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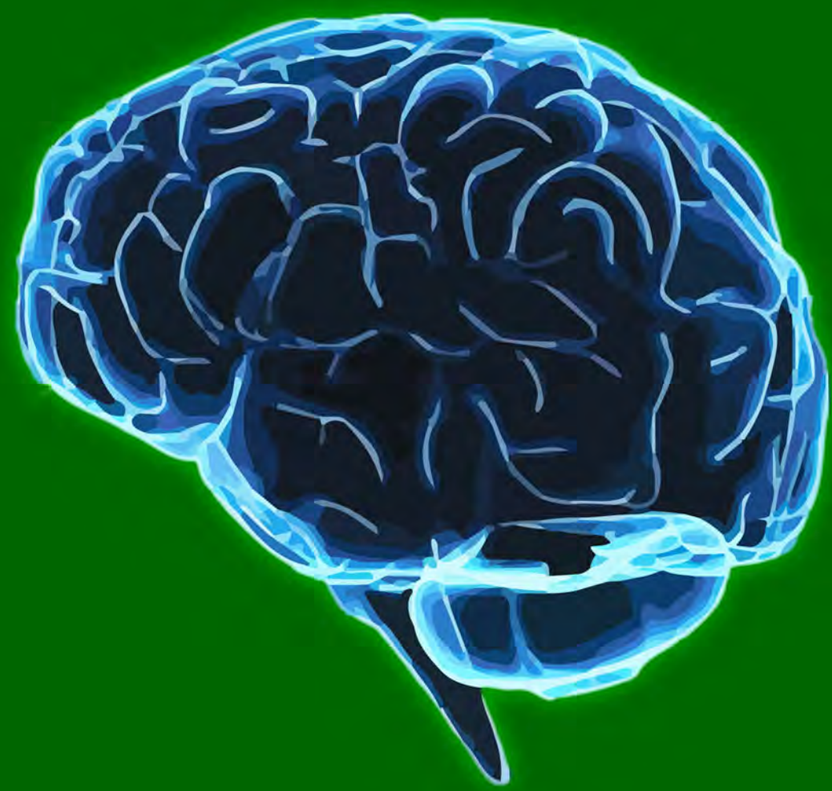

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Iranian Journal of Neurology

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

Details

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

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

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

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

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

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- Manuscripts should be submitted in 12 points, Arial font, with double line spacing and sufficient margins of 2.5 cm.
- The text should not be formatted.
- Each section of the paper should begin on a new page

The manuscript must include:

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

1. Title page:

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

2. Abstract page:

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

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

1. **Introduction:** The introduction should be as concise as possible and introduce the context of the paper to the reader; the paper should clearly state the research hypothesis and the objective of the study.
2. **Materials and Methods:** Description of the studied population or material should be detailed and include all information necessary to assess the reliability of results obtained in the study and/or allow the experiment to be repeated by other researchers; the section related to statistical analysis should have information on applied statistical tests and programs.
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In any time the evidence of plagiarism is detected, the manuscript will be withdrawn and the author will be sanctioned from publishing papers permanently.

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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Headache in relapse and remission phases of multiple sclerosis: A case-control study

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Keywords
Multiple Sclerosis; Headache; Relapse; Remission; Case-Control Studies

Abstract

Background: Headaches are one of the most frequent reasons for pain in multiple sclerosis (MS) individuals. Characterization of headaches and delineating possible relationships with MS-related determinants can ultimately circumvent headaches.

Methods: In a prospective case-control study, 65 Iranian relapsing-remitting MS (RRMS) patients and 65 healthy controls were recruited during patients' admission for attack-period treatment and asked about characteristics and co-symptoms of headaches they experienced in the preceding week and usage of disease modifying drugs (DMDs) and types of MS attacks were also inquired. The same questions were asked from the same patients 3 months later in a follow-up visit.

Results: A total of 57 patients and 57 controls were included in the final analyses. In total, 26 (45.6%) patients in relapse, 18 (27.7%) controls, and 22 (38.6%) patients in remission reported headaches and only significant difference existed between relapse patients and controls (P = 0.036). In headache prevalence was higher in patients in relapse phase having MS < 3 years compared to relapse patients with more than 3 years of MS (68 vs. 28.1%; P = 0.004). Other variables of interest did not differ among the three groups.

Conclusion: The RRMS patients in relapse phase suffer from headaches more than healthy people do.

Introduction

Amid the plethora of multiple sclerosis (MS) symptoms,[1,2] pain is vividly recalled by patients and apparently accompanies them throughout the entire disease period.[3,4] The latest systematic review considering prevalence of pain in adult MS subjects declared an overall prevalence of 63.0%; the most common instigator of pain in this meta-analysis was headache, with a prevalence of about 43.0%.[3] The very first documentation of headache occurrence in MS patients was revealed over 60 years ago.[5] Following this pioneer initiative, the association of MS and primary headaches has been commonly reviewed, and headache prevalence rates ranging from 4.0 to 76.3% have been acknowledged in MS patients.[2,6-19] Migraine without aura and tension-type headache (TTH) are the top two prevalent primary headaches seen in MS populations.[10,20] In addition, stabbing headaches are more commonly seen in relapses of relapsing-remitting MS (RRMS) subjects and migraine and TTH comprise most of the headaches experienced by RRMS individuals during remissions.[1,21] Of note, other types and manifestations of primary headaches such as

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cluster headache, migraine-like headache, cluster-like headache, and status migrainosus and also secondary headaches have been observed in MS patients.[6,7,10,22-25]

The sprouting of headaches during interferon-beta (INF-β) therapy has been cited by MS subjects as a major rationale for terminating INF-β use[26] and as RRMS patients are frequently given INF-β for their neurologic symptoms,[11] delineating the relationship between headache deterioration or establishment in RRMS and INF-β is important.

The emotional burden of headaches in MS patients is significant and those suffering from headaches throughout their disease period are likely entitled to a plunge in quality of life.[11,27,28] In particular, MS patients simultaneously affected by migraine will experience more symptoms of MS and eventually have poorer quality of life.[29,30] Furthermore, primary stabbing headache (PSH) has been proposed as a premonitory sign of acute demyelinating fallout in RRMS.[1,21,27] Consequently, rapid recognition and management of headaches in MS patients can potentially be of utmost importance. Studies evaluating headaches happening during relapses and remissions of RRMS and depicting the characteristics of these headaches and their possible relationship with different MS attack variants and factors such as depression and disease modifying drugs (DMDs) at the same time are scarce. Thus, in this current effort, we attempted to assess the prevalence of headaches during relapses and remissions of RRMS patients and define the attributes of these headaches and denote the possible interrelations between headaches and therapeutic determinants, co-symptoms such as depression and types of MS exacerbations.

Materials and Methods

A prospective study was initiated to assess characteristics of headaches in patients with RRMS visited in Sina Hospital (affiliated to Tehran University of Medical Sciences) in Tehran, Iran, between 2013 and 2015. Eligible patients for enrollment as case group included those with pre-existing MS experiencing an acute relapse of disease. The cases chosen were not randomly selected and were, in fact, available cases consecutively picked from the RRMS patients checking in for acute relapse treatment during the study period. Diagnosis of MS has been made according to the latest version of McDonald criteria.[31] Furthermore, diagnosis of types of headaches seen in MS patients and controls was in accordance with third edition (beta version) of the International Classification of Headache Disorders.[32] The control group was comprised of healthy individuals that were chosen consecutively and not randomly from people accompanying RRMS patients in the Neurology Clinic of Sina Hospital. These controls had no previous history of neurologic disorders such as MS, seizure and severe head trauma and were not affected by other chronic diseases such as hypertension, renal failure, etc. Individuals with these attributes were then asked if they suffer from headaches and if the answer was "yes," characteristics of their headaches would be entered in assessment forms and recorded. If the answer was "no," then only demographic data pertinent to them would be documented. Frequency matching was performed to have a control group similar to case group with respect to gender distribution and age (± 5 years). The study protocol was approved by the Ethics Committee at Tehran University of Medical Sciences and written informed consent was obtained from all study participants prior to enrollment.

Demographic information, current treatment protocol and DMDs used during the past 6 months were recorded. If patients were experiencing headache(s) during the past week, a predesigned structured questionnaire was used to record the features of the headache(s). The types of headaches documented were migraine, TTH or secondary headache. The severity of headache was assessed by a 10-point visual analogue scale (VAS), in which 1 indicates the lowest severity and 10 is considered as very severe headache. The VAS score was further categorized as follows: scores of 1, 2 and 3 were considered as mild, 4-7 as moderate and severe headache as VAS score of 8, 9 or 10. The quality of pain was recorded as compressing, pulsatile and stabbing. Patients were asked about the location of headache that could be orbital, frontal, occipital, vertex and a combination of mentioned sites. In addition, the presence of concomitant symptoms such as photophobia, phonophobia and nausea and vomiting were checked. Of note, the type of MS attack in relapse phase including blurred vision (optic neuritis), myelitis (spinal lesions), hemiparesis/hemihypoesthesia (hemispheric lesions) and symptoms such as ataxia, gaze palsy, crossed cranial nerve palsy and motor or sensory symptoms (brainstem and cerebellar lesions) was obtained from patients' files and recorded. Participants in the control group were also asked about any episodes of headache during the past 7 days and its features.

The following completion of the treatment protocol for acute relapse, patients were discharged and scheduled for a follow-up visit. The visit was set up for 3 months later to assess patients in remission phase of MS. Patients were excluded if they experienced any episodes of relapse during this period. The patients were requested to fill in the follow-up sheet questionnaire that included questions about headache

characteristics and any drugs consumed for headache prophylaxis or acute attacks. RRMS patients were also inquired about other non-DMD medications they took during remission period.

SPSS software for Windows (version 20, SPSS Inc., Chicago, IL, USA) was employed to perform the statistical analyses. Continuous variables are presented as mean and standard deviation and categorical variables are shown as percentage. The frequency of headaches was compared between case and control groups using chi-square and Fisher's exact tests both in baseline and follow-up visits. Within group comparison using McNemar's test was performed to evaluate any changes in the prevalence and characteristics of headaches in patients with MS during acute relapse and remission of the disease. $P < 0.050$ was considered as statistically significant in all tests.

Results

A total of 130 patients were enrolled (65 patients in each group). During the follow-up period, 8 patients in case group experienced another relapse attack and were excluded from the study and a total of 57 patients from case group were included in the final analyses. The median duration of disease was 4 years (interquartile range: 1.5-8.0). Baseline characteristics of study population are presented in table 1.

Among the patients in case group, 26 (45.6%) patients reported having headaches during the 7 days preceding admission for treatment of MS flare-up, of which 25 (96.1%) were females and 1 (3.9%) was a male. This number decreased to 22 (38.6%) patients in follow-up visit (remission). The corresponding figure in control group was 18 (27.7%) and out of the 18 control patients suffering from headaches, 4 (22.2%) were males and 14 (77.8%) were females. The frequency of headaches was significantly higher in patients with RRMS during relapse phase compared with control group ($P = 0.036$). Considering remission period, there were no differences comparing the mentioned figures between the study groups ($P = 0.247$). Taking headache-gender relation into account, no significant association was witnessed either in control ($P = 0.277$), relapse ($P = 0.132$) or remission group ($P = 0.0.87$).

Among patients with RRMS who experienced headaches during their relapses, the most common type of headache was migraine (n = 16, 28.1%) followed by TTH (n = 10, 14%). Most patients reported the severity and quality of their headaches as severe (22.8%) and compressing (28.1%), respectively. Fronto-orbital was the most common location of headache, as reported by 10 (17.5%) patients. Finally, 15 (26.3%) patients reported that they were experiencing photophobia and phonophobia concomitantly and 8 (14.1%) patients complained of nausea and/or emesis. In the control group, 12 (18.4%) of the headache sufferers were diagnosed with migraine and 6 (9.2%) of them had TTH. Furthermore, the majority of controls declared their headaches to be moderate and pulsatile (13.8 and 18.4%, respectively). In addition, most headache subjects in control group (n = 5, 7.7%) experienced frontal headaches. At last, 6 (9.2%) of the controls noted accompanying phonophobia and photophobia and 8 (12.3%) controls had nausea and/or vomiting as co-symptoms during their headaches. Comparing the participants in control group with headaches and RRMS patients in relapse phase with headaches, none of the aforementioned headache characteristics differed between the two groups significantly and this finding also held true for type of headaches and headache co-symptoms (all corresponding P values> 0.050).

Table 1. Baseline characteristics of study population

Characteristics	Case (n = 57)	Control (n = 65)
Age (mean ± SD)	31.84 ± 9.32	36.37 ± 11.34
Gender [n (%)]		
Male	8 (14.0)	10 (15.4)
Female	49 (86.0)	55 (84.6)
Educational level [n (%)]		
College graduate	13 (22.8)	12 (18.4)
High school diploma	22 (38.6)	30 (46.2)
Less than high school	9 (15.8)	17 (26.2)
Missing	13 (22.8)	6 (9.2)
Marital status [n (%)]		
Married	30 (52.6)	41 (63.1)
Single	15 (26.3)	16 (24.6)
Missing	12 (21.1)	8 (12.3)

SD: Standard deviation

About 3 months after the flare-up of the disease and during the remission period, the most frequent type of headache was still migraine type (26.3%), but the severity of the headaches decreased and 12 (21.1%) patients reported they were experiencing moderate headaches during the remission follow-up period. No major change was observed in the common location and quality of headaches during these 3 months. Detailed information regarding the features of headache attacks during relapse and remission phases in case group are presented in figure 1 (A-E).

Comparing features of headaches between the two phases via McNemar's test, no significant differences regarding type (P = 0.379), severity (P = 0.528), quality (P = 0.092), or location of headaches (P = 0.506) and presence of concomitant symptoms including photophobia and phonophobia (P = 0.669) or nausea and/or vomiting (P = 0.905) were detected. To be noted, none of the controls or RRMS patients who had headaches used preventive medication for headaches, but two controls (3.1%) and three MS patients (5.7%) encountered medication overuse headache (MOH). Moreover, five headache-positive RRMS patients (8.7%) and two headache-negative MS cases (3.5%) used anti-epileptics and anti-depressants (tricyclic anti-depressants) for pain and psychiatric purposes during remission phase, respectively.

