicular transport, protein aggregation, and RNA metabolism are relevant to ALS pathology.[14,17,18] Importantly, various ALS genes potentially have roles in the etiology of several other neurodegenerative diseases.[15] For example, mutations in the ALS gene C9orf72 have been observed in frontotemporal dementia and Parkinson's disease patients.[15]

Mutations in superoxide dismutase 1 (SOD1) and C9orf72 are the most common genetic causes of ALS, although their relative contribution varies in different populations.[12,17,19-25] SOD1 encodes copper-zinc superoxide dismutase (Cu/Zn SOD). C9orf72 mutations are more common than SOD1 mutations in Western populations.[4] SOD1 mutations among Iranian patients are more frequent than C9orf72 mutations, having been observed, respectively, in approximately 12% and 2.6% of patients. The frequency of SOD1 mutations is even higher among Iranian FALS cases (38.5%).[12] Whereas SOD1 was identified as an ALS gene in 1993 and was the first gene to be identified, C9orf72 was identified only in 2011.[17,19,25] Worldwide, more than 170 ALS causing mutations in SOD1 are reported in Human Gene Mutation Database (HGMD 2014.2; http://www.hgmd.org/).

As already stated, clinical features of ALS patients are variable. It is expected that this variation may partly be due to differences in causative gene, to different mutations in the same gene, or to variations in genetic background of individuals that carry identical mutations in the same gene. Clearly, it is expected that among these groups, there would exist least variation in the clinical features of patients with the same mutation in the same gene. For SOD1 mutations studied till now, there is generally no clear genotype/phenotype correlation for different SOD1 mutations.[26] Other words, patients with different mutations may have similar presentations and different patients with the same mutation may have different presentations. In this regard, mutations p.Ala4Val, p.Gly85Ser, p.Asp90Ala, and p.Leu144Ser may be exceptions. P.Ala4Val and p.Gly85Ser almost always cause rapidly progressive ALS.[6] p.Asp90Ala and p.Leu144Ser are associated with long survival time.[12,13] As SOD1 mutations are relatively common among Iranian patients, we were interested to further explore genotype/phenotype correlations of SOD1 mutations. In this context, we here identified a relatively rare SOD1 mutation (c.260A > G that causes p.Asn86Ser) in an Iranian ALS family. The mutation was earlier reported in one Pakistani and one Japanese ALS family, and we aimed to the best of our ability to ascertain whether a genotype/phenotype correlation for this mutation exists by comparing the clinical features in the Iranian family to the features in the previously reported families with the same mutation.[26,27] The genotype/phenotype correlation for this mutation was not previously investigated.

Materials and Methods

The research was performed in accordance with the Helsinki Declaration and with approval of the Ethics Board of the University of Tehran, Iran. The patient studied agreed to participate after being informed of the nature of the research. The patient was recruited in 2014 from the Neuromuscular Clinic of Shariati Hospital, affiliated with Tehran University of Medical Sciences, where the diagnosis had been made. The clinical parts of the research were performed at the same hospital. The genetic studies were done at the College of Science of the University of Tehran.

The proband of family ALS187 (III-1) was definitively diagnosed with ALS by a neuromuscular specialist (SN) according to El Escorial criteria.[28] Weakness, hyperreflexia, spasticity, progression over time, nerve conduction data, and electromyography results are among the factors included in the diagnosis protocol. According to the criteria, the involvement of at least three regions of lower and upper motor neurons allows for definitive diagnosis of ALS. The patient belonged to a small FALS pedigree that in addition to the proband included one additional ALS patient who was deceased at the time of this study (Figure 1).

Genomic DNA from peripheral blood of the proband was isolated using a standard phenol-chloroform method. The five exons of SOD1 and flanking intronic sequences were amplified by polymerase chain reactions (PCR) (Tables 1 and 2).[12] The nucleotide sequences of primers used are presented in table 3. All PCR products were subsequently sequenced with the same primers used in the PCRs, using the ABI big dye chemistry and an ABI Prism 3700 instrument (Applied Biosystems, Foster City, CA, USA). Sequences were analyzed with the Sequencher 4.10.1 software (Gene Codes Corporation, Ann Arbor, MI, USA).

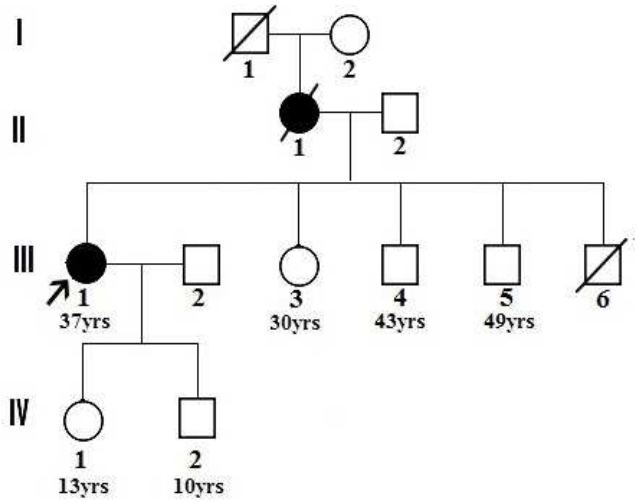

Figure 1. ALS187 pedigree. ■ and ●, ALS affected individuals; □ and ○, asymptomatic individuals. Arrow shows proband. Present age on some individuals is shown. Cause of death of I-1 and III-6 is unknown.

SOD1 reference sequences used were NC_000021.8, NM_000454.4, and NP_000445.1. On identification of a putative disease-causing variation, evolutionary conservation of the affected amino acid was assessed by comparison to amino acid sequences of SOD1 proteins from 16 species (http://www.uniprot.org/uniprot/). The sequences were aligned using ClustalW2 software (http://www.ebi.ac.uk/Tools/msa/clustalw2/). In addition, the SIFT; (http://sift.bii.a-star.edu.sg/www/SIFT_seq_submit2.html), PolyPhen (http://genetics.bwh.harvard.edu/pph2), Panther (http://www.pantherdb.org/tools/csnpScoreForm.jsp), and SNAP (https://rostlab.org/services/snap/submit) bioinformatics tools were used to predict the potential pathological effects of the mutation. Having identified the disease mutation, a correlation between genotype and phenotype was assessed by comparison of available clinical data on patients from three ALS families who carried the same mutation in SOD1. Two families were from Pakistan and Japan, and the third was the family from Iran reported in this study.[26,27]

Results

Clinical data

The ALS patient studied here is a member of a FALS pedigree that includes two affected individuals distributed in two consecutive generations. Available clinical information on the patients is presented in table 4. Age at onset of symptoms in both was in the mid-third decade of life. Sites of earliest manifestation in II-1 and III-1 were, respectively, in the arms and legs. Whereas the mother (II-1) died 1-year after onset, her daughter is alive and relatively functional 4 years after onset.

Genetic analysis

Heterozygous mutation c.260A > G that causes p.Asn86Ser in the encoded SOD1 protein was observed in the DNA of the proband (Figure 2).

Table 1. Polymerase chain reactions **(**PCR) conditions for five exons (E1-E5) of superoxide dismutase 1 (SOD1)

PCR ingredients	E1	E2	E3	E4	E5
Buffer (×10) (µl)	2.0	2.0	2.0	2.0	2.0
$MgCl_2$ (mM)	1.0	1.0	1.0	1.0	1.5
dNTP (mM)	0.2	0.2	0.2	0.2	0.3
Primer F (pM)	5.0	5.0	5.0	5.0	6.0
Primer R (pM)	5.	5.0	5.0	5.0	6.0
DNA template (ng)	150.0	150.0	150.0	150.0	200.0
Taq polymerase (unit)	1.0	1.0	1.0	1.0	1.0
DMSO (%)	7.50%	-	-	-	-
Betaine (M)	-	-	-	1.0	-
ddH_2O	13.0	13.0	13.0	13.0	12.0
Total volume	20.0	20.0	20.0	20.0	20.0

PCR: Polymerase chain reactions, dNTP: Deoxynucleotide triphosphates

Table 2. Thermocycler conditions for polymerase chain reactions (PCR) of five exons (E1-E5) of superoxide dismutase 1 (SOD1)

Cycling steps	E1	E2	E3	E4	E5
Initial denaturation	94 °C/5 min	94 °C/5 min	94 °C/5 min	94 °C/5 min	94 °C/5 min
Denaturation	94 °C/1 min	94 °C/1 min	94 °C/1 min	94 °C/1 min	94 °C/1 min
Annealing	61 °C/50 s	62 °C/50 s	63 °C/50 s	62 °C/40 s	58 °C/1 min
Extension	72 °C/50 s	72 °C/50 s	72 °C/50 s	72 °C/50 s	72 °C/50 s
Final extension	72 °C/5 min	72 °C/5 min	72 °C/5 min	72 °C/5 min	72 °C/5 min
Number of cycles	35	35	35	35	35

PCR: Polymerase chain reactions, SOD1: Superoxide dismutase 1

Table 3. The nucleotide sequences of primers.

Primer name	Sequence 5' to 3'	Primer name	Sequence 5' to 3'	Product Size (bp)
SOD1-1F	GTTCTGGACGTTTCCCGGCTG	SOD1-1R	GTGACTCAGCACTTGGGCACC	542
SOD1-2F	AGAGCAGTTAAGCAGCTTGCTG	SOD1-2R	CATGAGGATCAATGGAGCCTG	477
SOD1-3F	TCACTGTGGCTGTACCAAGGTG	SOD1-3R	CCAGGAAGTAAAAGCATTCCAGC	394
SOD1-4F	CCAGAGCATTAGTGTGTAGACG	SOD1-4R	TGAGAAACCCAATCCTGGCAAG	600
SOD1-5F	AGGTAATGTCTTTGCAACACCAAG	SOD1-5R	CCTATTTGTCTAAGCAGAGTTGTG	826

SOD1: Superoxide dismutase 1

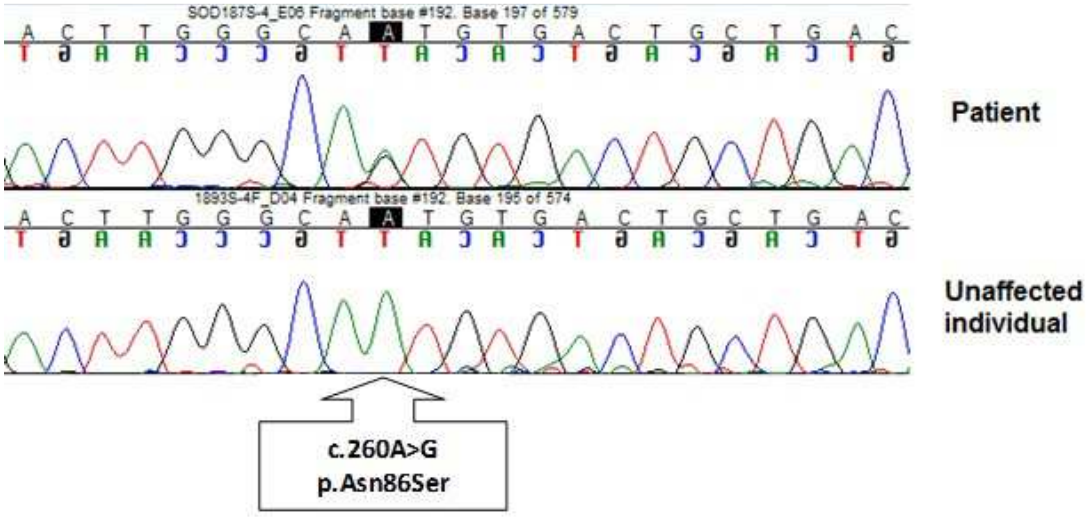

Figure 2. DNA sequence chromatograms showing the c.260A > G mutation and the wild-type sequence. The mutation that causes p.Asn86Ser is evident in the in the heterozygous state in the chromatogram of the proband

Table 4. Description of Amyotrophic lateral sclerosis (ALS) diagnosed individuals with p.Asn86Ser mutation in superoxide dismutase 1 (SOD1)

Patient	Iranian		Pakistani		Japanese	
ID	II-1	III-1	patient 1α	patient 2α	patient 1β	patient 2β
Sex	Female	Female	Female	Male	Male	Female
Present age	Dead	38 year	Dead	Dead	Dead	36 year
Age at onset (year)	37	34	13	33	52	34
Survival time	1 year	> 4 year Δ	14 week	11 month	4 year	> 11 year
Site of earliest manifestation	Arms	Legs	Legs	-	Upper body	Lower limb
Genotype*	wt/mut**	wt/mut	mut/mut	wt/mut**	wt/mut	wt/mut

* wt: wild type allele; mut: p.Asn86Ser; ** inferred genotype; Δ: still alive; α, belong to same Pakistani family; β, belong to same Japanese family

No additional variation was detected. Segregation analysis in the pedigree was not possible because the only other affected individual in the pedigree (II-1) was deceased and the living asymptomatic members of the pedigree did not want to know whether or not they carried the mutated allele. However, an asparagine at positions corresponding to p.86 in the human SOD1 protein is highly conserved across species from Caenorhabditis elegans to Homo sapiens (Table 5). The SIFT, PolyPhen, Panther, and SNAP tools predicted, respectively, that the substitution is deleterious, probably damaging, deleterious, and non-neutral. Finally, the same variation was previously reported as a cause of ALS in two families, one from Pakistan[26] and the other from Japan.[27] The sum of these data allowed us to conclude that the p.Asn86Ser causing variation in SOD1 was the probable cause of ALS in the proband and her affected mother. The inheritance pattern of ALS in the pedigree appears to be autosomal dominant, consistent with observation of a single mutated allele in the proband who was born to non-consanguineous parents and whose mother was also affected (Figure 1).

Discussion

In the present study, we identified a mutation in SOD1 that causes p.Asn86Ser in the proband of Iranian FALS pedigree ALS187. ALS inheritance in the pedigree was autosomal dominant, without evidence of anticipation. The p.Asn86Ser mutation was twice reported previously, once in a Pakistani pedigree and

once in a Japanese pedigree.[26,27] Comparisons of phenotypic features among patients of Iranian, Pakistani, and Japanese origin reveal notable intra-familial and especially interfamilial variability in disease presentation (Table 4). Age at onset of symptoms ranged from 13 to 52 years among the six patients of the three pedigrees. Age at onset was similar for the two patients of the Iranian pedigree, but it differed by about 20 years in the patients of both the Pakistani and the Japanese families. Although the very early onset at the age of 13 years in one of the Pakistani patients may be partly due to the homozygous status of her mutated genotype, both patients in the Japanese family were heterozygotes. The two affected individuals in the Pakistani family had a niece-uncle relationship. The parents of the affected 13-year-old child, who are presumably obligate carriers, were reported to be asymptomatic in the third decade of their lives. Survival time was similarly variable among the patients, with three surviving < 1-year after onset and three surviving for over 4 years. Survival time differed by at least 7 years in the two patients of the Japanese family. The earliest manifestation was in the limbs for all five patients with available data, but in the lower limbs in three and in the upper limbs in two. In regard to site of earliest manifestation, there was intrafamilial variation in the Iranian and in the Japanese families. In all the families, the earliest presentation was asymmetric. Furthermore, known cause of death was respiratory failure in all four deceased individuals. Taken together, the data emphasize the absence of a tight genotype/phenotype correlation for the p.Asn86Ser mutation in SOD1. Clearly, variability in expression may be due to differences in genetic backgrounds, to environmental factors, or to stochastic events during development. The existence of multiple ALS causing genes begs the consideration of whether these genes can have collective or modifying effects. Specifically, it is possible that even polymorphisms in other ALS causing genes will affect subtle features of disease presentation in patients with the p.Asn86Ser mutation in SOD1. Lack of tight association between genotype and phenotype renders counseling and prognosis problematic.

Other than the p.Asn86Ser mutation, the only other SOD1 mutations ever reported in the homozygous state in ALS patients are p.Leu84Phe, p.Asp90Ala, and p.Leu117Val.[10,12,29] The sum of data in families harboring these mutations do not definitively show that mutations in the homozygous state result in a more severe phenotype. With respect to p.Asn86Ser, the extent of phenotypic variation between the homozygote and heterozygote patients in the Pakistani family may be comparable to the extent of variation between the two Japanese patients who are heterozygous carriers. It appears that the consequences of the p.Asn86Ser mutation in SOD1 is not strictly uniform with respect to age at onset, site of presentation, and duration of the disease irrespective of being in the homozygous or heterozygous state.

Table 5. Conservation of p.Asn86 in superoxide dismutase 1 (SOD1) proteins

Organism	Seq ID	Amino acid sequence*
Homo sapiens	P00441	RHVGDLG**N**VTADKDGVA
Pan troglodytes	P60052	RHVGDLG**N**VTADKDGVA
Macaca mulatta	Q8HXQ0	RHVGDLG**N**VTAGKDGVA
Bos taurus	P00442	RHVGDLG**N**VTADKNGVA
Equus caballus	P00443	RHVGDLG**N**VTADENGKA
Cavia porcellus	P33431	RHVGDLG**N**VTAGADGVA
Sus scrofa	P04178	RHVGDLG**N**VTAGKDGVA
Ovis aries	P09670	RHVGDLG**N**VKADKNGVA
Canis familiaris	Q8WNN6	RHVGDLG**N**VTAGKDGVA
Oryctolagus cuniculus	P09212	RHVGDLG**N**VTAGSNGVA
Rattus norvegicus	P07632	RHVGDLG**N**VAAGKDGVA
Mus musculus	P08228	RHVGDLG**N**VTAGKDGVA
Gallus gallus	P80566	RHVGDLG**N**VTA-KGGVA
Prionace glauca	P11418	RHVGDLG**N**VEANGNGVA
Xiphias gladius	P03946	RHVGDLG**N**VTADANGVA
Caenorhabditis elegans	P34697	RHVGDLG**N**VEAGADGVA

Seq ID: Sequence ID numbers at the Uniprot server; * Position of amino acid change is shown in bold

Conclusion

The p.Asn86Ser mutation in SOD1 appears to cause disease with variable clinical presentations. There is no clear genotype/phenotype correlation for the p.Asn86Ser mutation; the clinical phenotype associated with this mutation may be influenced by the genetic background of the patient and possibly by environmental factors.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Keywords
Stroke, Cerebrovascular Disorders, Epidemiology, Shiraz

Abstract

Background: Stroke is the main cause of physical disability and the second leading cause of death worldwide. Two-thirds of all strokes occur in the developing countries. Despite being preventable, stroke is increasingly becoming a major health issue in these countries. The aim of this study was to evaluate the epidemiology of stroke in Shiraz, Iran, one of the main referral centers in the southwestern part of Iran.

Methods: A cross-sectional study was conducted on all stroke patients admitted to the Namazee Hospital, affiliated to Shiraz University of Medical Sciences, between August 2010 and January 2011. Patients' demographic data, atherosclerosis risk factors, type of stroke, drug history, outcomes, and neurological signs were recorded. Chi-square test, Kolmogorov–Smirnov test, t-test, and Mann–Whitney U-test were used to analyze the data.

Results: A total of 305 patients with stroke, aged 27-97 years (mean ± SD = 68.33 ± 12.99), 269 patients (88.2%) had ischemic stroke (IS) and 36 (11.8%) had hemorrhagic stroke (HS). 133 patients (43.6%) were men and 172 (56.4%) were women. 11.4% of the patients with IS and 40.6% with HS died during hospitalization, causing 12.1% death in all stroke patients [Odds ratio (Or) = 5.34, 95% Confidence intervals (CI) = 2.35-12.11]. Hypertension, ischemic heart disease, diabetes, and recurrent stroke were the most common risk factors.

Conclusion: This study provides evidence that the epidemiology of stroke in the southwestern part of Iran may be similar to other places. However, it seems necessary and helpful to design a registration system for patients with stroke in Shiraz Namazee Hospital.

Introduction

According to the World Health Organization, stroke is the rapid progression of signs and symptoms, caused by limited or widespread disruption of brain function, that has vascular origin and takes more than 24 h.[1,2] Stroke can be generally divided into two categories: Ischemic stroke (IS) and hemorrhagic stroke (HS).[1]

Stroke is the second leading cause of death worldwide which is considered as the third one in the United States and other industrialized countries.[3-8] Each year, 55 million deaths occur in the world that 10% of them are due to the stroke.[9] In the United States, about 780,000 strokes occur each year (one in every 40 s) while 87% are IS and 13% are HS.[9-11] Annual mortality of the disease in this country is 150,000 people (one in every 4-3 min), so it is estimated that one out of every 16 Americans dies due to stroke.[9]

The deaths occurring within 28 days after the stroke in the Middle East and North Africa vary from 10% in Kuwait to 31.5% in Iran.[4] Two-thirds of all strokes occur in the developing countries which, in spite of their preventable nature, are increasingly becoming a major health problem.[12,13] It is expected that the deaths resulting from stroke will nearly double in the Middle East and North Africa by 2030.[4]

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A major risk factor for the stroke is increasing age as every 10 years after age 55 the risk of stroke doubles.[8] Another risk factor is high blood pressure, which is the most common preventable cause of the disease.[11] Other risk factors are diabetes, smoking, obesity, lack of exercise, taking a diet which is high in cholesterol and salt, alcohol, atrial fibrillation, family history, and oral contraceptive pill usage.[7,11,14,15] In addition, gender is a determinant factor in this disease. In general, stroke is more common in men. However, because of the longer life expectancy for women and a high incidence of stroke in the older ages, the number of women with stroke is higher than men.[16]

Stroke, as the main cause of physical disability worldwide, is one of the main reasons for prolonged hospital stay that can lead to a significant increase in the cost of treatment.[7,8] The direct and indirect cost of the stroke in the United States was 65.5 billion in 2008.[17]

A few studies conducted in Iran reported that the incidence of stroke is about 43 patients per 100,000 population.[18] In a population-based study conducted in Mashhad, Iran, IS was 81.9% and HS was 15.1% of all the patients.[1] The most common risk factor was high blood pressure with a prevalence rate of 54%.[18,19] Incidence of stroke was slightly higher in women in all age groups (51-53%). However, in the age group of 15-45 years, stroke was more common in men, while the average age of its incidence is in the seventh decade of life. The hospital-based 28 days case fatality rate is reported at 19.2%[20] and 31.5%[21] in Iran. Another study refers to an unknown situation of this disease in the Middle East, that mismatch with data in the Western Countries that once again shows the need for more studies in this regard.[1]

One of the few studies conducted in Shiraz, Iran, in this field investigated early brain hemorrhage due to high blood pressure in patients referring to the hospitals of Shiraz University of Medical Sciences during 2002-2004.[22] Another retrospective study investigated the documents of 16351 patients with stroke from 2001 to 2010 in Shiraz.[23] Regarding the preventable nature of the disease, it is necessary to do more studies to determine the risk factors and the underlying causes in a particular population in order to outline and plan to prevent it.[18]

Considering that few epidemiological studies have been previously conducted in Shiraz, we conducted this study in Shiraz Namazee Hospital as a referral center for patients with stroke in the Fars province and southwestern part of Iran to obtain general information about the status of the disease in this region.

Materials and Methods

This prospective cross-sectional study was conducted in Shiraz Namazee Hospital between August 2010 and January 2011. All patients with stroke, who were diagnosed based on their clinical manifestations and imaging (magnetic resonance imaging or computerized tomography scan), were included in the study and the patients with transient ischemic attack were excluded. Patients' demographic data, atherosclerosis risk factors, type of stroke, drug history, neurological signs, duration of admission, and final outcomes were recorded.

SPSS software for Windows (version 16, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the data. Chi-square test was used for the comparison between categorical variables and Kolmogorov–Smirnov test was used to report normally distributed quantitative data. In the case of normal variables, t-test and Mann–Whitney U-test were employed. $P < 0.050$ was considered statistically significant.