Patients were divided into two groups based on the duration of disease; 32 (56.1%) patients were diagnosed with MS more than 3 years ago and 25 (43.9%) subjects were diagnosed during the past 3 years. Seventeen patients (68.0%) in the latter group reported headaches during flare-up of disease, which was significantly higher than the frequency of headaches among patients with disease-duration of more than 3 years (n = 9, 28.1%) (P = 0.004). Such association was not observed for the prevalence of headaches during remission phase (52.0 vs. 28.1%, P = 0.066).

Of the 26 RRMS patients who suffered from headaches during their relapses, 8 (14.1%) of them went through an optic neuritis flare-up, 10 (17.5%) subjects experienced hemiparesis/hemihypoesthesia, 4 (7.1%) individuals faced brainstem or cerebellar symptoms during their flare-up and 4 (7.1%) patients suffered a myelitis attack. For their no-headache MS counterparts, the following numbers were seen: nine patients (15.8%) with blurred vision at attack, 14 (24.6%) individuals with hemispheric lesions at relapse, 7 (12.3%) subjects with cerebellar and brainstem lesions at flare-up and 9 (15.8%) patients with myelitis at exacerbation of MS. Ultimately, there was no significant correlation between a specific type of MS attack and headache prevalence (P = 0.273).

From the DMD perspective, four RRMS patients stated that their headaches got worse after INF-β treatment [1 used Ziferon (INF-β 1b), 2 treated with ReciGen (INF-β 1a) and 1 consumed CinnoVex (INF-β 1a)] (Iranian version of Betaferon, Rebif and Avonex). On the other hand, none of the MS patients using fingolimod or glatiramer acetate (GA) noticed headache exacerbation after DMD therapy.

Another finding that should be mentioned is that in one of the RRMS patients, exacerbation of a pre-existing migraine headache was the possible first presentation of MS, as it forced the patient to seek medical care and led to the diagnosis of MS in that patient.

Discussion

Nowadays, the notion that headaches of different types are associated with MS has gained acceptance and this specifically goes for migraine.[21] Nevertheless, the properties of this association still remain vague. Scientists have delved into the enigmatic pathophysiological and epidemiological relationship between headaches and MS and most of these efforts have been made in the area of migraine and MS. About half a century ago, Watkins et al. carried out a case-control study in which they demonstrated that MS subjects are 2 times more likely to have positive family history of migraine compared to healthy controls.[16] Zorzon et al.[33] confirmed this finding as they too declared that people with migraine running in their family have a higher chance of developing MS.

In the early 90s, when three MS individuals experienced migraine during MS flare-up, serotonin was incriminated for bridging the gap between MS and migraine; serotonin was implicated earlier before in migraine pathology and as MS patients were already "out of" serotonin, serotonin perturbations could have possibly played a role in MS attacks.[34] Simple co-morbidity of headaches like migraine and MS is another elucidation in the headache-MS path.[19,30,33] Another piece of evidence for common ground between MS and headaches is the drop in circulating T8 lymphocytes in both settings.[35,36] Pregnancy is another part of the thread between MS and migraine, as both pregnant migraineurs and pregnant MS patients enjoy a less debilitating course of disease during pregnancy.[37] In the mid-2000s, neurologists laid out an explanation for migraine-MS interrelationship; they suggested that migraine, especially migraine with aura, switches on particular matrix metalloproteinases that in turn destruct the blood-brain barrier and render myelin autoantigens vulnerable to autoreactive T-cells present in the bloodstream and this process can ultimately culminate in MS.[38,39] Furthermore, migraine episodes and MS attacks apparently share common cytokine profiles.[19,40] Common genetic and environmental determinants present in MS, migraine and TTH are also on the agenda of headache-MS association.[8]

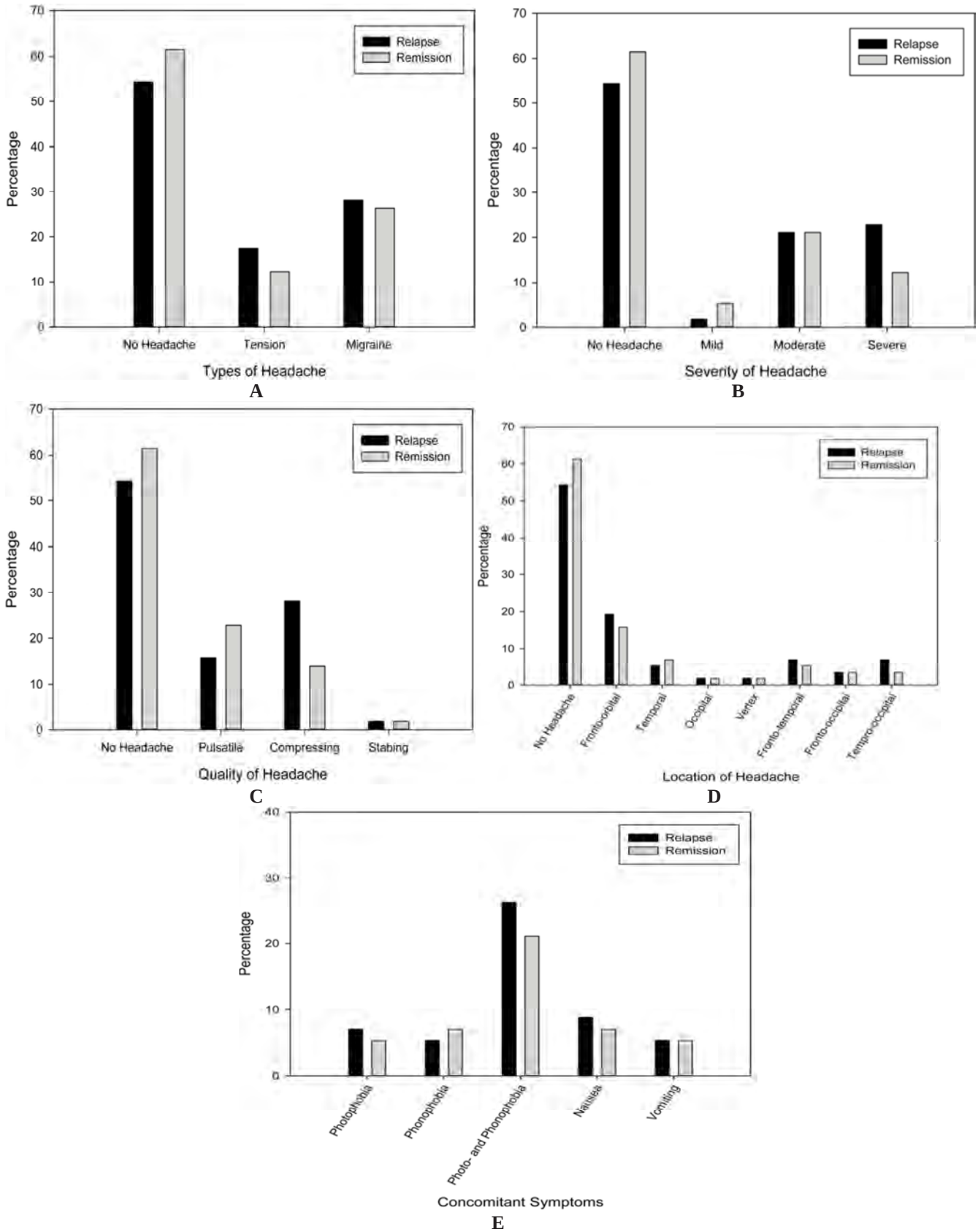

Figure 1. Features of headache attacks during relapse and remission phases among patients with relapsing-remitting multiple sclerosis, (A) Types of headache, (B) severity of headache, (C) quality of headache, (D) location of headache, (E) concomitant symptoms

The prevalence rate of headaches in relapse and remission subsets of our study was 45.6% and 38.6%, respectively, which is in accord with the last systematic review on headaches in MS patients, that announced a crude headache prevalence rate of 42.5% in MS patients.[3] However, two distinct studies in the past 7 years have manifested high headache prevalence numbers in RRMS populations, i.e., 74.7% (83 RRMS subjects) and 76.3% (118 RRMS patients), in order.[14,15] In this current study, we showed that our RRMS patients confronted headaches in their relapse phases significantly more frequent than the controls did. On the contrary, RRMS patients failed to retain this significance in remission period, although they did encounter headaches more often than controls. Furthermore, headache prevalence rates in relapse and remission time periods were comparable in our effort. Ergun et al.[1] conducted a study in which they assessed headaches in two separate sets of relapse phase and remission phase-RRMS patients and they declared that a significantly higher proportion of RRMS patients in remission period complained of headaches compared to their relapse phase-RRMS counterparts (73.5 vs. 38.9%, respectively).

The difference witnessed between the prevalence rates of their study and ours can be explained by the fact that the number of subjects in relapse and remission in their study were approximately a half and a third of ours, respectively, and this subsequently lowers the power of their study. Furthermore, their relapse and remission patients were two distinct groups of people, but our relapse phase-RRMS patients were the same ones assessed in remission period. Therefore, intervening factors related to different sets of patients could have skewed the results of Ergun et al.'s study.[1] In addition, no healthy controls took part in their study.

Taking types of headaches into account, no significant difference was observed comparing those in remission and relapse and controls; more than 60.0% (28.1% of all RRMS patients in relapse) of headaches in our relapse period were of migraine type and the rest were TTHs and the percentage of migraineurs in remission and control subsets was 68.0 and 66.6%, respectively. Conversely, PSHs (27.8%) constituted most headaches seen in relapse patients of Ergun et al.'s study,[1] with migraine and MOH counting for 11.1 and 5.9% of patients in relapse, in order.

However, the distribution of types of headaches in remission was similar to ours (i.e., migraine 41.2% and TTH 20.6% of patients). Two distinct RRMS cohorts reported prevalence of migraine to be 49.8 and 34.1%, in order, and 27.17% of subjects in the latter group were diagnosed with TTH.[41,42] In a questionnaire-based study carried out in 2013, 46% of 673 MS patients announced that they were battling with migraine and migraine headaches significantly accompanied RRMS patients.[4] Villani et al.[14] and D'Amico et al.[6] have also demonstrated a significant association between RRMS and migraine headache.

In a meta-analysis performed by Pakpoor et al.,[28] MS patients displayed an over two-fold increment in likelihood of acquiring migraine headaches compared to controls. In addition, a cross-sectional study showed that the chance MS patients have for confronting co-morbid migraine is trice than controls.[30] Contradictory to these studies, two different case-control studies[13,19] carried out stated in 2007 and 2009 non-significant difference between MS cases and controls regarding headache type distribution. Katsiari et al.[43] also noticed no significant correlation between exacerbations of MS and other autoimmune diseases and different categories of headaches.

Considering severity and quality of headaches, most of our RRMS patients in relapse had severe and compressing headaches, which were alleviated by remission and turned into moderate headaches in that period. Nevertheless, no significant difference with regard to these factors existed when controls and patients in remission and relapse were compared and this insignificance was replicated when assessing photophobia/phonophobia, nausea and/or vomiting and location of headaches in the groups. With the aid of a questionnaire, Tabby et al.[27] indicated that headache-related pain in their 72 MS patients was throbbing, stabbing or sharp most of the times and bilateral headaches were more common than unilateral ones. In Moisset et al.'s survey[4] most MS patients notified the researchers that their headaches were moderately painful.

In the study of Moisset et al.[4] patients who were diagnosed with MS < 15 years before the time of study had a higher probability of having migraine. In our current effort, we also showed that RRMS patients in relapse phase with shorter disease-duration (< 3 years) were more prone to headaches than those coping with RRMS for more than 3 years. Of note, we did not detect this significant relationship in subjects in remission. One explanation for this finding could be that MS patients are less neurologically-disabled in their first years and therefore, pay more attention to headaches compared to those suffering from more neurological-related disabilities that prevent them from correctly detecting the presence of headaches. From another point of view, the neuro-inflammation played out in the first couple of years of RRMS could possibly explain the association between RRMS and headache occurrence in these years.

Our results indicated that most of the RRMS

patients, with or without headaches, experienced optic neuritis attacks in relapse. However, no significant association between type of attack (and subsequently site of involvement by MS lesions) and headache prevalence was found. In a cohort of 127 Japanese MS patients, no significant correlation between brainstem-spinal, optico-spinal, and conventional MS clinical variants and headache prevalence was detected.[7] In the aforementioned Ergun et al. study,[1] total headache occurrence was significantly linked to periventricular lesions, TTHs happening in remission were more frequently associated with lesions involving the spinal cord and overall headache incidence in relapse was significantly intertwined with brainstem lesions. In a retrospective research, Gee et al.[44] declared that MS patients with lesions found in the periaqueductal grey (PAG)/midbrain area are more likely to suffer from migraine-like headaches and TTHs. Several case-reports have revealed a possible association between brainstem and PAG MS plaques and migraine incidence[45,46] and several other have demonstrated a link between cluster headache occurrence and MS lesions infiltrating trigeminal nerve entry zone in the brainstem.[22,47]

More than a decade ago, speculations were made regarding the role of DMDs in exacerbating headaches in MS patients[12] and current scientific evidence points out a significant positive correlation between emergence of new headaches or worsening of old headaches in MS patients and INF-β treatment.[42,48-50] In a recent report, novel fingolimod usage in MS patients has been linked to the happening of new headaches.[51] Natalizumab was another DMD investigated in this regard and Villani et al.[48] announced that it does not make comorbid migraines worse in those suffering from MS. In addition, researchers have claimed that GA does not significantly increase the frequency or severity of headaches in MS subjects who already have headaches.[12,52] An important limitation that we faced, in our study, was that patient information regarding use of DMDs was incomplete and many of them did not use these medications on a regular basis and although four patients using INF-β mentioned exacerbation of headaches after this kind of therapy and not a single patient experienced aggravation of their headache post-GA and fingolimod consumption, proper statistical evaluation was not possible.

Headache can be the presenting symptom of MS, as we have also showed in this study. Therefore, prompt intervention at headache onset in MS patients with contrast-enhanced magnetic resonance imaging could reveal novel plaques and if so subsequent pulse of methylprednisolone can prevent an ensuing MS relapse.

Conclusion

We suggest that RRMS patients in relapse phase suffer from headaches more than the general population does and those who complain of headaches in relapse phase have probably been diagnosed with RRMS in the preceding 3 years.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Case fatality rate and disability of stroke in Isfahan, Iran: Isfahan stroke registry

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Keywords
Stroke; Case Fatality Rate; Disability Evaluation; Epidemiology; Risk Factors

Abstract

Background: Few investigators have reported case fatality and disability of Iranian patients with stroke. This study was designed to collect morbidity and case fatality data of hospitalized patients with stroke, and stroke care quality in Isfahan, Iran.

Methods: From 2006 to 2011, from overlapping sources (discharge diagnoses, attending physicians, and hospitalization wards), all hospitalized patients with possible strokes were enrolled in the study, their hospital records were summarized by experienced personnel and reviewed by a neurologist with stroke experience. Patients were followed by phone calls or visited to their addresses and their 28th day functional status was checked by translated modified Rankin Scale (mRS). Forms and methods were derived from the World Health Organization (WHO) Monitoring Trends and Determinants in Cardiovascular Disease and STEPS projects.

Results: A total of 9487 patients were identified to suffer from stroke. Their ages' mean was 68.98 ± 13.63 years, and 50.0% were females. In hospital, case fatality was 16.5% and the 28th day case fatality was 25.6%. The greatest case fatality was among intracerebral hemorrhage (ICH) patients and the least among ischemic stroke (IS) ones. Case fatality was greater among female and older patients and those with the previous history of stroke. Among survivors, only 26.9% were functionally independent (mRS < 3) which was the greatest among subarachnoid hemorrhage (SAH) patients and least among ICH patients. None of the patients were admitted to specific stroke units or received thrombolytic therapy.

Conclusion: The hospitalized patients with stroke in Isfahan have unfavorable outcome compared with their mates in developed countries. A low quality of stroke care may be responsible, and urgent attention is needed.

Introduction

Stroke is the second most common cause of death worldwide at the beginning of the 21st century and caused approximately 10.0% of the total deaths.[1,2] Regional differences in stroke incidence have been reported, including the existence of a stroke belt in some countries, but causes of these disparities have not yet been fully understood.[3]

One of the most sophisticated measures to reduce stroke case fatality and morbidity is stroke unit. It is an area inside of a hospital where physicians, nurses, and other assisting personnel who have high-quality training and experience in stroke management, provide care for patients. Management of acute stroke in this type of medical facility has been shown by several studies to reduce death and disability by

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approximately 20.0% and improve patients' chance of recovery and independent living.[4] Unfortunately, there are few established stroke units in Iran at the present time.

Ischemic stroke (IS) and intracerebral hemorrhage (ICH) are the two most common types of stroke. Right now, we do not have any specific treatment for ICH, and intravenous administration of tissue plasminogen activator (tPA) is the only Food and Drug Administration (FDA)-approved therapy for IS. However, few patients benefit from tPA administration because of the limited time window (first 3.0-4.5 hours after symptoms onset) in which tPA benefits outweigh its side effects (hemorrhages).[5]

Studies about stroke epidemiology in Iran are scarce. No published study has reported disability outcome of Iranian patients with stroke. Few published studies have reported case fatality among Iranian hospitalized patients with stroke, who were among the greatest reported.[6,7] In two other cross-sectional, hospital-based studies conducted in Qom, a well-known religious city of Iran, the case fatality rate within the 1st month was reported at 24.6% in 2001 and at 15.3% in 2006-2008. Although, these figures showed an apparently declining rate over time in that region but were still more than western countries' and less than other developing countries'.[8-12]

This study was designed to collect morbidity and case fatality data of hospitalized patients with stroke, and the frequency of tPA use and hospitalization in specific stroke units in all hospitals that admit such patients in Isfahan, Iran.

Materials and Methods

Isfahan is the third largest city in Iran. Its metropolitan population is about 2000000 inhabitants and < 15.0% of them live in rural areas. Like other parts of the country, it has a young population, with about 55.0% of the population younger than 30 years.

From 2006 to 2011, 6 hospitals were mainly admitting patients with stroke in Isfahan, and none of them had stroke unit. Three of them had specific neurology wards, and all had general Intensive Care Units (ICU). In hospitals without neurology wards, patients with stroke were mostly hospitalized in internal medicine wards.

According to the World Health Organization (WHO) definition, stroke is a clinical syndrome characterized by rapidly developing neurological symptoms and/or signs, focal and at times global [applied to patients in deep coma and those with subarachnoid hemorrhage (SAH)], with symptoms lasting more than 24 hours unless interrupted by surgery or leading to death, and with no apparent cause other than that of vascular origin.[13] This definition includes stroke due to cerebral infarction (IS), ICH, intraventricular hemorrhage, and SAH; it excludes subdural hemorrhage, epidural hemorrhage, or ICH or infarction caused by infection or tumor. With this clinical definition, silent stroke on imaging is not considered a stroke, and imaging confirmation is not required for stroke diagnosis. Hence, the study is based on clinical diagnoses, which have been shown to be reliable.[14]

The WHO Monitoring Trends and Determinants in Cardiovascular Disease[7,14] project is related to events, not persons. Events are classified as first or recurrent and as fatal or nonfatal. A period of 28-day was used to define the case fatality rate and to distinguish between events. Diagnostic criteria were applied to symptoms, clinical findings and investigations undertaken within 28 days of onset. Transient ischemic attacks and events associated with trauma, blood disease or malignancy were not included.[14] Events were categorized as "definite stroke," "not stroke" or "unclassifiable." Only definite stroke events which fulfilled the criteria when the available information permitted a clinical diagnosis were included in the study.

Procedures are different according to how events are identified and registered: based on their admission to hospital "hot pursuit" or by utilization of post-discharge records to obtain patient's information retrospectively "cold pursuit".[15,16] A cold pursuit method has been used in this study: records of patients, who were hospitalized in either neurology or other departments under the complete or partial supervision of neurologists in Isfahan hospitals, were evaluated for possible signs and symptoms of stroke events. Search for potential stroke records was done by overlapping methods: looking through discharge diagnoses (stroke, cerebrovascular accident, ICH, SAH, vertebrobasilar insufficiency (VBI), cerebral venous thrombosis, and transient ischemic attack); looking through records by name of attending, and looking through records by wards of hospitalizations. Apart from the main mentioned 6 hospitals, patients who possibly had stroke during hospitalization and were discovered by surveillance department personnel [myocardial infarction (MI) surveillance unit] were included in the registry. All potential stroke records were evaluated by one experienced health personnel member who has continuously been under education in this regard. She summarized proper records in special checklists which were evaluated by a stroke fellow (one of the authors) to see if stroke

was the diagnosis, and to determine stroke type (IS, ICH, SAH, unknown). Because Isfahan city is the center of Isfahan province, its hospitals have a referral from other cities of the province.

All hospitalized patients who were discharged alive were followed by their address or by telephone. The patients or their close family members were asked about the patients' health status. If a patient had died during the first 28 days after the event, a death scenario was questioned, and she/he was pretend to have died because of stroke only if other etiologies, such as a motor vehicle accident could be ruled out. In the follow-up interview, patients' functional status was questioned by use of translated modified Rankin Scale (mRS).[17]

The term "stroke hospital admission rate" refers to both first and recurrent events. T-test was used for comparison of means, and chi-square test was used for comparison of proportions. Multiple regression was used to control confounding and extraneous variables' effects. All the analysis was done with SPSS software (version 20, SPSS Inc., Chicago, IL, USA).

Results

A total number of 10191 patients with primary diagnoses of stroke were recorded from 2006 to 2011. However, only 9487 (93.1%) patients met our stroke diagnostic criteria, and the rest were either labeled with other diagnosis (4.6%) or stayed unknown (2.3%). 9446 (99.6%) of patients were hospitalized and managed in the main 6 hospitals. Stroke subtypes were classified by the results of computed tomography (CT scan) done on patients presenting with stroke symptoms. Stroke verified cases constitute the sample of further analysis.

Patients' demographic data are summarized in table 1. More than 50.0% of patients were males; mean age was 68.98 ± 13.63 around 69 with the youngest 13 and the oldest 114 years old. While SAH patients were the youngest group with their mean age about 14 years less than total average, patients with IS were the oldest ones. More than 85.0% of them were coming from urban areas, especially Isfahan city. Stroke subtypes are also shown; 79.6% of stroke events were of the ischemic type.

In hospital, case fatality rate for all types of stroke was 16.5%. Table 2 shows potential confounding factors' effect on in hospital case fatality. Stroke subtype significantly affected in hospital case fatality rate ($P < 0.001$), with the greatest rate (33.9%) among patients with ICH. Patients who got dead were about 3 years older ($P < 0.001$), and death happened a little, although statistically significant, more in females ($P = 0.042$). Likewise, the rate was more among subjects with positive stroke history ($P = 0.002$). When all the above variables were put in a logistic regression (Table 3), sex was not further a significant risk factor of in hospital case fatality rate. The strongest risk factor was stroke subtype.

The follow-up was successful in 83.0% of cases in different years. Compared with patients with successful follow-up, missed patients were a younger (66.82 ± 14.29 vs. 69.44 ± 13.45, $P < 0.001$), were less positive in history of stroke (23.2 vs. 26.7%, $P = 0.004$), and had the same sex frequencies (50.6 vs. 48.0% were female, $P = 0.006$). Furthermore, missing was less seen among ICH patients (15.0%) than among ischemic (17.7%) or SAH (18.6%) ones ($P = 0.003$).

Table 1. Stroke subtypes and patients demographic data in Isfahan hospitalized patients with stroke, from 2006 to 2011

Variable	Stroke			Subtypes
	Ischemic	ICH	SAH	
Total [n (%)]	7548 (79.6)	1628 (17.2)	183 (1.9)	9487 (100)
Sex [n (%)]				
Male	3893 (51.7)	838 (51.6)	76 (41.8)	4881 (51.4)
Female	3639 (48.2)	787 (48.4)	106 (58.2)	4586 (48.3)
Age (years) (mean ± SD)	69.77 ± 13.12	66.75 ± 14.52	54.96 ± 16.65	68.98 ± 13.63
Min	14	13	18	13
Max	114	110	113	114
Settlement [n (%)]				
Urban				8089 (86)
Isfahan city	4820 (64.3)	893 (55.4)	99 (55.3)	5916 (62.9)
Other cities	1658 (22.1)	449 (27.8)	51 (28.5)	2173 (23.1)
Rural				1322 (14)
Isfahan city area	341 (4.6)	77 (4.8)	6 (3.4)	426 (4.5)
Other cities areas	673 (9.0)	194 (12.0)	23 (12.8)	896 (9.5)

Figures in parentheses indicate percentages.
ICH: Intracerebral hemorrhage; SAH: Subarachnoid hemorrhage; SD: Standard deviation

Table 2. Potential confounding factors' effect on case fatality rate among Isfahan stroke hospitalized patients, from 2006 to 2011

Variable	In hospital	P	28th-day	P
All stroke subtypes [n (%)]	1534 (16.3)	< 0.001	1984 (25.6)	< 0.001
Ischemic	940 (12.5)		1318 (21.2)	
ICH	551 (33.9)		620 (44.8)	
SAH	43 (23.5)		46 (30.9)	
History of previous stroke [n (%)]		0.002		0.001
Negative	1052 (15.5)		1363 (24.3)	
Positive	438 (18.2)		578 (28.2)	
Sex [n (%)]		0.042		0.006
Male	758 (15.6)		986 (24.2)	
Female	784 (17.2)		1013 (27.0)	
Age (year) (mean ± SD)		< 0.001		< 0.001
Alive	68.39 ± 13.68 (n = 7881)		68.08 ± 13.43 (n = 5831)	
Dead	71.96 ± 13.06 (n = 1542)		73.37 ± 12.71 (n = 1999)	

ICH: Intracerebral hemorrhage; SAH: Subarachnoid hemorrhage; SD: Standard deviation

Table 3. Multiple logistic regressions of in hospital and 28 days case fatality odds on potential risk factors

Variable	In hospital case fatality			28 days case fatality		
	OR	P	95% CI of OR	OR	P	95% CI of OR
Age (centered on 70)	1.03	< 0.001	1.02-1.03	1.04	< 0.001	1.04-1.05
Female sex	1.11	0.09	0.98-1.24	1.14	0.018	1.02-1.27
Type of stroke		< 0.001			< 0.001	
SAH versus ischemic	3.40	< 0.001	2.37-4.89	3.13	< 0.001	2.14-4.56
ICH versus ischemic	4.04	< 0.001	3.55-4.60	3.65	< 0.001	3.20-4.16
Positive history of stroke	1.29	< 0.001	1.14-1.47	1.27	< 0.001	1.13-1.43

OR: Odds ratio; CI: Confidence interval; SAH: Subarachnoid hemorrhage; ICH: Intracerebral hemorrhage

The 28 days case fatality rate of Isfahan stroke hospitalized patients was 25.6% and is shown in table 2. Confounding factors' effects were the same as in hospital case fatality: ICH had the greatest case fatality and case fatality was more in females, elders, and subjects with previous strokes. Furthermore, when all the above variables were put in a logistic regression, stroke subtype was the strongest risk factor, although sex remained significant.

Table 4 shows functional disability of survivors and its associated factors. Of all the patients who were alive after stroke at 28th day, only 26.9% had mRS < 3 (Table 4). The outcome was affected by stroke subtype and the previous history of stroke; about 50.0% of SAH subjects were functionally independent (mRS < 3), while only 15.0% of subjects with the previous stroke were. Male subjects had somehow better functionality than female ones. Moreover, patients with mRS < 3 were in average 7 years younger than patients with mRS ≥ 3. All the above variables were put in a logistic regression to see which one explains more of the variance in the functional independence; stroke history was the most powerful followed by stroke subtype (ICH) (Table 5).

Among subjects who were functionally independent before their strokes, 34.2% still had mRS < 3 on the 28th-days after the strokes. SAH patients had the best outcomes; with 60.0% of alive held mRS < 3 on day 28 after their strokes, followed by ischemic (34.5%) and ICH (27.8%) ones (P < 0.001).

Table 6 shows the distribution of sex and age in the study sample in comparison with one study performed in Brazil and another in the USA with the same methodology of patient recruitment as ours.