Results

A total of 305 patients were included, aged between 27 and 97 years (mean ± SD = 68.33 ± 12.99). 7.9% of patients had ages of 45 or less. 133 patients (43.6%) were men and 172 (56.4%) were women. The age of most of them was between 61 and 80 years. 269 patients (88.2%) had IS and 36 (11.8%) had HS. The mean age of the patients with IS was 66.84 ± 16.94 and those with HS was 66.22 ± 12.14. 64 patients (21%) had a recurrent stroke. Data analysis did not reveal a statistically significant difference between mortality rates in the age groups (P = 0.993) (Table 1).

Table 1. Age groups and mortality rates in the patients, admitted to Shiraz Namazee Hospital, 2010-2011

Age group (year)	Frequency (%)	Mortality (%) within age group
≤ 40	8 (2.6)	2 (25.0)
41-50	21 (6.9)	2 (9.5)
51-60	60 (19.7)	7 (11.7)
61-70	72 (23.6)	9 (12.5)
71-80	81 (26.6)	9 (11.1)
≥ 81	56 (18.4)	8 (14.3)
Missing	7 (2.3)	-
Total	305 (100)	37 (12.1)

About 12.1% of all the patients died during the hospitalization. 11.4% of the patients with IS and 40.6% with HS died [Odds ratio (OR) = 5.34, 95% Confidence intervals (CI) = 2.35-12.11]. Although the difference in the mortality rate was not statistically significant (P = 0.362), the rate was higher in men (17.4%) than in women (13.3%). Sex and age-adjusted OR for the mortality rate between the patients with HS in comparison and those who had IS was 5.30 (95% CI = 2.32-12.09).

Hypertension, ischemic heart disease, diabetes, and recurrent stroke were the most common risk factors (Figure 1). The prevalence of hyperlipidemia, ischemic heart disease, and diabetes was significantly different between the age groups. Hyperlipidemia, diabetes, and ischemic heart disease were more common in age groups of 41-50, 41-60 and above 60, respectively (Figure 2). There was no significant relationship between the risk factors and mortality of the patients.

The most common neurological signs were hemiparesis and dysarthria (Figure 3). In general, there was no significant relationship between neurological signs and the mortality rate except for dysarthria. The patients with dysarthria had significantly less mortality (P = 0.019).

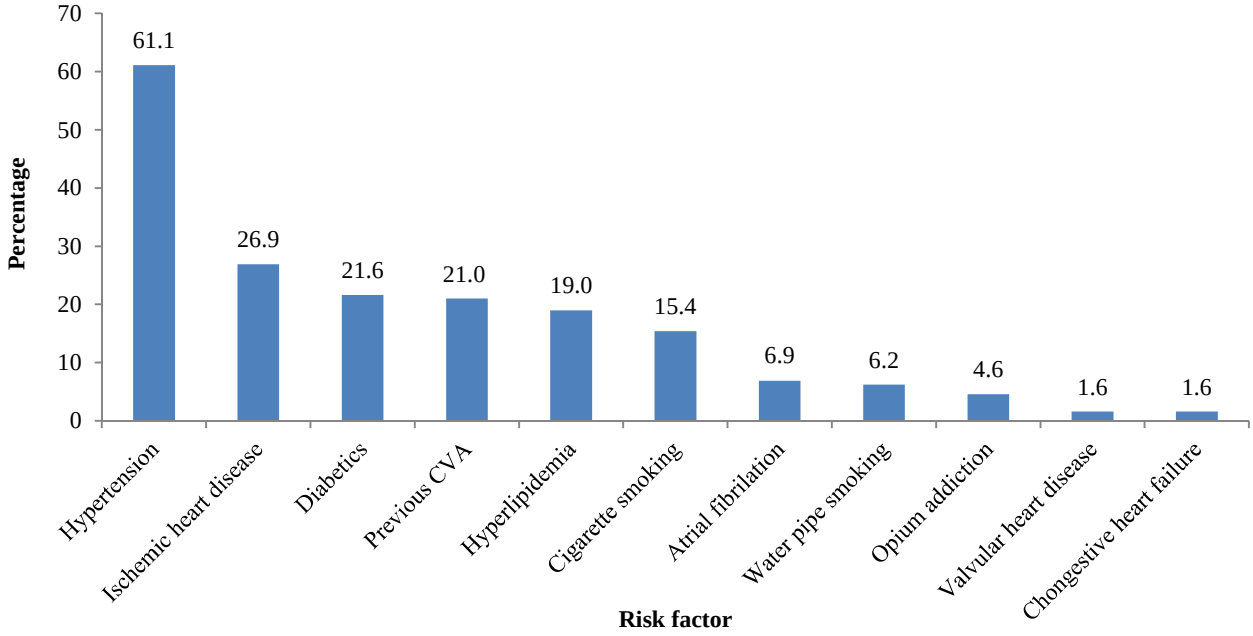

Figure 1. Prevalence of risk factors in the patients with stroke, admitted to Shiraz Namazee Hospital, 2010-2011

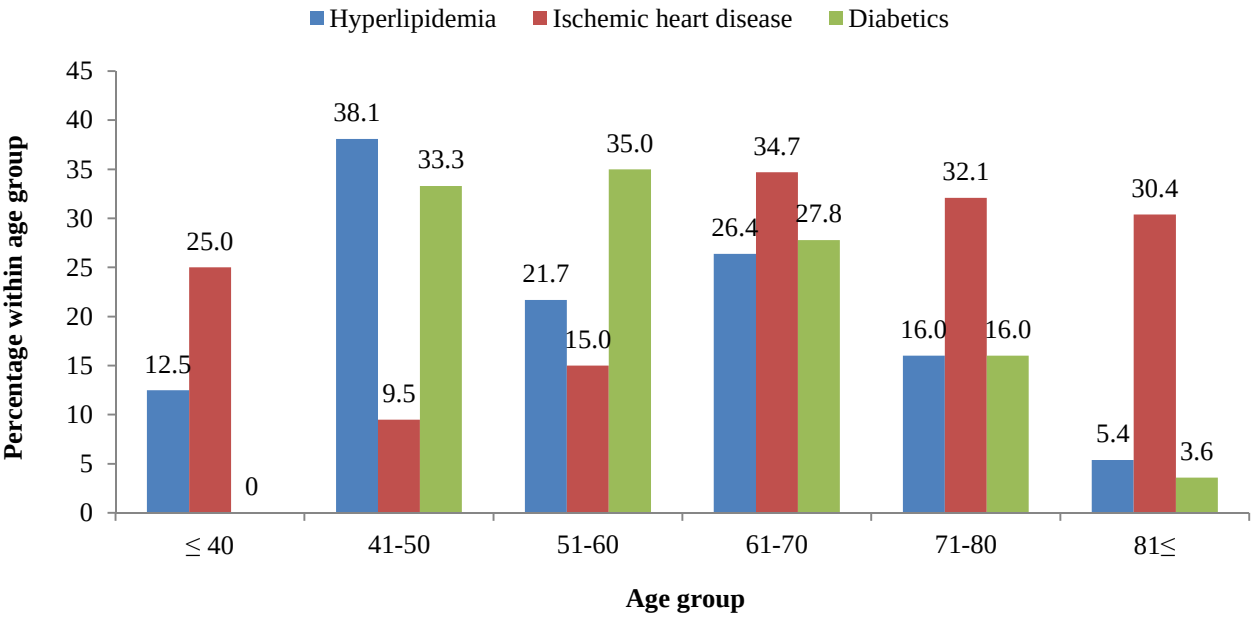

Figure 2. Risk factors in age groups of the patients with stroke, admitted to Shiraz Namazee Hospital, 2010-2011
Three risk factors had different prevalence rates in the age groups: hyperlipidemia (P = 0.010), ischemic heart disease (P = 0.480), and diabetes (P < 0.001).

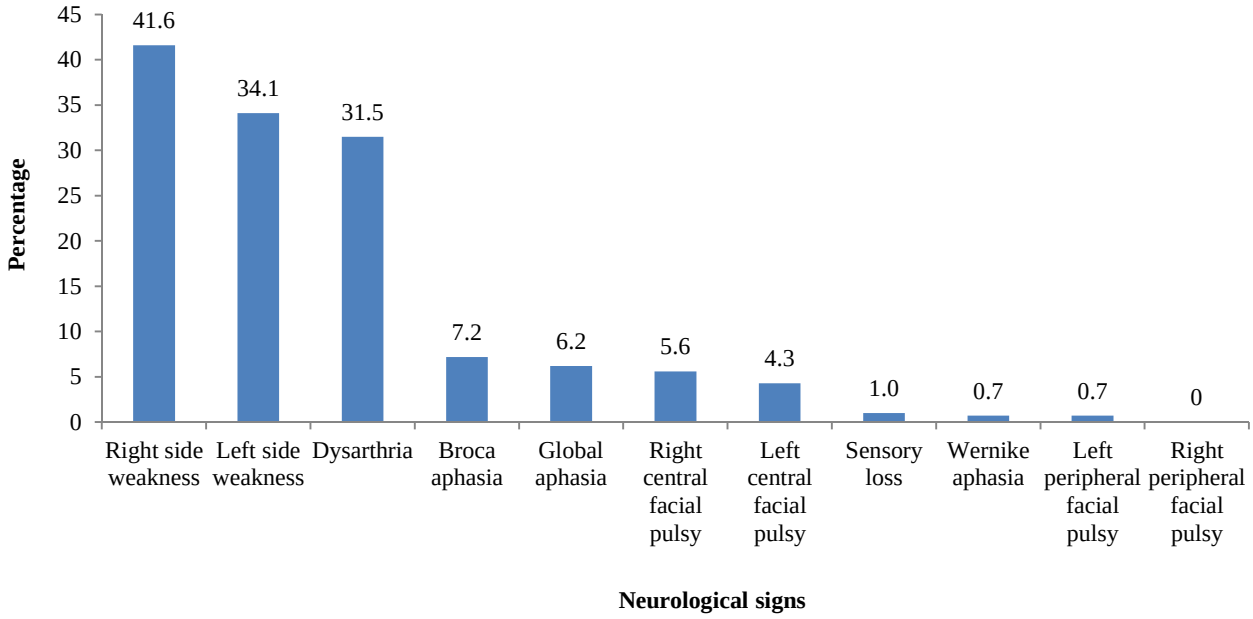

Figure 3. Prevalence of different neurological signs in the patients with stroke, admitted to Shiraz Namazee Hospital, 2010-2011

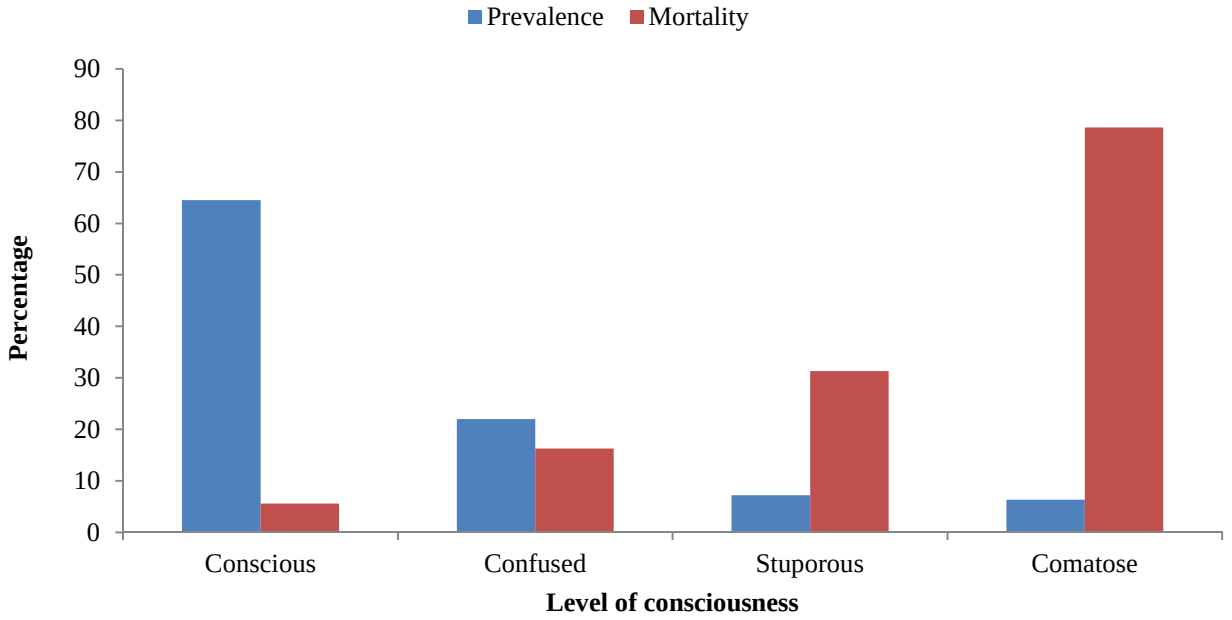

Figure 4. Relation between the level of consciousness and mortality in the patients with stroke, admitted to Shiraz Namazee Hospital, 2010-2011

Data analysis showed the lower the level of consciousness is, the higher the mortality will be ($P < 0.001$)

There was a reverse relation between the level of consciousness and mortality rate ($P < 0.001$) (Figure 4). Mean of systolic blood pressure was higher in the patients with HS than IS (160 mmHg vs. 145 mmHg, $P = 0.006$). The mean of diastolic blood pressure of the patients with HS was higher than those with IS as well (90 mmHg vs. 83 mmHg, $P = 0.013$). Median length of hospital stay was 2 days for both types of strokes, the discharged and expired patients.