Discussion

In this study, 9487 patients with stroke were enrolled from Isfahan's hospitals, over a period of 5-year. In hospital, case fatality rate in this study was 12.5% for ischemic and 33.9% for ICH stroke subtype which were considerably more than a similar study conducted with 56969 patients enrolled in the USA, yielding an overall case fatality rate of 6.8%, 5.7% case fatality for IS, and 22.7% case fatality for hemorrhagic strokes.[18] On the contrary, our findings had a resemblance to a recent study which was done with 2407 patients evaluated in Brazil. The overall in hospital case fatality rate was 20.9%, IS case fatality rate was 17.0%, and ICH case fatality rate was 34.1%.[19] The stroke subtype 28 days case fatality in our study reached 21.2% for IS and 44.8% for ICH. These percentages can be compared to the 28 days

case fatality rates in low and middle-income countries classified by the World Bank for IS at 16.7% and ICH at 38.7%.[20] Although about 17.0% of our patients were lost in their follow-ups, there was a little clinically significant difference between groups with successful and unsuccessful follow-ups: for example, there was only 2.7% difference in missing rate between ICH and ischemic patients. Furthermore, in hospital and 28 days death variables that had different missing proportions (in hospital death had 0.5% missing data while 28 days death had 17.0% missing data) had nearly the same odds ratios with presumed risk factors in logistic regressions. This is another piece of evidence that missing in our study might be non-biased and did not affect our results.

Table 4. Potential confounding factors' effect on functional outcome at 28th day among Isfahan stroke hospitalized patients, from 2006 to 2011

Variable	mRS < 3 (total)	P	mRS < 3 (if pre-stroke mRS < 3)	P
All stroke subtypes [n (%)]	1573 (26.9)	< 0.001	1569 (34.2)	< 0.001
Ischemic	1339 (27.4)		1335 (34.5)	
ICH	157 (20.6)		157 (27.8)	
SAH	51 (49.5)		51 (60.0)	
History of previous stroke [n (%)]		< 0.001		
Negative	1309 (30.8)			
Positive	230 (15.6)			
Sex [n (%)]		0.001		
Male	886 (28.7)			
Female	683 (24.9)			
Age (year) (mean ± SD)		< 0.001		
mRS < 3 (n = 1569)	62.62 ± 14.59			
mRS ≥ 3 (n = 4262)	70.09 ± 12.38			

SD: Standard deviation; mRS: Modified Rankin Scale; ICH: Intracerebral hemorrhage; SAH: Subarachnoid hemorrhage

Table 5. Multiple logistic regressions of functional independence (MRS < 3) at day 28 among survivors of stroke

Variable	In hospital case fatality		
	OR	P	95% CI of OR
Age (centered on 70)	0.96	< 0.001	0.96-0.97
Male sex	1.29	< 0.001	1.14-1.46
Type of stroke		< 0.001	
SAH versus ischemic	1.28	0.250	0.84-1.95
ICH versus ischemic	0.52	< 0.001	0.43-0.64
Positive history of stroke	0.45	< 0.001	0.38-0.52

OR: Odds ratio; CI: Confidence interval; SAH: Subarachnoid hemorrhage; ICH: Intracerebral hemorrhage; mRS: Modified Rankin scale

Table 6. Comparison of Isfahan hospitalized patients with stroke, from 2006 to 2011, with Brazil's and USA's

Variable	Brazil	USA	Iran
Age (mean ± SD)			
Total	67.70 ± 14.40	69.6 ± 0.1	68.98 ± 13.63
Ischemic	69.14 ± 13.60	-	69.77 ± 13.12
ICH	62.70 ± 14.90	-	66.75 ± 14.52
Sex (female) (%)			
Total	51.8	53.3	48.3
Ischemic	50.1	-	48.2
ICH	47.5	-	48.4
Previous history of stroke (%)			
Total	42.9	-	18.2
Ischemic	46.2	30.7	-
ICH	33.3	20.3	-

ICH: Intracerebral hemorrhage

This greater in hospital and 28th day case fatality rate in our study relative to developed countries could be due to differences in stroke severity in admission. However, it could reflect using low-quality standards for the care of patients with acute stroke. These may include significant delays in hospital admission, diagnosis, and evaluation with neuroimaging, the absence of thrombolytic use for

ISs, and lack of stroke units for treatment of patients.

Table 6 shows our study sample sex and age distribution in comparison with Brazil's and USA's, which are nearly the same.[19,20] This excludes confound effect of age and sex in the differences seen among the countries. Since the factor of the previous history of stroke was significantly less frequent in our study, it could not also explain the greater case fatality observed in Iran. The fact that hospitalized patients were a source of recruitment in the three studies excludes a difference in study methodology (population-based vs. hospital-based) as a potential explanation for studies' findings.

Independent factors associated with early functional outcome were investigated using the MRS (range 0-6, 6 denotes death and was excluded for this analysis). This analysis demonstrated five factors: ICH stroke subtype, pre-stroke disability/dependency, positive history of previous stroke, older age and female sex, which were strongly associated with a poor functional outcome (MRS ≥ 3) at the 28th day post stroke. Furthermore, another factor explaining this finding might be the differences in medical care in Iran, which are different than in the most developed countries. Indeed, none of our study patients were managed in a stroke unit which might contribute to an increased case fatality and poor functional outcome, and hence necessitate the use of early interventions. Stroke units are a highly evidence-based approach shown to improve outcomes after stroke. A systematic meta-analyses investigating stroke units showed 18.0% reduction in the risk of case fatality and dependency.[20] One of the major limitations to the implementation of stroke units in Iran is the restricted availability of stroke specialists as well as technical and financial limitations. Other possible obstacles are a deficiency in health resources, considering stroke as not being a prior health problem, and inadequate health personnel training.

Strengths of our study are prospective collection of data from all hospitals in Isfahan, successful follow-up in more than 83.0% of patients and acquisition of functional status in the follow-up. However, our study is a non-population-based one, and it did not cover patients with stroke who were not hospitalized. Other limitations were the use of hospital records to get patients' history and risk factor profiles, and lack of magnetic resonance imaging for all possible ISs with normal CT scans.

Conclusion

The global impact of stroke in Iran, similar to other low and middle-income countries, is taking a disproportionate toll on its people. This study of 9487 patients with stroke from Isfahan's hospitals highlights the great early case fatality and disability due in part to the lack of stroke units. Standards of care were limited by lack of local resources and evidence. Opportunities for simple, inexpensive interventions to improve outcomes or reduce recurrent stroke and case fatality should be identified. In future work, we hope to facilitate implementation of widely accepted, and locally feasible, standards of care through building stroke units that have the potential to reduce the burden of stroke in Iran and other neighboring nations facing this problem.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Persian version of frontal assessment battery: Correlations with formal measures of executive functioning and providing normative data for Persian population

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Frontal Lobe; Executive Function; Outcome and Process Assessment; Mental Status; Persian; Iran

Abstract

Background: Cognitive impairment in patients with Parkinson's disease (PD) mainly involves executive function (EF). The frontal assessment battery (FAB) is an efficient tool for the assessment of EFs. The aims of this study were to determine the validity and reliability of the psychometric properties of the Persian version of FAB and assess its correlation with formal measures of EFs to provide normative data for the Persian version of FAB in patients with PD.

Methods: The study recruited 149 healthy participants and 49 patients with idiopathic PD. In PD patients, FAB results were compared to their performance on EF tests. Reliability analysis involved test-retest reliability and internal consistency, whereas validity analysis involved convergent validity approach. FAB scores compared in normal controls and in PD patients matched for age, education, and Mini-Mental State Examination (MMSE) score.

Results: In PD patients, FAB scores were significantly decreased compared to normal controls, and correlated with Stroop test and Wisconsin Card Sorting Test (WCST). In healthy subjects, FAB scores varied according to the age, education, and MMSE. In the FAB subtest analysis, the performances of PD patients were worse than the healthy participants on similarities, fluency tasks, and Luria's motor series.

Conclusion: Persian version of FAB could be used as a reliable scale for the assessment of frontal lobe functions in Iranian patients with PD. Furthermore, normative data provided for the Persian version of this test improve the accuracy and confidence in the clinical application of the FAB.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by gradual impairment of affective, cognitive, and motor function.[1] Although motor symptoms such as resting tremor, bradykinesia, rigidity, and postural instability are the hallmark of this disorder, cognitive, and psychiatric non-motor symptoms are equally

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disabling and directly impact the quality of in PD patients.[2]

Recent reports show that even after controlling for duration and severity of motor symptoms, cognitive abilities, such as executive and visuospatial functions, remain as the main problem in management of PD.[3]

Executive functions (EFs) consist of higher order processes including working memory, reasoning, task flexibility, and problem-solving as well as planning and execution.[4,5] The identification of executive dysfunctions is useful for diagnosis and prognosis of brain diseases.[5]

Frontal assessment battery (FAB) was designed as a fast and efficient bedside battery to detect frontal lobe dysfunction in a variety of patients.[6] FAB is divided into six subtests, each one assessing an "executive" function thought to be subserved by the frontal cortex.[4]

FAB has been largely used in several groups of patients such as Alzheimer's disease,[7] frontotemporal dementia,[8] PD,[9] Huntington's disease,[10] and other conditions.[11]

Oguro et al.[12] have demonstrated the FAB sensitivity to differences in the executive dysfunction profiles of Alzheimer's and vascular dementia patients (patients with vascular dementia had the worst performance).

Normative data have also been provided for healthy population samples. Studies showed that in healthy participates FAB were influenced by age and education (they were lower as age increased and education decreased).[13,14]

There is no information about the correlation of the FAB with formal measures of EF for screening executive dysfunctions in Iranian patients with idiopathic PD.

Aims of this study were to determine the validity and reliability of FAB in Iranian patients with PD and to establish normative data derived from a healthy sample of the Persian population.

Materials and Methods

Among 76 patients diagnosed as idiopathic PD who were being followed up in the Shohada-e-Tajrish Hospital's, Movement Disorders Clinic from 2012 to 2014, 49 patients (31 men and 18 women) were included in this study. PD diagnosis was made on the basis of the UK Brain Bank Criteria.[15]

The normative study involved 149 (86 men and 63 women) healthy subjects, who were among the caregivers of patients, and also among people who attended the hospital for a routine check-up.

All patients and controls were from various regions of Iran who were referred to our hospital. None of the participants had a current or past history of alcohol or drug abuse, current depression or psychiatric diseases, history of traumatic brain injury, neurological illness, or other reported conditions that could affect mental state as assessed by an individual clinical interview.

Those who had < 5 years of education, those with Mini-Mental State Exam (MMSE)[16] < 24, and other differential diagnoses of parkinsonism were excluded through neurologic examinations and radiologic evaluations.

Translation of FAB into Persian: FAB has been validated for PD,[5-17] showing high correlation with classic frontal neuropsychological tests and significant differences between patients and controls.[18-20] Functional brain imaging studies have shown significant correlation between FAB performance and perfusion in the medial and dorsolateral frontal cortex.[21]

FAB takes about 10 minutes to be administered and can be applied by any practitioner. It consists of six subtests: conceptualization (similarity), mental flexibility (fluency), motor programming (Luria motor series), sensitivity to interference (conflicting instructions), inhibitory control (Go-No-Go Task), and environmental autonomy (prehension behavior). Each subtest is scored between 0 and 3; a composite score ranging between 0 and 18 indicates whether or not executive dysfunction is present and, if yes, indicates the severity.

The FAB was adapted from the original English version into Persian.[5] The battery was first translated independently by five persons with an advanced understanding of English. Different translations were combined by two independent experts, minor inconsistencies solved, and a preliminary version was produced. After that, the consensus version was then back-translated into English by another person fluent in the both languages and was then compared conceptually with the original text.

According to our pilot study, a linguistic adaptation was made in one of the subtests: the letter used in the original lexical fluency subtest, "S," was replaced by "B," which is as frequent in Farsi as "S" is in English. This is because in Persian language there are different words with "S" sound that might be confusing especially for people with lower levels of education. After reaching consistency for all verbal instructions and performing some pilot administrations, the final version of the Persian FAB was wrote.

Patients were tested in the "on" state when the medication minimizes or eliminates motor symptoms. After a brief clinical interview and collection of demographic features, unified PD

Rating Scale,[22] MMSE, Stroop test, Wisconsin Card Sorting Test (WCST),[23] and the Persian version of FAB were applied to all patients.

Healthy participants were tested individually by a neurologist. As for PD patients demographic features, MMSE and the Persian version of FAB were administered. To determine the reliability of this study, the FAB results were compared with those of the Stroop test and WCST, which are sensitive to frontal lobe functions; and the frequently used the MMSE, which assesses the general cognitive functions. Internal consistency, inter-rater reliability (n = 28), and test-retest reliability (n = 29) were examined to test reliability of Persian version of FAB. Moreover, convergent validity was used in examining the validity of the Persian version of FAB. In the convergent validity approach, non-parametric correlations of simultaneously applied FAB and Stroop test, FAB and WCST and FAB and MMSE tests were calculated. It is expected that these comparisons would indicate a relationship because the Stroop test and WCST assess frontal lobe functions, as does the FAB.

This study was approved by the Shahid Beheshti University of Medical Sciences Ethics Committee, and patients included in this study gave their informed consent to participate.

The SPSS software (version 19, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Cronbach's alpha was used to test the internal consistency, and the intraclass correlation coefficient was used for inter-judge reliability and test-retest reliability. In both tests, a score close to 1 indicates higher reliability. Pearson and Spearmen correlation tests were used for the correlation of FAB scores with age, education, and MMSE as appropriate. $P < 0.050$ were considered statistically significant.

Results

The demographic features of patients with PD and healthy participants are shown in table 1. Internal consistencies of FAB scores in PD patients and in the control group are 0.68 and 0.53, respectively. High alpha values were obtained in both control groups and patients with PD. Statistically significant consistency [r = 0.89; 95% confidence interval (CI): 0.72-0.95] was observed in the test results conducted monthly. High intra-rater reliability rate was also found (r = 0.90).

Concurrent validity was analyzed by calculating partial correlations between scores on the FAB, MMSE, WCST, and Stroop test (Table 2). Means and standard deviations (SD) of the total FAB scores stratified by age and education, for healthy participants are presented in table 3.