Discussion

This study describes the epidemiology of stroke in Shiraz Namazee Hospital as an important referral center for the patients with stroke in the southwestern part of Iran. Our findings are in line with the findings reported by other studies. Proportion of the patients with IS and those who had HS in this study was 88.2%

and 11.8%, respectively, which is comparable with the results of a population-based study conducted in Mashhad.[1] The finding reported by Azarpazhooh et al.[1] is also similar to the prevalence of the types of stroke in the United States.[6,11,17] However, the prevalence of IS was less in Argentina and Latin America.[9]

Similar to the findings reported by other studies in Iran and the USA, the mean age of patients with stroke in our study was 68.3.[16,18] Regarding the sex pattern of stroke in previous studies conducted in Iran,[18] the present study confirms that women are more likely to experience stroke than men, but some studies have documented that 55% of the patients with stroke are male in the USA.[7] It is difficult to explain this difference, but it might be related to different types of studies. However, similar to other studies,[2] we found no sex difference in stroke mortality.

In our study, the mortality of different types of stroke in the average 2 days of hospitalization after stroke incidence is similar to 28 days mortality of other studies conducted in Iran and the USA.[11,17,18] Nevertheless, the whole mortality in our study (12.1%) is less than what has been reported by other studies.[2,18] This might be because of different study designs and the fact that, despite the others, we just considered the hospital course of the patients in their follow-up. However, it was higher than 28 days stroke mortality in our neighbor country, Kuwait.[4] In addition, although HS is less prevalent than IS, its fatality is considerably higher.[11] In the present study, we showed that HS was five times more fatal than IS.

Similar to our study, investigations in Iran and other countries show that the hypertension is the most prevalent risk factor for stroke.[9,11,18] Ischemic heart disease and diabetes are the second risk factors, but other studies show that smoking is the third prevalent risk factor in Iran and the second one in Argentina and Latin America.[9,18] A possible explanation for this difference might be due to the fact that we separated cigarette smoking, water pipe smoking, and opium addiction from each other.

Our findings showed that right and left side weakness and dysarthria are the most common neurological signs, which are in agreement with previous findings.[6] An important finding of the present study was that both systolic and diastolic blood pressures were significantly higher in the patients who had HS that shows that the control of hypertension plays an important role in the reduction of stroke mortality.

There are several limitations in this study. First, it was a hospital-based study that has less accuracy in comparison with population-based studies. Second, the source of our data was patients' documents that because of their defects, some data missing happened. Third, some case missing occurred due to the difficulties in coordination between different admission wards. We suggest that more detailed future population-based studies may be warranted for better healthcare planning in this regard and to further investigate the other aspects like economical and psychosocial burden of stroke.

Conclusion

This study showed that the epidemiology of stroke in the southwestern part of Iran is similar to other places. However, because stroke is a serious health problem, there is an urgent need to design a stroke registration system in Shiraz for a better health planning. In addition, in the realm of prevention, our emphasis is on better control of hypertension to decrease the burden of stroke

Conflict of Interests

The authors declare no conflict of interest in this study.

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Short Communication

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Alterations in semen parameters in men wıth epilepsy treated with valproate

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Keywords
Valproate, Male Infertility, Epilepsy, Antiepileptic Drugs, Reproductive Dysfunction

Abstract

Background: Besides the well-known adverse effects of valproate (VPA), disorders related to male reproductive functions have been reported. Furthermore, only a limited number of previous studies have reported the relationship between VPA dose and impairment of the hormonal axis and semen quality. A patient with reversible changes that occurred in the sperm parameters after a dose increment of VPA.

Methods: A 34-year-old male patient who was diagnosed with juvenile myoclonic epilepsy almost 15 years ago was admitted to our clinic. His seizures responded well to high doses of VPA treatment.

Results: As the VPA dose was increased, consecutive semen analyses were performed and averaged for each dose; the results showed a remarkable decline in the sperm count and a manifest loss of sperm motility. VPA treatment was gradually diminished and stopped; meanwhile, treatment with another antiepileptic (lamotrigin) was initiated to control the patient's seizures. Nine months later, the patient's semen analysis was within normal ranges. After modification of the patient's treatment regimen, he and his wife had a healthy baby.

Conclusion: We suggest that VPA-dependent impairments in the hormone and semen analysis parameters were reversible after the termination of medical treatment, and that the VPA treatment did not cause permanent hormonal deregulation and, these side effects are dose dependent.

Introduction

In the population of epileptic male patients, dysregulation of the gonadotropic hormones, impairments of semen analysis parameters, sexual dysfunctions and a decline in fertility capacity have been reported. One probable cause of the reduction in fertility capacity, which has been reported in some previous studies, is the effect of antiepileptic drugs.[1]

Valproate (VPA) is a broad spectrum antiepileptic agent which is effective in the treatment of many types of generalized and partial seizures. It has proven to be especially effective in treating primary generalized, tonic-clonic, myoclonic, and absence seizures; furthermore, it can be successfully used to treat juvenile myoclonic epilepsies where all of the previously mentioned seizure types may occur.[2]

Gastrointestinal side effects, weight gain, abnormalities in blood parameters, tremor, sedation, hair loss, and impairment in liver function are some of the most frequent adverse effects encountered during VPA treatment. Besides the aforementioned adverse effects, disorders related to male reproductive functions have been reported. Alterations in the hormonal axis and impairments in semen parameters have been especially emphasized.[3-5] A limited number of previous studies have reported a relationship between VPA dose and impairment of the hormonal axis and semen quality.[6]

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This case describes reversible changes that occurred in the sperm parameters after a dose increment of VPA in a male patient with a diagnosis of juvenile myoclonic epilepsy.

Materials and Methods

A 34-year-old male patient who was diagnosed with juvenile myoclonic epilepsy almost 15 years ago was admitted to our clinic for follow-up; his main complaint was an increase in the frequency of his seizures. Myoclonic jerks were symmetrically and involved the arms. Previously, his seizures responded well to high doses of VPA treatment. Subsequently, his medication doses were gradually reduced under the supervision of his doctor. He had been receiving 500 mg/day of VPA for 6 years. His dose was upgraded to 1500 mg/day, and seizure control was achieved.

The patient had been married for almost 7 years and had regular follow-ups at a urology clinic for the last 3 years due to infertility issues. At the moment, his spermiogram parameters were within normal ranges, although close to the lower cut-off values. His wife was healthy and her reproductive function was completely normal.

Results

As the VPA dose was increased, consecutive semen analyses were performed and averaged for each dose; the results showed a remarkable decline in the sperm count and a manifest loss of sperm motility. In addition to these impairments in the semen analysis, anomalies in the sperm morphology were also reported (Table 1).

The patient's hemogram and routine biochemical parameters were in the normal range. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) measurements in the serum of the patient were below the cut-off value; on the other hand, dehydroepiandrosterone and testosterone measurements were above the normal range. The patient was consulted to the urology department for further evaluation and exclusion of other causes of infertility (obstruction, testicular infection, febrile disease in the recent past, and use of another drug). The semen for infertility research was obtained and analyzed using World Health Organization (WHO) guidelines and sperm morphology was performed using teiberg criteria.[7-9] After a differential diagnosis accounting for other possible causes of infertility, the patient's condition was diagnosed as oligoasthenospermia when VPA dose is 1000 mg/day and then azoospermia when dose is 1500 mg/day related to VPA. VPA treatment was gradually diminished and stopped; meanwhile, treatment with another antiepileptic (lamotrigin) was initiated to control the patient's seizures. 9 months later the patient's semen analysis was within normal ranges.

20 months after modification of the patient's treatment regimen, he and his wife had a healthy baby.

Discussion

VPA is a wide-spectrum and successful antiepileptic agent used to treat many different types of epileptic seizures; it is also frequently used for medical conditions apart from epileptic seizures.[2]

The underlying mechanism of VPA that affects the male reproductive system is not yet fully understood. One of the most important suggested mechanisms is oxidative stress. Reactive oxygen species production can cause direct damage to DNA, proteins or lipids and/or by altering signal transduction of gene expressions. It is well known that VPA act as histone deacetylase inhibitor and modulate several gene expressions by histone hyperacetylation. The histones have multiple post-translational modifications, which are critical to the regulation of spermatogenesis.[10] On the other hand, the histone to protamine transition is the major step for healthy spermatogenesis.[11] Protamines are the important nuclear proteins in sperm cells. These proteins provide the correct packaging of the paternal DNA. Many studies have found that abnormal changes of protamine expressions leading to male infertility.[12-13]

Another suggested mechanism is the inhibition of the liver enzymes, which results in a decline in the estradiol level. This hypothesis suggests that decreasing estradiol levels in the blood have a negative feedback effect on the hypothalamus, and via the hypothalamohypophyseal axis, it affects the hypophyseal gland.[14]

Table 1. Patient's consecutive semen parameters results

Valproate dose (mg/day)	500 (for 6 year)	1000 (for 4 months)	1500 (for 2 year)	9 months after stopped the treatment
Valproate level (μg/ml)	21	61	109	< 3
Sperm concentration (10^6/ml)	87	2	5,1	91,2
Sperm viability (%)	55	20	20	70
Progressive motility (%)	25	5	5	35
Total motility (%)	42	10	10	60
Normal morphology (Tygerberg criteria) (%)	8	1	0	28

Another hypothesis asserts that VPA causes impairment to the serotonergic and GABAergic steroid metabolisms, resulting in an increase in dehydroepiandrostenedione sulfate (DHEAS) concentration in the blood. An increase in DHEAS concentration triggers a decrease in the hypophyseal hormones such as LH and FSH and this decrement in hypophyseal hormones manifests clinically as a reproductive disorder.[14] In our case, the patient's testosterone levels were above the normal range; on the other hand, LH and FSH levels were below the normal value.