Table 1. Demographic features of Parkinson's disease patients and healthy participants

Variable	Groups				P
	PD (n = 49)		Healthy participants (n = 149)		
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
Age	61.73 ± 9.13	39-80	59.32 ± 8.01	48-81	0.700
Education	9.65 ± 3.36	7-14	11.30 ± 2.23	7-14	0.510
Sex (Male/Female)	31/18		86/63		
FAB	12.96 ± 2.93	7-18	15.680 ± 1.701	13-18	< 0.001*
MMSE	28.02 ± 1.38	28-29	28.19 ± 1.47	25-30	< 0.001*
Disease duration	6.3 ± 3.1	1-15	0	0	-
UPDRS (I-III)	45.29 ± 18.62	10-96	0	0	-

*P < 0.050 significant

FAB: Frontal assessment battery; MMSE: Mini-Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; PD: Parkinson's disease; SD: Standard deviation

Table 2. Concurrent validity of frontal assessment battery, Stroop test, Wisconsin Card Sorting Test, and Mini-Mental State Examination

Tests	Groups	
	PD patients (n = 49)	Healthy participants (n = 149)
Stroop duration	-0.286*	-0.314*
Stroop error number	-0.384*	-0.280*
Stroop error correction	-0.405*	-0.385*
WCST number of categories	-0.373*	-0.271*
WCST perseverative errors	-0.408*	-0.324*
MMSE	-0.708*	-0.628*

*Pearson correction coefficient (all comparisons are significant at level of P < 0.050)

WCST: Wisconsin Card Sorting Test; MMSE: Mini-Mental State Examination; PD: Parkinson's disease

Table 3. Mean total frontal assessment battery scores by age and education for the healthy sample

Education (years) (mean ± SD)	Age (year)			
	30-49	50-69	70-89	Total
1-4	14.1 ± 5.7	13.4 ± 3.4	12.3 ± 4.6	13.2 ± 1.4
5-8	14.8 ± 1.3	14.1 ± 2.4	13.2 ± 2.8	14.3 ± 2.1
9-12	16.1 ± 2.5	15.7 ± 2.1	14.9 ± 7.1	15.8 ± 6.4
> 12	16.7 ± 4.1	16.6 ± 6.7	15.8 ± 4.9	16.6 ± 3.4
Total	15.7 ± 6.2	14.6 ± 4.9	13.8 ± 4.7	15.0 ± 1.7

SD: Standard deviation

Table 4. Frequency distributions of the scores in the single subtests of the frontal assessment battery for the healthy participants (n = 149)

Score	Subtests [n (%)]					
	Similarity	Fluency	Luria's motor series	Conflicting instructions	Go-No-Go task	Prehension behavior
0	0 (0.0)	10 (6.7)	7 (4.6)	3 (2.0)	13 (8.7)	0 (0.0)
1	12 (8.0)	19 (12.8)	23 (15.4)	34 (22.8)	16 (10.7)	0 (0.0)
2	76 (51.0)	59 (39.6)	56 (37.5)	53 (35.5)	24 (16.1)	0 (0.0)
3	61 (40.9)	61 (40.9)	63 (42.3)	59 (39.5)	96 (64.4)	149 (100)

Table 5. Frequency distributions of the scores in the single subtests of the frontal assessment battery for Parkinson's disease patients (n = 49)

Score	Subtests [n (%)]					
	Similarity	Fluency	Luria's motor series	Conflicting instructions	Go-No-Go task	Prehension behavior
0	7 (14.3)	9 (18.4)	1 (2.0)	4 (8.2)	2 (4.1)	0 (0.0)
1	10 (20.4)	19 (38.8)	2 (4.1)	6 (12.2)	7 (14.3)	0 (0.0)
2	26 (53.1)	16 (32.7)	9 (18.4)	18 (36.7)	19 (38.8)	0 (0.0)
3	6 (12.2)	5 (10.2)	37 (75.5)	21 (42.9)	21 (42.9)	149 (100)

A multiple regression analysis was performed to check the influence of demographic variables and MMSE score in normal participants. Total FAB scores were taken as the dependent variable and age, gender, education, and MMSE total score as independent variables. The resulting regression model excluded gender; age, education, and MMSE could explain 41.6% of the total variance of the FAB [$R^2 = 0.513$; $F_{(4,143)} = 28.42$, $P < 0.010$]. There was a strong positive effect of education [coefficient = 0.489, t (143) = 4.85, $P < 0.050$], a negative effect of age [coefficient = −0.386, t (143) = −2.143, $P < 0.010$], and a positive effect of the MMSE score [coefficient = 0.708, t (143) = 2.43, $P < 0.010$]; thus, FAB results are lower in older and less educated subjects with lower MMSE scores.

Table 4 reports the frequency distribution of the scores in each FAB subtest. Three of them, i.e., similarities, fluency, and Luria motor series, were the most discriminative. By contrast, all subjects had the maximum possible on prehension behavior. The distribution of the subscores as well as of the total score is skewed toward higher values.

The performance of PD patients on the FAB subtests is shown in table 5. As for normal controls, a multiple regression analysis was calculated to check the influence of age, education, and MMSE on the total FAB scores. The regression model excluded gender, but it included age, education, and MMSE. It could explain 40.5% of the total variance [$R^2 = 0.375$; $F_{(4,47)} = 5.21$, $P < 0.002$]. There was a negative effect of age [coefficient = −0.386, t(47) = −2.29, $P < 0.030$], a positive effect of the MMSE score [coefficient = 0.708, t(47) = 4.23, $P < 0.040$], and education [coefficient = 0.489, t(47) = 2.49, $P < 0.030$]. As with normal controls, mean FAB scores were negatively correlated with age and positively with education and MMSE.

Even after adjusting for age, education, and MMSE, which were entered as covariates in an ANCOVA, PD patients obtained lower total FAB scores than normal controls [PD patients = 12.8 vs. normal controls = 14.9; ANCOVA, $F_{(1,199)} = 15.9$, $P < 0.010$]. This result indicates the good discriminant validity of the FAB.

Table 6 shows the mean values of FAB subtests in PD patients and healthy participants.

Discussion

Impairments in EF and learning in PD patients are due to deficient dopaminergic input from the basal ganglia to the prefrontal cortex.[24]

Previous studies showed that there are independent parallel loop circuits between the basal

Table 6. Mean values of frontal assessment battery subtests in Parkinson's disease patients and healthy participants

Subtests	Groups		P
	PD patients (n = 49)	Healthy participants (n = 149)	
	Mean ± SD	Mean ± SD	
Similarity	1.63 ± 0.88	2.33 ± 0.62	< 0.050*
Fluency	1.35 ± 0.90	2.15 ± 0.88	< 0.050*
Luria's motor series	2.67 ± 0.65	2.17 ± 0.65	< 0.050*
Conflicting instructions	2.14 ± 0.93	2.13 ± 0.83	0.920
Go-No-Go task	2.20 ± 0.84	2.47 ± 0.88	0.660
Prehension behavior	2.86 ± 0.50	2.94 ± 0.23	0.120

*P < 0.050 significant; SD: Standard deviation

ganglia, cerebral cortex, and thalamus. This connection could affect by dopamine deficiency during PD.[25]

In the striatum, sensorimotor, cognitive, and limbic regions can be distinguished, based on their connections with the cerebral cortex.[26,27] It has been suggested that dysfunction in the caudate nucleus connection with dorsolateral prefrontal cortex, and the lateral orbitofrontal cortex is contribute to the cognitive impairment in PD.[28,29]

EFs are among the most frequently described cognitive changes in patients with PD. These functions refer to principles of cognitive organization and mental processes involved in the changing situations of daily life.[30,31]

The FAB is a simple scale for the assessment of EFs, which has not yet been validated in Iran. This study examined the applicability of the FAB in Persian population with PD. FAB scores in PD patients were lower comparing to healthy participants. It indicates that this battery has good discriminant validity. Furthermore, significant correlations were obtained between results on the FAB and on the other measures of EFs, which indicate that the FAB has good concurrent validity. Good internal consistency, measured by Cronbach's alpha in PD patients and healthy participants, was found as well.

This study found a positive correlation between MMSE and FAB scores in healthy individuals and in the patients with PD.

The study by Dubois et al.[6] did not find high correlation between FAB and MMSE scores, but a positive correlation was reported by Kenangil et al.[32] in patients with PD, by Kugo et al.[33] in cases with dementia, by Tunçay et al.[34] in patients with Alzheimer's disease, Schizophrenia, and PD, by Castiglioni et al.[35] in cases with Alzheimer's disease and frontotemporal dementia, by Lima et al.[9] in healthy individuals and cases with PD; and by Beato et al.[36] in healthy individuals. This could be explained by the weak distinctiveness and discriminant validity of FAB as well as the assessment of some frontal functions through MMSE. However, the relationship of the cognitive functions of FAB with general measurements and further data, such as sub-group analysis of MMSE, are required to clarify the relationship between FAB and MMSE.

In some previous studies age and educational level did not have any effect on the FAB scores.[5-33] However in others and in the present study, FAB scores in healthy participants and participants with PD were found to be positively correlated with education and negatively correlated with age.[9-38] In our study, FAB score in healthy participants and PD patients were found positively correlated with education level and negatively correlated with age. These findings support those of previous studies and emphasize the importance of these two factors in neurocognitive assessment.

For example, in the study by Kugo et al.,[33] they found the higher FAB scores in comparison with the control group of Mok et al.'s study.[37] One reason of this result may be the relatively low educational level and advanced age of the Mok et al. group.[37]

Another probable reason of differing results may be linguistic and cultural differences. For example, FAB scores that reported in the control cases of Kenangil et al.[32] and Lima et al.[9] were lower than FAB score in the control group of original study that was conducted in French.[5]

It was also observed that the FAB subtests are not equally discriminative, the finer ones being similarities, fluency, and Luria's motor series (Table 6). Similarities and fluency were also found to be the most discriminative by Appollonio et al.[13] The least discriminative was prehension behavior, a subtest that aims to evaluate environmental autonomy. This subtest has rarely elicited a score lower than 3 in healthy participants, and in clinical groups such as Alzheimer's disease.[12-14]

Another goal of this study was to establish the concurrent validity of Persian version of FAB for use with Iranian PD patients. FAB scores were significantly correlated with a number of categories and perseverative errors in the WCST, Stroop error correction, and Stroop error number. These

correlations strongly indicate that the Persian version of FAB does measure EF, and it has good concurrent validity.

Conclusion

FAB scores of the PD patients were lower comparing to the healthy population. This study concludes that the Persian version of FAB could be used as a reliable scale for the assessment of frontal lobe functions, giving helpful information for the diagnosis of this disease and for evaluation of cognitive decline in Iranian patients with PD. Furthermore, we provide a normative data for Iranian healthy populations that improve accuracy and confidence in the clinical use of the FAB.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Original Paper

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Effects of fasting during Ramadan on cerebrovascular hemodynamics: A transcranial Doppler study

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Keywords
Fasting; Cerebrovascular Circulation; Transcranial Doppler; Blood Flow Velocity

Abstract

Background: To determine whether Islamic fasting would change cerebral blood flow during Ramadan.

Methods: The study group comprised 20 subjects (16 males and 4 females) on a regimen of 1 month food and water intake restriction, according to Islamic fasting ritual. Subjects were evaluated for cerebral bolo flow through a middle cerebral artery (MCA) by means of transcranial Doppler (TCD), the day before starting Ramadan fasting and the day after the month of Ramadan.

Results: Our results showed no statistically significant changes after Ramadan in cerebrovascular hemodynamic, in comparison before Ramadan.

Conclusion: Although some studies showed metabolic changes during Ramadan fasting (increasing hematocrite, decreasing amount of hemoglobin, dehydration, platelet aggregation, and lipid profile alternations) the findings suggest that Islamic fasting has no significant effects on cerebral blood flow.

Introduction

The Islamic ritual of fasting during the month of Ramadan requires Muslim to abstain from eating, drinking, and smoking during the hours of daylight.

During the daylight hours of Ramadan fasters undoubtedly get dehydrated. Several measures have been used to give estimates of hydration status of individuals, including a significant increase in hematocrite, serum albumin and serum creatinine indicating dehydration due to water deprivation.[1]

Ramadan fasting led to decrease in the platelet aggregation factors [adenosine 5'-diphosphate (ADP) and collagen] it also causes an increase in bleeding time (BT) and coagulation time.[2]

Hence, we decided to determine whether Islamic fasting which causes hemodynamic and metabolic blood changes has any significant effect on brain hemodynamics. According to the literature review most of the previous studies either evaluated metabolic alterations due to fasting or blood components fluctuation furthermore, none of them have decelerated fasting effects on brain hemodynamic. Thus, our study was designed to perform this evaluation in fasters. We aimed to measure the impact of blood alternations due to fasting on cerebrovascular hemodynamics through middle cerebral artery (MCA) velocity by means of transcranial Doppler (TCD). We hypothesized that fasting will result in decreased MCA peak systolic velocity (PSV), pulsatility index (PI) and resistance index (RI) by two mechanisms: a decrease in

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hematocrit and an improved lipid profile, which are immediate and late effects of fasting, respectively.

Materials and Methods

An observational study was performed in Firoozgar Academic Hospital affiliated with Iran University of Medical Sciences (IUMS), Tehran, Iran, between June 2012 and July 2012. The study protocol was approved by Research Committee of IUMS, and the ethical standards set out in the Helsinki Declaration of 1975.

Duration of fasting was about 16 hour, with average climate of 36.4 °C and 40.0% humidity in Tehran. The mean number of consecutive fasting was 28 ± 2 days. A total number of 20 volunteer, (16 male and 4 female) with a mean age of 33.50 ± 9.16 year (range: 21-55 year). Inclusion criteria included healthy persons who indicated that they were going to fast during Ramadan, with general good health and no taking medications for chronic disease. Exclusion criteria included any chronic or acute disease, taking medications, cigarette smoking. Furthermore, none of the female subjects were pregnant or using contraceptive pills.

A consent form was taken from all the recruited cases and referred to the Neurology Laboratory of Firoozgar Hospital. After recruitment of participants a day before beginning Ramadan, and the day after finishing Ramadan, TCD was performed for all of the cases to measure blood flow velocity of both right and left MCAs. All the TCD measurements were performed by the same experienced neurologist. Cerebral blood flow was estimated by 2 MHz TCD ultrasound probe (Atys-Looki, France).

The probe fixed over the temporal window to insonate the proximal segment of MCA (M1). Once the optimal signal-to-noise ratio was obtained, the probe was covered with an adhesive ultrasonic gel and secured with a headband device (Multigon) to maintain optimal insonation position. Optimization of the Doppler signals from the MCA was performed by varying the sample volume depth in incremental steps and at each depth, varying the angle of insonance to obtain the best-quality signals from the Doppler frequency. The depth of recorded parameters was the same in pre and post TCD measurements. Both right and left MCAs velocities were monitored reporting the main indexes including PSV, end diastolic velocity (EDV). Consequently, other indexes such as PI and RI were calculated using the following formulas:

PI = (PSV-EDV)/Mean flow volume
RI = (PSV-EDV)/PSV

Qualitative and quantitative variables were described by frequency percentages, mean and standard deviation (SD), respectively. Collected data were subjected to statistical analysis using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Data distribution was assessed by the Kolmogorov-Smirnov test in all groups; the Mann-Whitney U-test and paired sample t-test were used on occasion, to evaluate the statistical significance of differences before and after Ramadan. A $P < 0.050$ was considered to be significant. Data were presented as mean ± SD [95% confidence interval (CI)].

Results

About 20 healthy volunteers male/female (80/20) the mean age of subjects was 33.5 (range 21-55 years, SD = 9.16). None of demographic, baseline was significantly different between our subjects except for age ($P < 0.001$). All data were normally distributed in each group according to the Kolmogorov-Smirnov test.

TCD findings of right and left MCAs were compared between before and after Ramadan fasting, PSV, EDV, PI, RI were all similar before and after fasting (Tables 1 and 2). Hence, there were no significant correlation between velocity indices before and after Ramadan fasting [the mean (95% CI), Figure 1].

Discussion

To our knowledge, there are no reports on the effect of Islamic fasting on cerebrovascular hemodynamic. In this study, Ramadan fasting caused no significant fluctuations on brain blood flow velocity indices, which is in favor of low risk for cerebrovascular events.

Table 1. Comparison of transcranial Doppler findings of left middle cerebral artery between before and after Ramadan

Velocity index	Before Ramadan	After Ramadan	P
PSV (cm/s)	79.70 ± 13.38	78.10 ± 13.62	0.570
Range	(51-104)	(56-106)	
EDV (cm/s)	34.45 ± 9.20	39.85 ± 9.90	0.610
Range	(24-69)	(21-65)	
RI	0.56 ± 0.70	0.55 ± 0.92	0.490
Range	(0.33-0.67)	(0.26-0.66)	
PI	0.94 ± 0.20	0.55 ± 0.92	0.830
Range	(0.62-1.60)	(0.26-0.66)	

PSV: Peak systolic velocity; EDV: End diastolic velocity; RI: Resistance index; PI: Pulsatility index

Table 2. Comparison of transcranial Doppler findings of right middle cerebral artery between before and after Ramadan

Velocity index	Before Ramadan	After Ramadan	P
PSV (cm/s)	78.25 ± 13.58	83.65 ± 16.65	0.530
Range	(0.59-1.05)	(58-125)	
EDV (cm/s)	34.40 ± 8.71	35.50 ± 8.62	0.590
Range	(0.24-0.69)	(24-58)	
RI	0.55 ± 0.60	0.59 ± 0.95	0.430
Range	(0.39-0.64)	(0.47-0.95)	
PI	0.91 ± 0.11	0.93 ± 15.00	0.850
Range	(0.70-1.10)	(0.59-1.15)	

PSV: Peak systolic velocity; EDV: End diastolic velocity; PI: Pulsatility index; RI: Resistance index

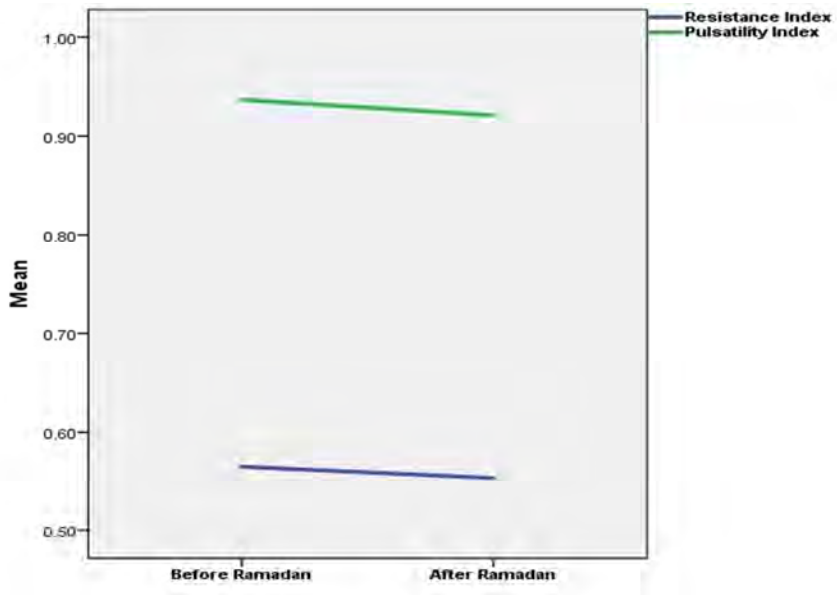

Figure 1. Resistance and pulsatility indices before and after Ramadan

The variability in daily fasting time is one of several confounding variables that influence the effect of Ramadan fasting on health-related biomarkers. The period in which the person fasts may vary depending on the geographical location of the country and the season of the year, and can be as long as 18 hours/day in the summer of temperate regions. This seasonal shift dramatically impacts the amount of daily fasting time that occurs in any given location, but the average time is 12 hours in length.[3-5]

Ramadan fasting resulted in significant weight loss, however, most of the weight loss will be regained during 2 weeks after Ramadan. The basis for the potential effects of Ramadan fasting on different biochemical parameters has been found in investigations which reports various metabolic effects that have been produced either by a decrease in meal frequency.[6-9]

A previous investigation compares pre and post Ramadan lipid profile and lipoproteins. Lipid profile including plasma total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride (TG) were measured, these parameters revealed a significant reduction in energy intake, plasma total cholesterol, LDL and TG levels toward the end of Ramadan in fasting group despite non-fasting group, indeed impact of Ramadan on improving lipid profile may have positive effect on atherosclerosis incidence.[10-15]

Another recent study by Mirghani et al., declerated the effect of maternal fasting on uterine blood flow during midtrimester (by means of Doppler flow velocitometry). Both uterine arteries velocity indexes (PSV, EDV, RI, PI) were similar in both case and control groups. It shows that maternal fasting is not associated with significant changes in uterine artery Doppler flow velocitometry.[16]

During the daylight hours of Ramadan fasting practicing probably causes dehydration by the mass of body. Water minus the amount of metabolic water that is produced over this period.

According to the literature review, studies show that Ramadan fasting does not affect the overnight urine volume or osmolarity but sample collected during afternoon were very high in level of osmolarity and showed a decrease in urine volume.

No detrimental effects on health have as yet been directly attributed to intermittent water negative balance (dehydration during light hours and water compensation during night).[17]

Another study shows, in healthy persons, fasting Ramadan does not induce abnormalities of urinary volume, osmolarity, pH, solute, and electrolyte excretion. Changing urea and creatinin are usually insignificant, and sodium and potassium fluctuations are negligible.[18]

Ramadan fasting leads to decrease in the platelet aggregating agents (e.g. ADP and collagen) in vitro and also causes an increase in BT and clotting time which shows platelet activation, but these changes remained within physiological limits, however, platelet count did not change during fasting.[2]

Compared to the previous study, it has been reported hematological parameters such as hemoglobin, pack cell volume[19] and count of erythrocyte, showed a significant decrease during Ramadan which resulted in an increase in anemia prevalence, in order to avoid iron deficiency anemia, the consumption of iron-rich food is recommended.

The burdens of excess weight and hypertension may be alleviated, and it could be beneficial in the long-term by reducing cardiovascular risk.[20]

Although our study has some limitations including small sample size and considering short-term effect of fasting, it must be taken to account that our investigation about the effect of fasting on cerebrovascular alternations were done for the first time, and it was not reported before. In conclusion, Ramadan fasting conditions in healthy persons does not effect cerebrovascular hemodynamic. It is strongly recommended to evaluate the brain changes during fasting in larger sample size and by means of other techniques such as duplex and neuroimaging, and also it is important to consider climate circumstances in which fasting is done.

Conclusion

The results of our study showed that 1 month of daily fasting has no statistically significant effect on cerebral circulation indices including PSV, EDV, PI, and RI. To our knowledge, this is the first study evaluating the effects of fasting on cerebrovascular circulation. Future studies are needed to examine the reproducibility of our results in elder populations.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Original Paper

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Comparing the production of complex sentences in Persian patients with post-stroke aphasia and non-damaged people with normal speaking

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Keywords
Stroke, Nonfluent Aphasia; Agrammatism; Production; Sentence

Abstract

Background: Cerebrovascular disease leading to stroke is the most common cause of aphasia. Speakers with agrammatic non-fluent aphasia have difficulties in production of movement-derived sentences such as passive sentences, topicalized constituents, and Wh-questions. To assess the production of complex sentences, some passive, topicalized and focused sentences were designed for patients with non-fluent Persian aphasic. Afterwards, patients' performance in sentence production was tested and compared with healthy non-damaged subjects.

Methods: In this cross sectional study, a task was designed to assess the different types of sentences (active, passive, topicalized and focused) adapted to Persian structures. Seven Persian patients with post-stroke non-fluent agrammatic aphasia (5 men and 2 women) and seven healthy non-damaged subjects participated in this study. The computed tomography (CT) scan or magnetic resonance imaging (MRI) showed that all the patients had a single left hemisphere lesion involved middle cerebral artery (MCA), Broca`s area and in its white matter. In addition, based on Bedside version of Persian Western Aphasia Battery (P-WAB-1), all of them were diagnosed with moderate Broca aphasia. Then, the production task of Persian complex sentences was administered.

Results: There was a significant difference between four types of sentences in patients with aphasia [Degree of freedom (df) = 3, $P < 0.001$]. All the patients showed worse performance than the healthy participants in all the four types of sentence production ($P < 0.050$).

Conclusion: In general, it is concluded that topicalized and focused sentences as non-canonical complex sentences in Persian are very difficult to produce for patients with agrammatic non-fluent aphasia. It seems that sentences with A-movement are simpler for the patients than sentences involving A`-movement; since they include shorter movements in compare to topicalized and focused sentences.

Introduction

Cerebrovascular disease leading to stroke is the most

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common cause of aphasia.[1] Broca's aphasia is one of the non-fluent aphasia types that were characterized by the symptoms such as slow speech rate, effortful production, short phrases, restricted speech output, short sentences, and simple structured sentences and agrammatism. The agrammatic speech patterns include the use of the subject-verb-object (in English) structure.[2]

Agrammatic speakers have difficulties in the production of movement derived sentences such as passive sentences, object relative clauses, object clefts, topicalized constituents, Wh-questions, and even yes/no questions (in languages that require movement to higher nodes in these constructions),[3-13] but they have better performance in the production of canonical structures.

The basic word order in Persian is subject-object-verb and it is called the canonical word order, any changes in this constituent ordering or any kind of movement of constituents from their base position results in what is called non-canonical structure.

In the linguistic tradition, the structure of sentences has long been represented in the form of tree diagrams. Several hypotheses have been proposed with regard to syntactic movement in agrammatism. Friedmann and Grodzinsky[14] supported Hagiwara's hypothesis[15] of hierarchical degradation of the syntactic tree structure and argued that complementizer phrases (CPs) always impair in agrammatism because they are the highest projections. They named their hypothesis "tree pruning hypothesis." Bastiaanse and van Zonneveld[16] proposed derived order problem hypothesis. According to their hypothesis, overt movement of any constituent (including verbs) in a sentence resulting in a derived order is difficult for Dutch agrammatic speakers, regardless of the landing site of the moved constituent in the syntactic tree.

Thompson et al.,[17] stated the complexity account of the treatment efficacy based on experimental studies. In several intervention studies, Thompson et al.[12,13,17,18] found that complex sentences is difficult for agrammatic patients. They have shown that training more complex forms facilitates learning of less complex structures. These hypotheses were tested on patients with agrammatic aphasia speaking different languages, such as English,[19] Japanese,[20] Korean and Spanish,[21] German,[22,23] Indonesian,[24] Dutch,[16] Turkish,[25-27] Russian,[28] Italian,[29] and Greek.[30] In general, it was found that production of complex structures is difficult for agrammatic patients.

In this present study, we used the basic assumptions of Minimalist Program as elaborated in Chomsky.[31] According to this syntactic model, there are two kinds of phrasal movements that are derived from the general rule of "move-alpha": Noun phrase-movement (NP-movement) and Wh-question movement (Wh-movement). NP-movement is involved in passives and raising constructions and Wh-movement is involved in Wh-questions or relativization. Production of sentences that involve these movements are difficult for agrammatic patients. Hence, it is necessary that sentences were designed which have been involved two movements. A`-movement is a position that elements move into spec of CP and this position do not participate in theta role assignment, but A-movement is land that elements move into spec of TP and this position participate in theta role assignment.

The aim of the study is assessing complex sentences production in Persian aphasic patients. Based on this aim, topicalized and focused sentences of A`-movement and passive sentences of A-movement were designed in Persian non-fluent aphasic patients. We supposed these sentences were non-canonical and complex sentences in Persian. In this study, a task should be designed to assess different types of sentences that were adapted to Persian structures. Production of four type sentences (active, passive, topicalized and focused sentences) was assessed in Persian agrammatic patients using this task. Then, patients' performances were compared with normal subjects.

Materials and Methods

In this cross-sectional study, 14 individuals including seven Persian stroke individuals with non-fluent agrammatic aphasia (5 males, 2 females; mean age = 54.28 years) and seven healthy normal subjects (5 males, 2 females; mean age = 53.85 years) participated in this study. computed tomography (CT) scan or magnetic resonance imaging (MRI) showed all patients had a single left hemisphere lesion that involving middle cerebral artery (MCA), Broca's area and in its white matter. They were right-handed and had left hemiplegia. Cerebral dominancy in all participants was left hemisphere. Post-stroke time was between 2 and 13 years. None of the subjects had a history of prior neurological or psychiatric disorders, developmental speech and language disorders and drug or alcohol abuse. All of the individuals were native Persian speakers and had normal or corrected-to-normal hearing visual acuity. All patients had mild or no apraxia (based on Yadegari[32]). If each patient would not like to enter this study, he/she was omitted. Aphasic subjects were selected from rehabilitation and speech therapy centers of Tehran University of Medical Sciences and Iran University of Medical Sciences, Iran. Seven

aged-matched individuals (5 males, 2 females; mean age = 53.85 years) with no neurologic impairment served as control group. All participants had, at least, a high-school education (mean = 12 years). Aphasic demographic data are given in table 1.

Language testing

The aphasia type was determined non-fluent based on the Bedside version of Persian Western Aphasia Battery (P-WAB-1),[33] scores of speech fluency were between 3 and 5 and aphasia question (AQ) was between 59.2 and 77.5. According to Nilipour et al.[34] study our patients were placed at moderate AQ range. Noun naming was measured by the picture naming test[35] (range: 55.04-94.50%, mean = 74.31%) and patients' performance was better than verb naming which was assessed by the picture verb naming test[36] (range: 50.00-82.57%, mean = 63.95%). A speech therapist assessed all of language tests for aphasia subjects.