In many previous studies, it has been reported that sperm analysis abnormalities can be seen in patients under treatment with VPA.[1] In a study conducted by Roste et al., comparing the effects of VPA and carbamazepine treatments on sperm analysis parameters, it was found that sperm tail abnormalities were significantly higher in patients receiving VPA treatment[1] And Roste et al. demonstrated men on VPA also had significantly lower carnitine levels, which may have implications for sperm motility.[15] In another study, Isojarvi et al. reported a higher risk of sperm motility disorders and a higher chance of encountering morphological abnormalities in patients under the treatment with VPA.[4] Although VPA's mechanism of action on the sperm is not fully understood, in in vitro research it has been proposed that VPA directly affects sperm motility by inducing membrane stabilization.[16]

In our case, the patient's sperm analysis parameters were in normal ranges, close to the lower cut-off values, when he was receiving 500 mg/day of VPA. An increase in the VPA daily dose was accompanied by a further impairment in semen analysis parameters. These results led us to think that the side effects of VPA are dose dependent. In a study comparing rats receiving low and high doses of VPA, rats under treatment with high dose VPA were observed to have a significant loss of testicular mass and also a severe grade of testicular atrophy.[6]

In our case, because of the potential side effects of the VPA treatment, the dose was diminished and finally cut off. After almost 9 months from the termination of VPA treatment, sperm analysis parameters were in normal ranges; sperm count, motility and morphology studies showed results within normal ranges, and afterward the patient fathered a healthy baby. Similar normalization of sperm analysis results and successful fertilization have been reported in previous case reports and clinical research.[17,18] We suggest that VPA-dependent impairments in the hormone and semen analysis parameters were reversible after the termination of medical treatment, and that the VPA treatment did not cause permanent hormonal deregulation.

Conclusion

Finally, in chronic medical conditions such as epilepsy where patients have to receive medical treatment for prolonged periods of time, we have to be careful about the potential side effects of these drugs. Especially in epileptic patients admitted to clinics with infertility disorders, we have to be careful about the selection of medical treatment and, if necessary, alternative medical treatments can be tried.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Iranian Journal of Neurology

Short Communication

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Effects of carbamazepine on semen parameters in men with newly diagnosed epilepsy

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Keywords
Carbamazepine, Epilepsy, Semen, Men

Abstract

Background: We investigated the effects of carbamazepine (CBZ) on semen parameters in men with newly diagnosed epilepsy, by performing semen analysis before starting any antiepileptic drugs, and then after starting CBZ, to determine the role and effects of CBZ in creating abnormalities in sperm analysis in these patients.

Methods: In this prospective study, eight male patients 20-40 years of age who were referred to the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Iran, from 2009 to 2012, due to new-onset seizure(s) were studied. A semen analysis was performed. CBZ was started and after at least 3 months of taking CBZ, another semen analysis was requested to determine the changes in semen quality. Statistical analyses were performed using non-parametric Wilcoxon test.

Results: Mean age of the patients was 28.5 ± 3.5 years. 7 (87.5%) patients had temporal lobe epilepsy and 1 (12.5%) had parietal lobe epilepsy. The mean follow-up period was 5.5 ± 0.9 months. We observed that semen quality (concentration, progressive motility, morphology) has significantly changed in patients with newly-diagnosed epilepsy after being treated with CBZ (P = 0.012 for all indices).

Conclusion: This study shows the direct effects of CBZ in causing changes in semen quality in men with epilepsy. Abnormalities in sperm concentration, morphology and motility, which were observed in the current study, might play a significant role in causing reduced fertility in men with epilepsy.

Introduction

Reproductive disorders are more common among men with epilepsy than in the general population.[1] Both epilepsy and antiepileptic drugs (AEDs) may play a role in creating these problems, however, the underlying mechanisms have not yet been identified clearly and separating the direct effects of epilepsy versus AEDs has always been difficult.[2] Infertility, morphological changes in testes and abnormalities in sperm analysis have been reported in patients taking sodium valproate.[3-5] Carbamazepine (CBZ) had negative effects on sperm analysis in both animal and human studies.[6-8]

In this study, we investigated the effects of CBZ on semen parameters in men with newly diagnosed epilepsy, by performing semen analysis before starting any AEDs, and then after starting CBZ, to determine the role and effects of CBZ in creating abnormalities in sperm analysis in these patients.

Materials and Methods

In this prospective study, eight male patients, who were referred to the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Iran, from January 2009 to January 2012, due to new-onset seizure(s) were studied. Inclusion criteria were patients aged 20-40 years at the time of referral; whose seizures were considered to be epileptic in nature [based on the clinical grounds and the

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electroencephalographic (EEG) and/or imaging studies]; who has not used even a single dose of any AED before their first visit; and finally, has not had any other medical or psychological disorders requiring long-term treatment in their life before. Out-patient EEG and brain magnetic resonance imaging studies were performed in all patients at the time of referral. After determining the nature of their epilepsy and when we considered that CBZ is an appropriate drug for their condition, we discussed the study procedures and purposes with the patients. When they signed the informed consent forms, a semen analysis was requested. All patients were instructed how to collect the samples. Sperm analysis was done by sperm quality analyzer IIC-P (Medical Electronic Systems, Los Angeles, CA). CBZ was started (after semen analysis was done) with 200 mg per day and titrated to 400-600 mg per day in 1-2 weeks. Our strategy was to prescribe CBZ 400 mg per day in patients with a single seizure, who were willing to take medicine, and administer CBZ 600 mg per day in patients who had more than one seizure before their referral. After at least 3 months of taking CBZ, another semen analysis was requested and performed at the same laboratory. All patients tolerated CBZ without any significant side-effects.

Statistical analyses were performed using non-parametric Wilcoxon test to determine potentially significant differences before and after taking CBZ. A $P < 0.050$ was considered significant. This study was conducted with approval by Shiraz University of Medical Sciences Review Board.

Results

Eight patients were studied. Mean age of the patients was 28.5 ± 3.5 years. 7 (87.5%) patients had temporal lobe epilepsy and 1 (12.5%) had parietal lobe epilepsy. The mean follow-up period was 5.5 ± 0.9 months. The results of the semen analyses of the patients before and after CBZ therapy are summarized in table 1.

Discussion

Reproductive disorders are common among men with epilepsy.[9] The etiology of reproductive and sexual dysfunction in men with epilepsy has been attributed to a number of possible etiologies; including psychosocial stress, AEDs, and epilepsy itself.[9] Separating the direct effects of epilepsy versus AEDs have always been difficult. Role of AEDs in sexual dysfunction among patients with epilepsy has been investigated repeatedly. It has been speculated that AEDs can induce various hormonal abnormalities; in particular, the use of the liver enzyme inducing AEDs, such as phenytoin and CBZ, which increases serum sex hormone binding globulin concentrations. This increase leads to diminished bioactivity of testosterone, which may result in diminished potency and thus reduced fertility.[10] In a number of studies, it has been reported that men with epilepsy treated with CBZ, had altered semen quality compared with healthy controls.[7,8] However, no human study has ever investigated the semen quality in patients with epilepsy, before and after treatment with any AEDs. In the current study, we observed that semen quality has significantly changed in patients with newly-diagnosed epilepsy after being treated with CBZ. This shows the direct effects of CBZ in causing changes in semen quality in men with epilepsy. Abnormalities in sperm concentration, morphology and motility, which were observed in the current study, might play a significant role in causing reduced fertility in men with epilepsy.[7] Our findings are concordant with the observation of reduced fertility among male patients with epilepsy reported in previous studies.[10] Further, larger studies with CBZ and other AEDs, particularly new AEDs, are necessary to determine the role of each AED in causing reproductive disorders among men and women with epilepsy.

Conclusion

This study shows the direct effects of carbamazepine in causing changes in semen quality in men with epilepsy. Abnormalities in sperm concentration, morphology, and motility, which were observed in the current study, might play a significant role in reduced fertility in men with epilepsy.

Limitation

The main limitation of this study is the small number of the patients enrolled in the investigation.

Table 1. Semen parameters before and after taking carbamazepine (CBZ) in men with newly-diagnosed epilepsy

Semen parameters	Before starting CBZ (mean ± SD)	While taking CBZ (mean ± SD)	Percentage change between means (%)	P
Mean volume (ml)	3.25 ± 1.46	3.50 ± 1.22	7.70	0.672
Mean concentration (million/ml)	78.37 ± 25.99	54.50 ± 32.36	−30.45	
Mean progressive motility (%)	50.75 ± 9.25	41.75 ± 14.50	−17.73	
Mean normal morphology (%)	35.00 ± 6.80	28.62 ± 9.27	−18.23	0.012
Mean motile sperm count (million/ml)	42.65 ± 20.75	26.66 ± 21.88	−37.49	
Mean functional sperm count (million/ml)	26.54 ± 16.99	15.48 ± 15.63	−41.67	
Mean sperm motility index	214.25 ± 70.82	152.12 ± 85.91	−28.99	

CBZ: Carbamazepine; SD: Standard deviation

Conflict of Interests

The authors declare no conflict of interest in this study.

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Clinical Notes

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Juvenile dermatomyositis without skin lesions

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Keywords
Juvenile Dermatomyositis, Skin Lesions, Iran

Introduction

An 8-year-old Iranian girl was referred because she had progressive muscle weakness predominantly in lower limbs since about 2 years ago. She was not able to stand from a sitting position without help and had difficulty climbing stairs. She walked slowly and could not run like before. She had no complaint of dysphagia or dysphonia.

She was born through a normal vaginal delivery and had a history of neonatal jaundice treated with phototherapy. She was taking no medications and had no history of cutaneous disease or photosensitivity. Her parents mentioned no recent weight loss.

Family history was negative for neuromuscular disorders. Her parents were not related.

On physical examination, the patient was an alert young girl with stable vital signs; Oral temperature: 36.8, Heart rate: 88 beats/min, respiratory rate: 22/min, and blood pressure 115/70 mm Hg. Her weight was 23 kg. She had mild lumbar lordosis without pes cavus, no kyphoscoliosis or other musculoskeletal deformities. She had waddling gait with positive Gower's sign. She was able to walk on heel and toe and had mild atrophy of hamstring muscles. There was no muscle tenderness.

She had no facial weakness and no dysphonia. Her muscle forces were as: neck flexion 4/5, neck extension 4/5, proximal upper limbs 4/5, proximal lower limbs 3+/5, foot dorsiflexion, and plantar flexion were normal.

Skin examination by an expert dermatologist showed no abnormalities on the face, hands or fingers.

Ancillary investigations showed: Serum creatine kinase activity as 78. Serum aldolase level was also normal. Aspartate aminotransferase was 37 and Alanine aminotransferase was 19. Fluorescent antinuclear antibody (FANA), anti-neutrophil cytoplasmic antibody, anti–double-stranded DNA antibodies, and rheumatoid factor were all negative. Thyroid function tests, complete blood count, and urine analysis were also normal.

Cardiological investigations were normal. Nerve conduction studies in upper and lower limbs were normal [including low-frequency and high-frequency repetitive nerve stimulation (RNS)]; but on needle examination all of the tested muscles in lower and upper limbs [deltoid], first dorsal interosseous (FDI), gluteus medius and maximus, rectus femoris, anterior, and gastrocnemius revealed typical myopathic pattern [small polyphasic motor unit action potentials (MUAPs) with early recruitment] without spontaneous activity [there was no fibrillation, positive sharp wave (PSW), myotonia or fasciculation].

She was referred for muscle biopsy and muscle biopsy from her left deltoid muscle reveal prominent typical perifascicular atrophy pattern in many fascicles (Figure 1a, 1C) with some foci of perimysial perivascular chronic inflammatory cell infiltration (Figure 1b). ATPase study revealed no fiber type grouping and atrophic fibers were both type 1 and 2.

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The diagnosis of dermatomyositis was made based on typical pathognomonic findings of her muscle biopsy.

The patient received methylprednisolone pulse (500 mg/day for 5 days), the muscle forces mildly improved and she was discharged with oral prednisolone (1 mg/kg/day).

On follow-up visit, 1-month later, she showed good response to treatment and her muscle forces had been improved significantly and she was able to run and stand without difficulty from sitting position but she had mild lumbar lordosis yet.

Idiopathic inflammatory myopathies are a group of disorders including dermatomyositis, polymyositis, autoimmune necrotizing myopathy and inclusion body myositis. Although polymyositis is rare in children, but juvenile dermatomyositis (JDM) is more frequent which is characterized by disease onset under the age 16.[1] Dermatomyositis is more common in females (female/male ratio is 2:1), but in juvenile DM males and females are equally involved (the F/M ratio is about 1:1).[2] Historically, dermatomyositis had been differentiated from polymyositis only by dermatologic features, but they are now known as two different diseases with different pathophysiology, pathology, and clinical courses. Perifascicular atrophy is a particular feature of dermatomyositis that is not seen in polymyositis.[3] DM is characterized by infiltration of inflammatory cells in muscle and skin capillaries and perifascicular inflammation and atrophy.