Experimental stimuli

We required Persian verbs and sentences for designing production task. Based on their occurrence of written frequency (range = 1-39522 per approximately 10 million),[37] 32 semantically reversible, two arguments, imageable verbs were selected which included 8 simple and 24 complex transitive verbs. Finally, 20 verbs were selected from a questionnaire and then 15 individuals including speech therapists and linguists were asked to score and confirm appropriate verbs for aphasic subjects. In this way, content validity for verbs obtained 63.87-94. Two animate nouns were selected for sentences based on their occurrence of written frequency (range = 821-5729 per approximately 10 million).[37] Content validity for nouns obtained 82.33-94. For each verb, four sentence types were designed and for each sentence; two black and white pictures were drawn by a graphist. One picture was depicted the target sentence and the other one, the foil sentence. Face validity for pictures obtained 85-96.67 by scoring speech therapists and linguists. The roles of subjects and objects were reversed in the target and the foil sentences. Four sentence types were composed of active, passive (A-movement), topicalized and focused sentences (A`-movement) for each verb (totally, 80 sentences).

Sentence production

The task contained 20 sentences for each four types of sentences (active, passive, topicalized and focusing). Production of the 80 sentences was assessed using a sentence production priming paradigm.[12] In this way, the examiner modeled the production of one type of sentence using the foil picture. Then participants were asked to produce a sentence with the same structure using the target picture. For example, the examiner produced a passive sentence with the foil picture, and the participant produced a passive sentence with the target picture which had the reverse subject and object. The 80 stimulus were presented to participants randomly, and their responses were written and recorded with audiotape, simultaneously. Scoring was based on correct response and responding time was 10 seconds. No feedback was presented for a correct or non-correct response. Each correct or incorrect response was checked and confirmed by a linguist, one more time. For example, the omission of morphological elements and word substitutions were considered correct.

Notably, this study was permitted by Ethics Committee of Tehran University of Medical Sciences with 93/130/1639 codes and the patient or his/her partner signed the study inform consent.

In this study all data were quantitative, therefore, to report findings of production of four types sentences, descriptive statistics was used to calculate percentages and means (standard deviation) of scores. Non-parametric statistics was utilized to analyze data since the data does not have a normal distribution.

The non-parametric Mann–Whitney U was used to compare the production of each four types of sentences between patient and control groups and within each group Friedman test and post-hoc Wilcoxon test by adjusted P value was used. In addition, we analyzed the production performance of two groups by these tests. The significance level was $P < 0.050$.

Table 1. Aphasic participants data (n = 7)

Name	Age (year)	Gender	Education (year)	Post onset time (year)	Lession	Etiology
BH	62	M	12	3	Left insula-putamen	CVA
SP	50	M	12	2	Left fronto-temporal	CVA
MP	65	M	12	1	Left fronto-temporal	CVA
SN	59	M	14	5	Left putamen	CVA
MY	53	M	12	13	Left fronto-tempo-pariatal	CVA
AR	43	F	16	9	Left fronto-temporal	CVA
MM	48	F	9	5	Left fronto-tempo-pariatal	CVA

M: Male; F: Female; CVA: Cerebrovascular accident

Table 2. Aphasic subjects' language test data

Number of subjects	S1	S2	S3	S4	S5	S6	S7
P-WAB-1							
Spontaneous speech content (n = 10)	6	6	5	6	5	7	6
Fluency of spontaneous speech (n = 10)	5	4	3	5	4	5	5
Auditory comprehension (n = 10)	10	6	10	10	10	9	10
Sequential commands (n = 10)	7	6	7	9	9	9	10
Naming (n = 10)	8	6.5	9	7	6	8.5	7
Repetition (n = 10)	10	7	7	7	9	8	8
AQ = 100	76.6	59.2	68.3	73.3	71.6	77.5	76.6
Syntactic comprehension of BAT (%)	90.80	58.62	74.71	91.95	81.61	67.81	80.46
Object naming (%)	69.72	55.04	61.46	78.90	86.23	94.50	74.31
Verb naming (%)	68.18	50	60.60	82.57	61.36	61.36	63.63
Sentence production (%)							
Active sentence	60	85	70	80	60	80	85
Passive sentence	70	55	35	65	20	5	25
Topicalized sentence	20	35	0	30	0	0	15
Focused sentence	15	0	0	40	0	0	15

P-WAB-1: Persian Western Aphasia Battery; AQ: Aphasia quotient; BAT: Bilingual aphasia test

Results

Sentence production

The results showed all aphasic patients had more difficulties in the production of passive, topicalaized and focused sentences (Table 2). Their score ranges were 5-70% (mean = 39.28%), 0-35% (mean = 14.28%), 0-40% (mean = 10%) for passive, topicalaized, and focused sentences, respectively. However, the best performance was obtained for active sentence production (mean = 74.28%). Table 3 indicates that there is a significant difference between four types of sentence in aphasic individuals [Degree of freedom (df) = 3, P < 0.001]. No error was produced by the control group, and their data were not presented.

All aphasic participants showed worse performance than the normal participants in the total of four types of sentence's production. Significant differences were shown in table 4.

Table 3. Statistical analysis comparing the production of all sentence types together in patients

Production	df	P*
Active sentence	3	< 0.001
Passive sentence		
Topicalized sentence		
Focused sentence		

*Kroskal–Wallis test, P value level < 0.050
df: Degree of freedom

Discussion

In this study, we assessed the production of canonical and non-canonical (complex) sentences in Persian post-stroke non-fluent aphasic patients. We compared patients' performance to healthy subjects without brain damage by a task that designed to assess four types of sentence's structures.

Table 4. Comparison of sentence production between patient and normal participants

Types of sentence	Z	P*
Active sentence production		
Normal		
Patients	-3.356	0.001
Passive sentence production		
Normal		
Patients	-3.343	0.001
Topicalized sentence production		
Normal		
Patients	-3.360	0.001
Focused sentence production		
Normal		
Patients	-3.390	0.001

*Mann–Whitney U-test, P value level < 0.050

Results showed that the production of active, passive, topicalized, and focused sentences is difficult for aphasic patients. However, the patients perform better in active sentences than the other types. In our task, two types of sentences were designed based on A`- movement structure (i.e., topicalized and focused sentences) and one sentence was designed based on A`-movement structure (i.e., passive sentences). The findings indicated that producing focused sentences were worse than topicalized ones in patients while passive sentences were better than topicalized and focused sentences. Nevertheless, there was a significant difference between productions of all four types of sentences.

In general, it is concluded that topicalized and focused sentences are non-canonical and complex sentences in Persian language, and their production is significantly difficult for agrammatic non-fluent aphasic patients. Several authors studied similar sentence structures in different languages and obtained results correspond to our findings for

agrammatic subjects.[6,7,12-14,23-28,30,38]

When the production of each four types of sentences between patients, and healthy groups were compared, significant differences were found. That is, agrammatic patients have more difficulties in the production of A-movement and A`-movement structures than control subjects. The study of Thompson and Shapiro,[12] reveals that agrammatic individuals rarely produce complex sentences, containing Wh-movement or embedded clausal structures. Persian aphasic patients had more difficulties in the production of complex sentences such as passive, topicalized and focused sentences. Furthermore, in production of passive sentences Persian agrammatic speakers performed better than topicalaized and focused sentences. It seems that A-movement structures are simpler than A`-movement structures in Persian because the length of passive sentences is shorter than topicalaized and focused ones. Active sentences are a canonical sentence and basic word order in Persian language, so both groups performed well in active sentences.

As be mentioned obviously, several hypotheses have been proposed with regard to syntactic movement in agrammatism. All of them state that production of sentences with longer movement in syntax tree is a more difficult than shorter movement and without movement in this tree. Therefore, findings in Persian agrammatic patients are accountable to these hypotheses in syntactic movement.

It should be noted that the control subjects without brain damage responded correctly to produce all kinds of sentences. These findings suggest that our task is suitable to elicit the production of all types of sentences for adults and it can elicit the sentences level production problems in agrammatic aphasic patients.

Although there are a lot of studies in the field of aphasic patients in other languages, there is lacking information about language abilities of this group in Persian to guide speech and language therapists during assessment and treatment planning. This finding helps to clinicians that improve production of sentences in non-fluent aphasia patients. Interventional findings show that training complex sentences not only improves production of these sentences but also simultaneously improves simpler structures. Furthermore, fewer treatment sessions are required for participants who receive treatment on complex forms first.

We suggest more research in finding of types of A-movement and A`-movement sentences in Persian. Furthermore, clinicians train types of these sentences to patients in the experimental studies.

Conclusion

It seems that sentences with A-movement are simpler for the patients than sentences involving A`-movement as they include shorter movements than topicalized and focused sentences. To conclude, our findings in Persian agrammatic patients correspond to Chomsky's theory (Minimalist Program).

Conflict of Interests

The authors declare no conflict of interest in this study.

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Spatial distance between anatomically- and physiologically-identified targets in subthalamic nucleus deep brain stimulation in Parkinson's disease

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Keywords
Parkinson's Disease; Deep Brain Stimulation; Intraoperative Monitoring; Anatomic Target; Physiologic Target

Abstract

Background: Subthalamic nucleus (STN) stimulation is the treatment of choice for carefully chosen patients with idiopathic Parkinson's disease (PD) and refractory motor fluctuations. We evaluated the value of intraoperative electrophysiology during STN deep brain stimulation (DBS) procedures in refining the anatomically-defined target.

Methods: We determined the spatial distance between the anatomical and physiological targets along x, y and z axes in 50 patients with PD who underwent bilateral subthalamic nucleus DBS surgery.

Results: The mean spatial distance between anatomical and functional targets was 1.84 ± 0.88 mm and the least distances in different methods were 0.66 mm [standard error (SE): 0.07], 1.07 mm (SE: 0.08) and 1.01 mm (SE: 0.08) on x, y and z axes, respectively, for the combined method.

Conclusion: The most physiologically-accurate anatomical targeting was achieved via a combination of multiple independent methods. There was a statistically significant difference between the anatomical and functional targets in all methods (even the combined) on the y coordinate, emphasizing the need for intra-operative electrophysiological monitoring to refine the anatomico-radiologically-defined target.

Introduction

Subthalamic nucleus (STN) stimulation is an effective therapy for the amelioration of Parkinson's disease (PD) motor symptomatology and drug-induced dyskinesias.[1-7]

STN deep brain stimulation (DBS) is the surgical treatment of choice for medically refractory PD in carefully selected patients.[6,8,9] However, the best means of targeting this nucleus still remains a matter of discussion. This is partly because of the small size of the STN, its biconvex shape, and triple oblique orientation.[8,10] Due to lack of contrast between the

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STN and surrounding structures on regular computed tomography (CT) and T1 weighted magnetic resonance imaging (MRI) sequences, information from these modalities are often complemented with T2 weighted MR images, printed and digitalized anatomical brain atlases, high-resolution T1-T2 maps, functional atlases, and databases. In addition, integration of multiple functional and anatomical references may also be employed to facilitate surgical targeting.[11]

The accuracy of DBS lead placement and electrode location planning is the key factor for therapeutic efficacy.[4,10,12,13] A small deviation in the electrode positioning may cause severe side effects such as speech disorders, muscle contractions, ocular deviations, or visual defects to name a few. Hence, it is critical to perform precise surgical target localization, reduce error at every stage of the procedure and perform electrode location planning to achieve optimal surgical outcomes.

The specific objectives of this cross-sectional retrospective study were to identify the distance between the anatomical and functional target based on each targeting method, evaluate the confidence provided by each anatomical targeting method and defining the spatial position of the functional target without performing post-operative conditionally safe MRI scans.

Materials and Methods

This retrospective cross-sectional study included data from 50 idiopathic PD patients referred to our department (41 males and 9 females) from July 2006 to September 2009, aged between 31 and 72 years for bilateral STN-DBS (a total of 100 procedures). Each patient was carefully selected by a team of specialists consisting of a movement disorder neurologist, a functional stereotactic neurosurgeon, psychologist and a neuropsychiatric.

Patients were selected as per the following criteria: age under 75 years, disabling motor fluctuations and drug-induced dyskinesia refractory to medical therapy. The exclusion criteria were as follows: the presence of cognitive impairment, major depression or marked cerebral (both cortical and ventricular) atrophy on neuroimaging studies.

The scope of the study is as shown in figure 1. It includes the pre-operative targeting based on multiple independent methods (direct, indirect and combined methods) which are compared to the intra-operative results of microelectrode recording (MER) and macroelectrode stimulation (MES). Postoperatively the spatial position of the functional target is calculated using a mathematical model without performing a post-operative MRI.

Acquisition of image data

Placement of the Leksell G stereotactic frame (Elekta Instruments AB, Stockholm, Sweden) with an attached MRI compatible localizer was performed prior to MRI for each patient. The frame was placed parallel to the orbitomeatal line using ear bars inserted into the patient's external auditory meatus that were attached to the base ring and then pivoting the base ring into the desired alignment.