In a retrospective study of 166 patients with JDM, children with untreated JDM were shorter and lighter than national norms which indicate the importance of the diagnosis and treatment of JDM.[2]

Most of the DM patients have both symptoms of myopathy and cutaneous involvement. Some patients have only dermatologic manifestations and are named "amyopathic dermatomyositis." Skin lesions usually precede muscle weakness but sometimes they may occur at the same time or even after myopathy.[1,4] Very occasionally patients have no skin rash, but the muscle biopsy shows dermatomyositis. These patients are called "dermatomyositis sine dermatitis." In this group, muscle biopsy leads to a correct diagnosis.[1,5]

In our patient, cutaneous manifestations may occur later (although we did not see cutaneous manifestations in our patient after 4 months follow-up).

This makes the role of muscle biopsy more important in diagnosis of inflammatory muscle diseases, since clinical features cannot always differentiate between subtypes of inflammatory myopathies or between inflammatory myopathies and hereditary myopathies such as muscular dystrophies or metabolic myopathies.

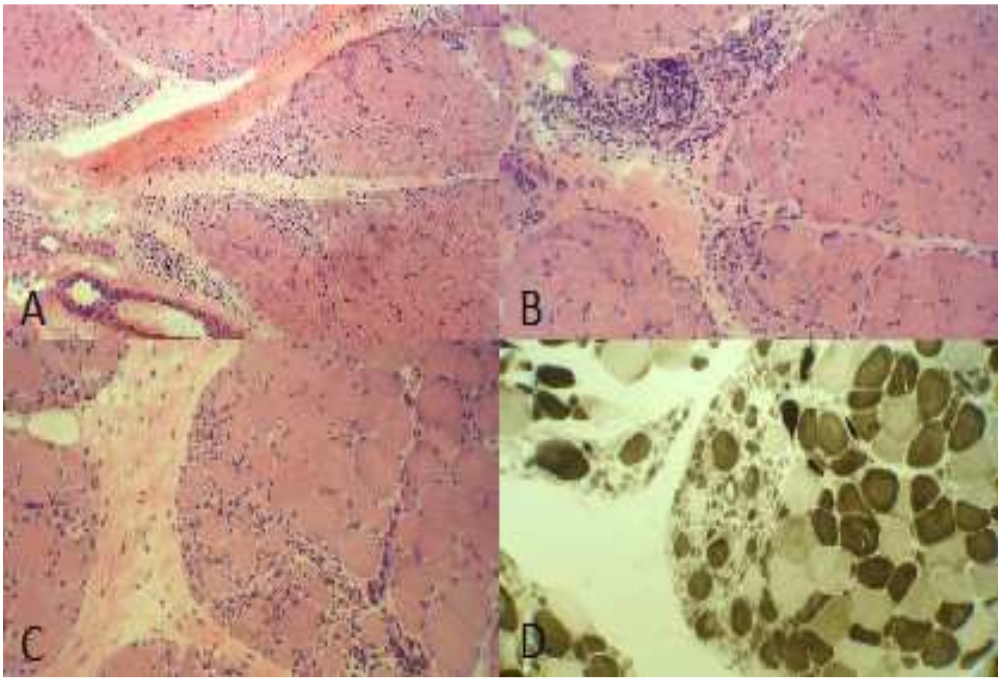

Figure 1. (a) Prominent fiber size variation with atrophy and degeneration/regeneration of the fibers exclusively arranged in the periphery of the fascicles (H and E, ×40). (b) Perimysial perivascular infiltration of chronic inflammatory cells with perifascicular degenerative/regenerative fibers and increased internalized nuclei (H and E, ×200). (c) Group atrophy with the typical perifascicular pattern (H and E, ×200). (d) Checkerboard pattern with no fiber type grouping (ATPase PH 4.63, ×200)

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We acknowledge patient who accepted to participate in this study.

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Clinical Note

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Disseminated cryptococcosis and active pulmonary tuberculosis co-infection in an otherwise healthy adult

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Keywords
Cryptococcosis, Pulmonary Tuberculosis, Coinfection

Introduction

Co-infection with Mycobacterium tuberculosis (MTB) and Cryptococcus is very rare in immunocompetent hosts,[1,2] and it is even more infrequent that the opportunistic yeast becomes disseminated in the presence of normal immune system and negative HIV test.[3] We present an extremely uncommon case of severe fatal pulmonary and meningeal cryptococcosis along with fungemia associated with active pulmonary TB in a 70-year-old Afghan man with normal CD4 and CD8 lymphocyte counts and negative HIV antibody test.

The patient was a 70-year-old Afghan man who had been immigrated to Iran 15 years ago, with an unremarkable medical history who was an active construction worker prior to initiation of his symptoms. He was admitted to hospital due to 40 days history of headache, weight loss, fatigue, anorexia, and occasional fever which was deteriorated in the last 10 days with superimposition of gait impairment, blurred vision, nausea and vomiting, mental confusion and memory loss. He didn't have any significant cough or expectorations. His family history was unremarkable and he did not mention any known exposures to TB. In the physical examination, he was afebrile, drowsy, and had mild neck stiffness. Cranial nerves were normal, deep tendon reflexes were absent with downward plantar reflexes and despite normal muscle forces he couldn't walk normally. Brain computed tomography (CT) scan without contrast showed communicating hydrocephalus and the brain magnetic resonance imaging (MRI) revealed slight degrees of basal meningitis followed by enlarged perivascular spaces and basal ganglia involvement in subsequent imagings (Figure 1). Cerebrospinal fluid (CSF) parameters were as follows: Opening pressure of 30 cm H_2O; total white blood cell count of 495 cell/µl with 76% polymorphonuclear; protein level of 100 mg/dl; and a glucose level of 21 mg/dl. Chest CT scan showed multiple nodules and upper lobe cavities in both lungs (Figure 2). Although MTB-polymerase chain reaction and direct smear of CSF for mycobacteria were negative and adenosine deaminase activity level was low (1.5 U/l), CSF direct examination with Indian ink showed budding yeast cells with capsules compatible with Cryptococcus neoformans and CSF and blood culture were positive for the same element. The diagnosis of concomitant TB infection and cryptococcosis was made following a bronchoscopy, when bronchial alveolar lavage specimens were highly

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positive for acid-fast bacilli along with fungal elements and the sputum smears were positive for mycobacteria for 3 times. While finding the co-existence of these 2 infections made us highly suspicious of positive human immunodeficiency virus (HIV) test or impaired immunity, the patient's HIV test was negative and flow cytometric findings showed normal CD4 and CD8 cell counts.

At first the patient was treated with a combination of anti-TB [isoniazid (300 mg daily), rifampin (600 mg daily), pyrazinamide (1500 mg daily) and ethambutol (1200 mg daily)] and steroid. When C. neoformans was detected on CSF culture, treatment with conventional amphotericin B was started because flucytosine and liposomal amphotericin B are not available in our country. After initiation of therapy, the patient was afebrile and his level of consciousness was improved, but 3 weeks later, he developed fever, drowsiness, and dyspnea. Further, CSF exam showed pleocytosis (with lymphocyte predominance), very low glucose level (< 10 mg/dl) and positive fungal smear and culture, and blood culture was persistently positive for the yeast. Despite treatment, the patient's general condition was deteriorated and he eventually expired due to pulmonary complications, although investigations showed no signs of superimposed pulmonary thromboembolism or nosocomial infection.

The present case report describes the exceptional co-occurrence of disseminated cryptococcosis and active pulmonary TB in an otherwise healthy adult. This co-infection is almost always indicative of compromised cell-mediated immunity. Thus, its occurrence is very rare in immunocompetent individuals.[1,4]

Considering that disseminated cryptococcosis-defined by a positive culture from at least two different sites or a positive blood culture - is also a rare entity in healthy individuals.[3] our unique adult case presents all of these rarities.

Up to now several cases of TB-cryptococcosis co-infection has been reported, but based on our knowledge there is only one other similar case which describes concurrence of severe infection with Cryptococcus gattii and MTB (central nervous system and pulmonary involvement) without positive fungal blood culture in an otherwise healthy 18 years old university student and without any evidence of CD4 cell count disturbance.[1] In 2 other reports which have described the concomitant occurrence of pulmonary and meningeal tuberculosis (TB) along with meningeal cryptococcosis in a young otherwise healthy student[2] and C. neoformans meningitis in a HIV-negative miliary TB-suspected patient,[5] some degrees of CD4 cell count alteration was mentioned.

Patient's treatment failure firstly can be due to his delay in referring to hospital, as although his symptoms had been emerged 40 days before admission he referred when the signs related to superimposed hydrocephalus was developed, and secondly because of unavailability of effective antifungal drugs (liposomal amphotericin B and flucytosine) in our country.

In conclusion, to prevent delay in diagnosis and initiation of therapy, the present case report emphasizes the importance of taking into account more than one infection occurring simultaneously in patients without significant comorbidities or immunodeficiency.

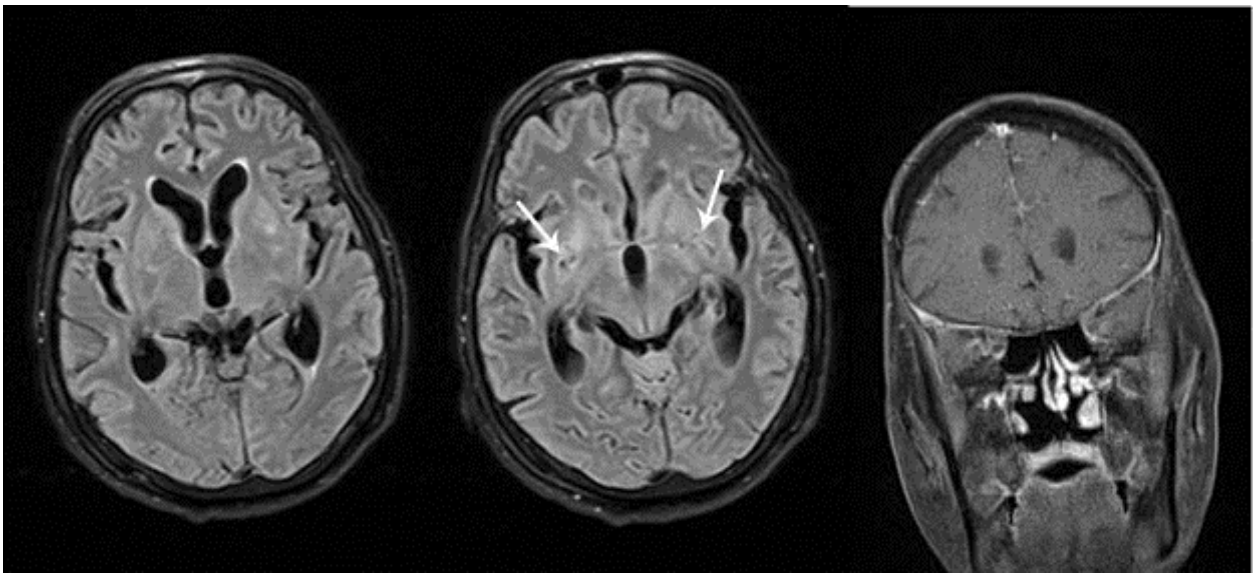

Figure 1. Brain magnetic resonance imaging (MRI) of the patient with cryptococcal infection shows bilateral enlarged perivascular spaces (white arrows) and basal ganglia hyperintensities in fluid-attenuated inversion recovery MRI along with bilateral mild basal leptomeningeal enhancement in contrast-enhanced MRI

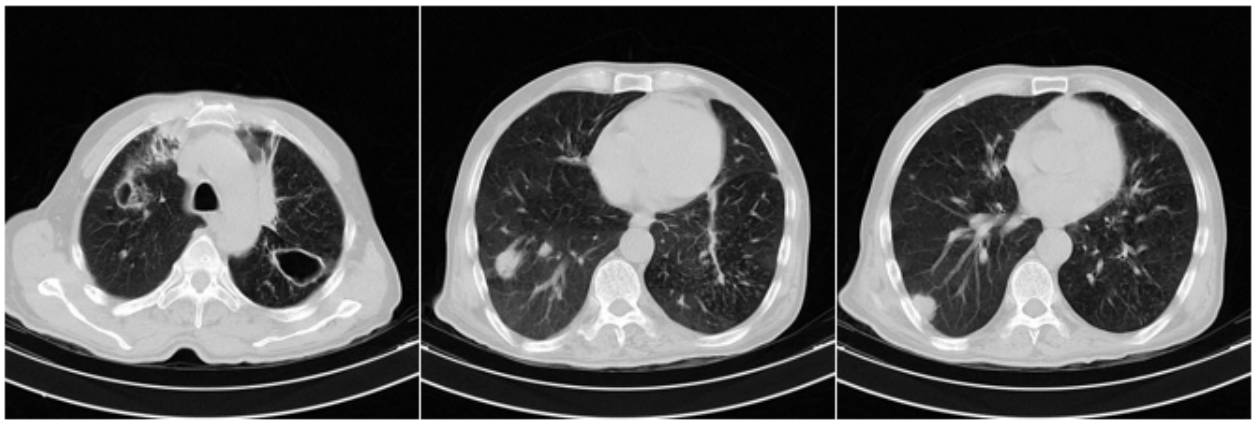

Figure 2. Chest computed tomography scan of our patient with positive bronchoalveolar lavage smear for tuberculosis and Cryptococcus neoformans show cavitations in both upper lobes along with bilateral multiple nodules

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We acknowledge all patients who accepted to participate in this study.

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Letter to Editor

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Wilson's disease presenting with unusual radiological features

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Keywords
Kayser–Fleischer Ring, Wilson Disease, Brain MRI, Ceruloplasmin, Copper

Wilson's disease (WD) is an inherited disorder of copper metabolism. It results in copper deposition in toxic concentrations in liver, brain, eye, etc. Radiological features in the form of extensive gray and white matter abnormalities are rare. Here we report a case of WD presenting with encephalopathy and unusual radiological features.

A 26-year-old male, born out of non-consanguineous marriage, presented with insidious onset difficulty in walking and sitting since 6 months and difficulty in speaking since 2 months. Patient was all right 6 months back, when gradual decline in academic performance and inability to carry out day-to-day activities with marked slowness was noticed. His past history was uneventful. There was no family history of similar complaints.

On general physical examination, he had stuporous look and vacant stare. He comprehended vocal commands but was unable to vocalize. Motor examination showed generalized dystonia, exaggerated deep tendon reflexes, and a positive bilateral Babinski's sign. The Kayser–Fleischer ring was visible on both sides by the naked eye, which was confirmed on slit lamp (Figure 1). On Abdominal examination, there was no hepatosplenomegaly. Chest and cardiac examination was normal.

On laboratory examination, complete blood count, total serum bilirubin, total serum protein, serum transaminases, and alkaline phosphatase showed no abnormalities. Viral serologies for human immunodeficiency virus, hepatitis B antigen, anti-hepatitis C virus Ab were negative. Upper gastrointestinal endoscopy was also within normal limits. His serum ceruloplasmin was decreased to 0.10 g/l (normal 0.20-0.60 g/l), serum copper level slightly raised to 141.25 g/dl (normal 70-140 g/dl), and his 24 h urine copper excretion was increased to 541.68 µg (normal 24 h urine excretion 20-50 µg).

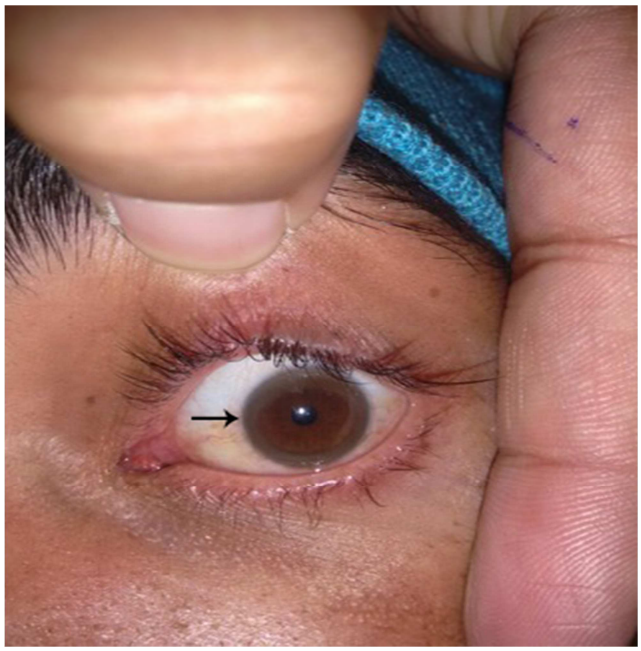

Figure 1. Kayser–Fleischer ring

His ultrasonography (USG) abdomen showed liver with coarse altered echo texture, portal vein diameter 10 mm at formation. Non-contrast computed tomography head showed hypodensity over bilateral white matter region. Findings on magnetic resonance imaging (MRI)

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brain revealed symmetrical hyperintensity on T2-weighted and fluid attenuated inversion recovery images over bilateral thalami, basal ganglia, claustrum, and dorsal mesencephalon with hypointensity at red nucleus. These hyperintense regions were hypointense on T1-weighted and diffusion weighted images. There was white matter T2 hyperintensity in the bilateral frontal white matter. There was gyriform enhancement in the bilateral frontal region. "Giant Panda face" sign was also present (Figure 2).

WD is an autosomal recessive disorder of copper metabolism. It is caused by a mutation in the copper transporting gene, ATP7B.[1]

An absent or a reduced function of the ATP7B protein leads to a decreased hepatocellular excretion of copper into bile. Copper first accumulates in the liver; after the liver storage capacity for copper gets saturated, copper gets redistributed, with accumulation in the nervous system, cornea, kidney, and other organs.[2] In WD with neurological presentations, the symptomatology is predominantly extrapyramidal, like dystonia, tremors, dysphasia, dysarthria, and ataxia. The neurological symptoms are secondary to cerebral copper deposition.

In the presence of typical neurological features, ophthalmological features, low serum ceruloplasmin, and increased 24 urinary copper levels. Liver biopsy is not required for the diagnosis of WD (Table 1).

In WD patients, abnormalities are noted in the gray matter of lentiform, caudate, and thalamic nuclei. Cerebral atrophy of frontal lobes and cerebellar atrophy have been described.[3] Our patient had gray matter abnormalities in bilateral thalami, pons, and red nucleus.

The gray matter abnormalities are manifested as hypodensities in computerized tomography head and as hypointensities on T1 and hyperintensities on T2 images of MRI brain. The findings on MRI brain can be due to underlying gliosis and necrosis.[3]

Our patient had extensive white matter abnormalities in bilateral frontal and parietal regions.

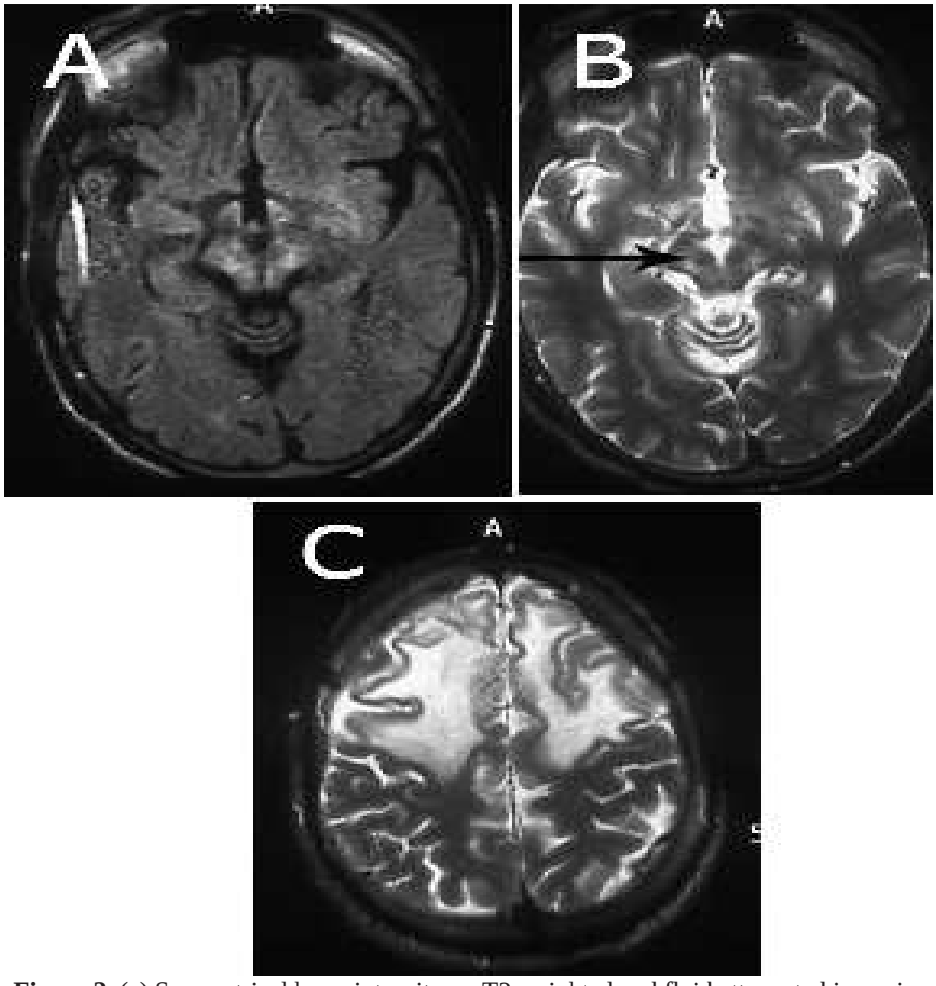

Figure 2. (a) Symmetrical hyperintensity on T2 weighted and fluid attenuated inversion recovery images over bilateral thalami, basal ganglia, claustrum, and dorsal mesencephalon, (b) giant Panda face, (c) T2 hyperintensity bilateral frontal white matter

Table 1. Diagnostic criteria for Wilson's disease as advocated by Steinlieb[4]

Low serum ceruloplasmin levels (< 20 mg%)
Kayser–Fleischer rings in eyes
High liver copper levels (> 250 µg/g dry wt)
High 24 h urinary copper levels (> 100 µg/d or > 1.6 µmol/d)
Radioisotope copper studies using 64Cu, 67Cu or 65Cu, which assesses ability to incorporate copper into ceruloplasmin

The white matter abnormalities can occur in both pyramidal and extrapyramidal systems and can be symmetrical or asymmetrical. The white matter areas that are predominantly affected are dentatorubrothalamic, pontocerebellar, and corticospinal.[5] These extensive white matter abnormalities are not common and are reported rarely in literature.

Conclusion

A high index of suspicion is required for WD while dealing with young adults with extrapyramidal signs and neurobehavioral abnormalities with typical neuroradiological features. The radiological features may also show extensive gray and white matter abnormalities. Hence, patients with WD should also be evaluated for these abnormalities.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Neurocinema: A brief overview

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Neurocinema, Consciousness, Cognitive Science

Abstract
Cinema is a multidimensional art capable of affecting our neurophysiologic structure in different ways. Studies show that different parts of the brain are activated while watching a structured film and consequently, the movie imitates consciousness structure. This imitation of the consciousness structure enables cinema to deeply influence the brain. The effect and its manner are the main themes of the newly-emerged science of neurocinema.

Introduction

Since the advent of cinema, it has always been considered by scholars working on the mind and its functions. Perhaps the earliest points on the relationship between the cinema and the brain were mentioned by Henri Bergson, the great French philosopher. He exemplified cinema explaining what goes on in the mind in the book "Matter and Memory." He tried to provide modern methods on thinking about movement through creating the concept of "movement-image."[1] In an intelligent theory proposed by Bertrand Russell, particularly when cinema was taking its first steps, he mentioned that cinema was the most important factor capable of destroying the free will. Russell truly referred to the effect of cinema on the mind and stated that many children learned about basic concepts of life like love, commitment, work, etc., through watching Hollywood movies and not by their free will and a thought unaffected by the elements of the modern world (such as cinema and modern education).[2] Thinking about the very theory, it might be surprising that one could have such an intelligent understanding of the cinema about a century ago. Following the development of the cinema, directors have tried to make a further influence on the audience's mind throughout this time. A clear example of the influence could be found in Hitchcock's movies. His movies create a complicated psychological atmosphere and keep the audience suspended; therefore, he takes the opportunity to escape from the mind of the audience. "Vertigo" or "Rear Window" are good examples of the Hitchcock's mentioned approach. Other great directors have their own methods of deeply influencing the mind of the audience. Would it be possible to watch Kurosawa's Rashomon or Ran and not be influenced? This will be extensively discussed. There are several movies which show the interest of the directors and scriptwriters in neurologic diseases that can serve as a topic for a separate article. However, the present article is trying to find a deeper expression of the relationship between the brain and cinema. How can cinema affect the brain and where is the limit? Is Russell's statement, a philosopher's warning or something rooted in the extraordinary nature of the cinema?

Cinema and Consciousness

Prior to commenting on the cinema and its relationship with the brain, we should learn about this phenomenon. According to Jean-Luc Godard, cinema is a multidimensional art using different complicated stimuli such as music, sound, and picture.[3] In addition to the mentioned stimuli, film editing has a significant role[4] as it integrates numerous pictures and sounds to provide a consistent structure. The combination of these factors creates a complicated phenomenon that can affect the mind of the audience multi-dimensionally.

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Perhaps one of the most considerable qualities of a movie is its flow. We are facing a series of events which are frequently and connectively targeting our minds like daily issues but with a purposeful and relevant structure. Is it possible to say that a filmmaking process copies and rebuilds the consciousness structure? In order to obtain a better understanding of the subject, consciousness, and its main qualities should be defined.

What is consciousness? Thomas Nagel answers this question in a short but very famous article entitled "What is it like to be a bat?"[5] Nagel considers the subjective state of an experience. In order to clarify what he means, Nagel exemplified a bat (What is it like to be a bat?). As he further explains, bats have a sensory, cognitive system different from "humans."

This sensory system based on reflection and echolocation enables the bat to recognize its surrounding world. It detects the distance, size, and form of an object in this way. Clearly, the system is quite different from the one that helps humans to know the external world. Nagel states that if this feeling is assumed as an experience by the bat, we should admit that there is something, and that is being a bat. In other words, Nagel holds that consciousness is tantamount to experience. What does the experience of seeing "red" look like? What does the experience of "smelling a flower" look like? This "look like" is determined by our consciousness. As Ned Block says, consciousness can be assumed a way through which we see, hear, or even experience the surrounding world.[6] Therefore, the conscious experience can be considered as recognizing a thing.[7] The consciousness plays an important role in our being as a human. Being exposed to a movie is a conscious experience because we are facing a multi-dimensional stimulator that can influence our cognitive abilities coherently and categorically. Indeed, the structural similarity of a movie to the concept of consciousness plays an important role.

In order to better understand the similarity, we need to study the formation of consciousness in humans from the point of neuroscience. According to the definition of William James, consciousness is a completely new concept. He refers to consciousness as a private, mental process that is continuous, purposeful, and unified[8] and transcendental thought and awareness are also formed in such settings. The definition implies that consciousness is not induced by the outer world although the process of learning is an important pillar of the mind; however, it is finally "we" or "the conscious self" who learns and learning should take place inside, or in other words, in our brain. Consciousness is not something separate from us.

Accordingly, a new window is opened to the manner of developing consciousness through neuroscience.

Gerald Edelman proposed the most important theory of consciousness in neuroscience. He believes that consciousness does not refer to the activity of a certain area of the brain or a specific type of neurons; instead, it is the result of a dynamic, fluid relationship between a vast range of neurons. The thalamo-cortical system is a major structure for conscious activity. The system is not only internally connected but is also linked to other parts of the brain. On the other hand, the content of our consciousness is associated with different parts of the cortex. Neuroscientifically, this complex system forms our consciousness power. However, Edelman goes beyond the system in describing consciousness and is seeking a theory based on natural selection to explain how it is formed. He believes that the brain is the result of evolution, and the consciousness theory should also be based on the Darwinian evolution. Consequently, he put forward the theory of Theory of Neuronal Group Selection (TNGS) or the theory of neuronal group selection according to which numerous different cycles are formed as connections between neurons and different areas of the brain. Then, natural selection and Darwinism determine the neuronal cycle that would remain. The selection is done through synapses and their capabilities. Paths and links with more positive input that are applicable in human experiences and their communication with the surrounding world have a higher chance of survival.[9] However, the gravity point of the TNGS theory as the generator of consciousness is a principle called the re-entry principle.[10] Re-entry is a kind of exchange; a fluid exchange of information through a vast range of parallel axonal systems that connects maps and cores of the brain in a mirror-like manner.[10] Consequently, a kind of synchronization is created among active cycles in all parts of the brain following the establishment of connections resulting from re-entry. Primary consciousness, like what is seen in more primitive organisms, turns into superior consciousness through a rich re-entrant activity between posterior and anterior parts of the brain with the ability to prioritize. This re-entrant activity is a neuronal basis for coordinating and creating what is called mental state or qualia.[10]

Edelman's definition clarifies that consciousness involves different parts of the brain in one single experience. This involvement is not only an anatomic event but also the regions activate in a sequential order and fluid form; this is what happens during watching a movie. As cited from Jean-Luc Godard, a movie is a multi-dimensional process with different elements influencing it. Every scene is a series of

pictures, sounds, music, and purposeful film editing; the scenes combine in a sequential order and create a fluid, unified ambiance, whose richness is a unique human experience, i.e., it associates a conscious experience with the mind. This is not just similarity but tests that confirm our hypothesis.

Cinema on neuroscience tests

The most important study conducted by Hasson et al. [11] examined the brain response and activity while watching a movie. He used fMRI in this study as well as a new method called "inter-subject correlation (ISC) analysis." Using this method, the degree of similarity in brain activities of different viewers could be measured, which plays an important role in neurocinematic study because important aspects of studying brain responses to a movie are not equal to a neuroscientific response, and reactions of a considerable number of viewers need to be investigated. This can also be interesting in filmography and for professional film critics. Why are the opinions of critics about featured movies similar? Why are viewers sometimes fascinated by a movie? Why are some scenes memorable?

The study performed by Hasson et al.[11] provides some answers to the questions. They showed that during watching movies like "The Good, the Bad, and the Ugly" as well as "Bang! You're Dead," ISC is remarkably higher when compared with scenes of everyday facts. This was also true in measuring the average eye movements of the viewers. The audience was free to look at any point while watching three different scenes. The study showed that eye fixation while watching the mentioned movies was considerably higher. The findings showed that a structured movie could significantly control the brain activity of the audience. In fact, ISC was high in a vast range of brain areas including the region related to vision, hearing, language perception (Wernicke's area), feelings, and emotions as well as multi-sensory areas. This confirms the previous discussion on the cinema and statements of the great director, Jean-Luc Godard, who refers to cinema as a multidimensional art. It was actually quite predictable that this multidimensional art could influence different areas of the brain. This is the origin of the most important similarity between the cinema and consciousness structure.

Role of cinema in transition and advancement of cognitive science

Cognitive Science Movie Index (CSMI) is a valuable collection of famous movies that showcase various aspects of cognitive science.[12] Motz properly pointed out that these movies could be tantamount to the cinematic examination of the mind.[12] However, CSMI does not take into account the cultural factors affecting cinematic reception of the mind and the presence of cognitive science in movies is considered just due to its scientific points. Nevertheless, all cultures have the potential to change the manner of arguing in the mind according to their requirements. I intend to introduce a few most remarkable Iranian movies and evaluate the role of cinema in determining the effect of culture on cognitive structures of the mind.

In recent years, despite the growing development of the Iranian cinema,[13] little attention has been paid to cognitive science. The Separation (2011) by Asghar Farhadi that won the Academy Award was one of the few Iranian movies that beautifully pictured Alzheimer's disease and its impact on people's lives. However, the impact of cognitive science on the Iranian cinema should be looked for in movies picturing internal conflicts of an Iranian individual that are undoubtedly an attribute of this cinema.

The identity of Iranian individuals has been influenced by the conflict between tradition and modernity. An Iranian person tries to find a relationship between a past loaded with historic honors, mysticism, and poem and the present world that is based on modernity and rationality; this conflict may sometimes create great conflicts in his mental and cognitive structures. Therefore, movies including similar issues would include the most important concepts of cognitive science for describing the mind of this individual. Ballad of Tara (1979) and Half Moon (2006) are simpler examples that show the contrast between two different worlds of historic past and mysticism and realities of the present world, respectively. This contrast practically brings about confusion for the (movie) hero. In a more thoughtful movie named Maybe Some Other Time (1987), a woman is after her past in her mind, and the search is full of nightmares and vague footprints in her memory. The movie demonstrates how nightmares and indistinct memories could change cognitive structures of the woman's mind. Yet, the most distinguished movie with this theme might be Hamoon (1990). Hamoon demonstrates the life of an Iranian intellectual depicting his internal conflicts and portraiting his fluctuations among faith and unbelief, love and hatred, and tradition and modernity. As he cannot make a rational relationship between them, the nightmares do not abandon him, his power of reasoning is impaired, and all his cognitive structures collapse.

Although the Iranian cinema does not purely peruse scientific issues, it can be considered a kind of a cognitive test showing how cultural issues can change cognitive structures of the mind, which reminds us of the theories of Levy-Bruhl[14] and Luria.[15]

CSMI can provide valuable opportunities for those interested in cognitive science to study the impact of culture on cognitive structures of the mind and also

offer a way for an inter-cultural conversation.

Future of neurocinema

It is now quite evident that neurocinema is opening a fascinating window in front of us. Perhaps the most important aspect of this study is to show the influence of cinema on the brain and its imitation of the structures of consciousness. This point has roots in the history and may even go further back to the prehistoric era. Studying the oldest animation of the world, currently preserved in the National Museum of Iran, explains this claim. The animation properly describes the present status of the cinema (Figures 1 a and b). A goat on a bowl approaches a tree in a few episodes and finally eats the leaves.[16] Before this, movement or movement-image, as mentioned at the beginning of the Bergson's article, was not a concern in human productions. A single image like what is seen in historic caves can stimulate different brain areas but can by no means remind the concept of movement in mind while what is seen on the Burnt City Bowl stimulates different parts of the brain at different stages and creates a kind of sequential order in the mind. This order, i.e., having one image or situation coming over another, reminds us of the concept of movement in the mind. It should be noted that this movement and, according to what was mentioned earlier, the continuous communication between one situation and another are the main principles of consciousness. The Burnt City's bowl could be considered as the first attempts of humans to control the mind, or in other words, the consciousness structure of the audience. Accordingly and in a historical approach, cinema is the effort of humans to manipulate and manage human consciousness, an effort that is continuously and seriously continuing. It seems that the application of new techniques has not only evolved the structure of the cinema but has also changed its effect on our mind and consciousness. Perhaps now, we can better understand the statements attributed to Bertrand Russell. What Russell refers to as the surprising effect of the cinema on our mind is not merely a moral concern but has roots in physiological bases of our brain and what is called neurocinema.

Conclusion

Neurocinema is a newly emerged field examining the relationship between the cinema and the brain. On the first look, the most superficial layer of the relationship includes several movies with the theme of various brain diseases; however, a deeper look suggests the manner in which the brain is influenced by the cinema on the one hand and the response of the brain to other movies on the other hand. Neuroscience is a powerful tool for studying phenomenon which can influence our mind and cinema is one of them. Neurocinema as a multidisciplinary science can help us to study the relationship between movies and minds. In addition, neurocinema provides a new field to create opportunities for planning tests to confirm or reject different hypotheses on cultural differences and brain functions in different cultures.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Figure 1. The first animation of the world (a and b)

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