General anesthesia was maintained during imaging and with the head frame fixed within the head coil. The patient remained immobilized during the MRI acquisition reducing potential movement-related artifacts. The following stereotactic brain MRI sequences were obtained using a 1.5 tesla Philips Gyroscan MRI scanner:

- Pre-operative three-dimensional (3D) T1 weighted volumetric sequence with an isotropic voxel (1 × 1 × 1 mm) acquired using an intravenous contrast to enhance the definition of blood vessels

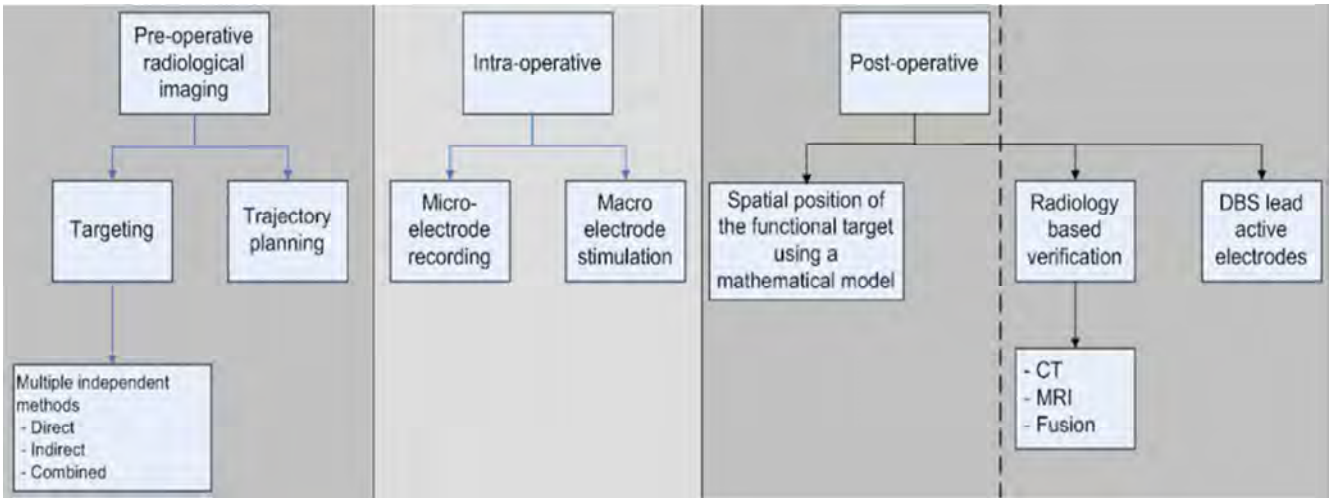

Figure 1. Scope of the study

• Two sets of coronally and axially oriented two-dimensional T2 weighted fast spin echo sequences (TR: 2800 ms, TE: 110 ms, flip angle 90°, NEX 4, square pixel of size: 1 × 1 mm, slice thickness 1.5 mm, inter-slice spacing 0 mm, matrix 256 × 256).

None of the above sequences had gantry angulation (zero tilt), and the sequences were strictly axial or coronal. The radiology department shimmed the magnets on a regular basis to minimize the distortion in MRI sequences.

Anatomical targeting

The coordinates were calculated with respect to the Leksell stereotactic system with the arc used in the lateral right configuration. No fusion was used in this approach to minimize the error of the fusion algorithms. The following six independent anatomical targeting methods were used:

Atlas-based targeting: We used the digitalized version of the Schaltenbrand and Wahren stereotactic brain atlas reformatted and linearly scaled to the anterior commissure-posterior commissure to fit the individual patient's anatomy (e.g., width of the third ventricle). The center of the motor part of STN on each side was chosen and its coordinates were determined.[14]

T2 weighted MRI-based direct targeting with manual calculations on axial and coronal orientations: The STN is located lateral to the red nucleus (RN), dorsal to the substantia nigra (SN) and medial to the posterior limb of the internal capsule, has a hypointense signal intensity on T2 weighted MRI. The anterior and lateral boundaries of the RN can be best visualized on an axial T2 weighted MRI. The anatomical relationship between these three structures can assist in the identification of the surgical target location within the STN. We used the axial and coronal planes of T2 weighted images separately to define the dorsolateral part of the STN for targeting and two sets of coordinates (X, Y, and Z) were determined. Calculations on the axial and coronal plane were done manually on the MRI console.

T2 weighted MRI-based targeting by Stereonauta software: Using above relationships between the three structures (SN, RN, and STN), after registration of the stereotactic images on the Stereonauta software (Estudios e Investigaciones Neurológicas, S.L., Madrid, Spain), we determined the target on axial and coronal T2 weighted images separately. Two sets of coordinates (X, Y, and Z) were determined. In all the 50 patients, we considered a mean error of < 0.5 mm for registration of the Leksell stereotactic frame in Stereonauta software.

Combined method: The last set of coordinates was a combination of the aforementioned five methods, which was defined by the stereotactic neurosurgeon as an average of all previous coordinates, heuristically considering outliers.

After defining the anatomical target, the safest trajectory for electrophysiological exploration (with five simultaneous trajectories) was determined on the 3D T1 weighted contrast enhanced MRI with a 6 mm circle of safety. A look ahead up to 10 mm beyond the target was done to reaffirm safety. These trajectory settings were arc and ring angles on the Leksell stereotactic system with the arc used in the lateral right configuration.

Surgical procedure

All patients gave their informed consent. Antiparkinsonian medications were withdrawn the night before surgery (the long acting medications withdrawn earlier as deemed appropriate by the movement disorder neurologist). Under general anesthesia, in semi sitting position the stereotactic frame was fixed, imaging and targeting performed and then attached to the Mayfield head holder. Under strict sterile conditions, a C-shaped incision on the coronal suture was made after marking the entry points on the skin with the stereotactic guidance and a cutaneous flap reflected. Two 14 mm burr holes were made on the uppermost part of the cranium according to planned trajectory about 4 cm from the midline and anterior to the coronal suture. The dura was opened in a circular shape of about 5 mm in diameter first on the left side. After completion of the procedure on the left side, the dura was opened in a similar manner on the right side. Continuous irrigation with normal saline minimized entry of intracranial air and possible brain shift.

Using a stereotactic micro-drive (microTargeting drive, FHC Inc., Bowdoin, MI, USA) five parallel platinum-iridium microelectrodes were inserted through the dural opening directed to the location of the combined anatomical target. These five electrodes were arranged in a "+ plus" configuration resulting in central, anterior posterior, medial and lateral parallel trajectories. The distance between the central trajectory to others was 2 mm, measured center to center. MER was started 10 mm above the anatomical target and continued in incremental steps of 0.5 mm, and the discharge pattern of neurons was identified. Below the thalamus we usually found some cells with a low firing rate that probably belong to a thin strip of gray matter located between the thalamic and lenticular fasciculi, the zona incerta. After this, a marked increase in the background noise defined the STN which cells have large amplitudes and an irregular firing pattern with a firing rate of around

25-50 Hz. Finally, without a clear border the electrodes entered the SN with low background noise and high-frequency tonic discharge.

The length of MER recordings along each trajectory was determined, and a 3D electrophysiological view of the STN was inferred. After that the recording electrodes, were withdrawn by 10 mm and the overlying macroelectrode in the selected trajectory was introduced (other macroelectrodes remained withdrawn to prevent a possible microsubthalamotomy effect). The therapeutic window (the difference between the intensity of electrical current thresholds of best clinical effects and side-effects) predicts clinical long-term efficacy and determines which trajectory and to which point along this trajectory, the permanent DBS lead should be implanted for optimal clinical results. This point is our gold standard (the physiological/functional target) according to which, the accuracy of other anatomical targeting methods could be assessed. The permanent DBS lead contains four electrodes, centered on this functional target each measuring 1.5 mm in width with 0.5 mm spacing in between them and a diameter of 1.27 mm (model-3389, Medtronic Inc., Minneapolis, USA).

Using propofol and dexmedetomidine for maintenance of general anesthesia with bispectral index (BIS) monitoring we could lighten the patients just before initiation of recording and stimulation. Clinical effects of stimulation were monitored with contralateral hand tremor, wrist rigidity, and bradykinesia. The beneficial effects of acute test stimulation were observed in the 1-3 mAmp range. Side effects secondary to stimulation included contralateral muscle contractions and/or eye deviation among others as mentioned in literature. MES up to a supramaximal threshold of 5 mAmps was considered acceptable to choose a trajectory for implanting the DBS lead with intra-operative fluoroscopic guidance using lateral crosshairs. A synopsis of side-effects of acute macro-stimulation in the STN region are summarized in table 1.

The day after both DBS leads were placed we implanted the implantable neurostimulator (model Kinetra, Medtronic Inc., Minneapolis, USA) in the left infraclavicular area subcutaneously. All patients underwent a post-operative brain CT scan to rule out possible complications especially intracerebral hemorrhage (ICH). We followed them for a minimum of 1 year for the onset of delayed complications such as infection.

Calculation of target deviation

As depicted in figure 2, plane P is the axial plane through combined anatomical point (A). Plane P' is the plane of "arc" (=) and line AE is the central trajectory in this plane defined with "ring" angle = β. Point F is the functional target along the trajectory AE.

According to the angle between plane P' and plane P, normal vector of P' is:

$$\overrightarrow{N_1} = 0\hat{i} - \sin\alpha\hat{j} + -\cos\alpha\hat{k} \quad (1)$$

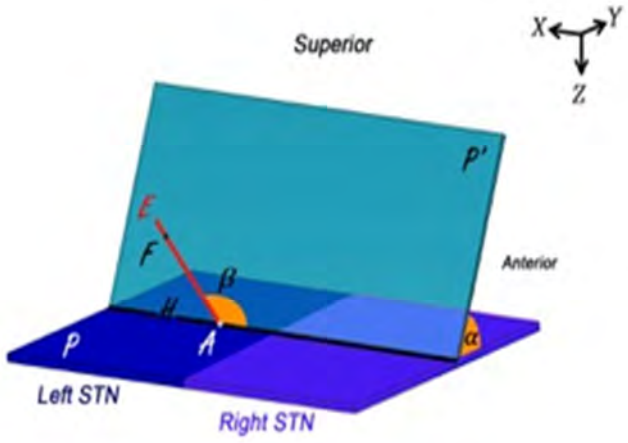

Figure 2. Schematic for calculation of target deviation

Since point A is in the plane P' and its coordinates are defined, the equation of plane p' could be expressed as:

$-z\cos\alpha - y\sin\alpha = -z_A\cos\alpha - y_A\sin\alpha$ (2)

Now, by equating dot product $\overrightarrow{AE}.\overrightarrow{AH}(|\overrightarrow{AH}| = 1)$ with cosine of the angle between them:

$$\cos(\pi-\beta) = -\cos\beta = \overrightarrow{AE}.\overrightarrow{AH} = \frac{(X_E-X_A)\hat{i}+(Y_E-Y_A)\hat{j}+(Z_E-Z_A)\hat{k}}{\sqrt{(X_E-X_A)^2+(Y_E-Y_A)^2+(Z_E-Z_A)^2}}.(l\hat{i}-o\hat{j}+o\hat{k})$$

$$\begin{cases} \text{with considering P' normal:} \dfrac{(y_E-y_A)}{(z_E-z_A)} = \cot\alpha \\ \text{E is an arbitrary point of line AE} \end{cases} \Rightarrow$$

$$\text{line equation AE:} \frac{(X-X_A)}{-\cos\beta} = \frac{(Y-Y_A)}{\sin\beta\cos\alpha} = \frac{(Z-Z_A)}{-\sin\beta\sin\alpha} \quad (3)$$

And direction vector of line AE can be also derived:

$$\overrightarrow{N_2} = -\cos\beta\hat{i} + \sin\beta\cos\alpha\hat{j} - \sin\beta\sin\alpha\hat{k} \quad (4)$$

As portrayed in figure 3 points A_1, A_2, A_3 and A_4 are respective to point A on other trajectories at the same level on the microdriver and the functional target could be also on trajectories other than central (points F_1, F_2, F_3 and F_4) with defined distance to points A_i (d). The functional target may be inferior than the anatomical target (−d), which is not shown in figure 3.

Table 1. The side-effects of synopsis acute macro-stimulation in the subthalamic nucleus region for Parkinson's disease (PD)

Motor	Occulomotor	Sensory	Autonomic	Affective	Limbic
Tonic at high frequency and tetanic at low frequency, used to distinguish between off-phase and stimulation-induced dystonia Evoked by current spreading to the corticobulbar and corticospinal tracts which surround the STN anterolaterally passing through the posterior limb of the internal capsule No habituation, consider a more medial or posterior trajectory if the threshold is very low resulting in a narrow therapeutic window Usually present as tonic contraction and phasic fasciculation contralaterally or bilaterally to stimulation in the face (forehead, eyebrow, eyelid muscles, cheek, lip or chin muscles), contractions of the contralateral upper limb intrinsic muscles more than the lower limb Dysarthia and dysphonia usually time locked with stimulation	**Extrinsic** Ipsilateral eye adduction, upward or downward deviation or lid retraction Side effects related to current spread to third cranial nerve fibers which pass ventromedially to the STN, close to the posterior border of the red nucleus and to the medial part of the substantia nigra, before leaving the brainstem Usually do not habituate If these occur at low or medium stimulation intensities consider a more lateral trajectory for evaluation Reduced voluntary ipsilateral conjugate eye deviation progressively resulting in conjugate controversive eye deviation (to the stimulation side) at higher intensities are related to stimulation of the occulomotor corticoganglionic loop inside the STN or the activation of the prefrontal-occulomotor projections to diecephalic and brainstem structures in the lateral part of the STN. Stimulation-induced conjugate ocular deviation rapidly habituates and even if elicited at low-intensity thresholds does not imply the need to explore another trajectory. **Intrinsic** Bilateral asymmetric mydriasis more marked for the ipsilateral side of stimulation can be induced by stimulation of the descending sympathetic fibers in the zona incerta (dorsomedially to the STN) or by stimulation of posteroventral hypothalamus, the so-called sympathetic hypothalamic area of Hess (anteriorly to the STN) These symptoms are rapidly adapting and usually these side-effects do not require a change in trajectory. Unilateral change in pupil diameter, homolateral to the stimulation side with or without an ipsilateral eye deviation occurs with the stimulation of the parasympathetic component of the third cranial nerve If the above occurs at low stimulation intensities a lateral trajectory has to be considered (as the trajectory may be located too medially)	Contralateral hemibody transient parasthesias could be the sensory-motor part of STN Dysesthesias at low stimulation intensities in the upper or lower limb could be due to stimulation of the red nucleus (which is more medial and posterior). Consider an anteriolateral trajectory Persistent parasthesias could be due to current spreading to the medial leminscus located posterioventral to the STN	Heat sensation, flushing, sweating, piloerection, nausea, vomiting, vasoconstriction, changes in hemodynamics Could be because of current spreading to the limbic part of STN or to the descending sympathetic fibers passing in the zona incerta (dorsomedial to the STN) or to the posterior part of the hypothalamus (anterior to the STN) These symptoms do not persist in the long term Stimulation site acceptable if there are optimal benefits on Parkinson's symptoms	Feeling electric current initially, dizziness, anxiety, breathing difficulties, discomfort in the chest, uncomfortable feeling in the head or with vision These side-effects cannot be related specifically to any anatomical sub-structure Usually tolerate and the trajectory can be used if there is optimal benefit on Parkinson's symptoms	Euphoria, hypomania or acute depressive states may occur time locked with stimulation rarely Pathologic or mirthful laughter or pseudobulbar crying May occur due to current spreading in the limbic part of STN or substantia nigra

STN: Subthalamic nucleus

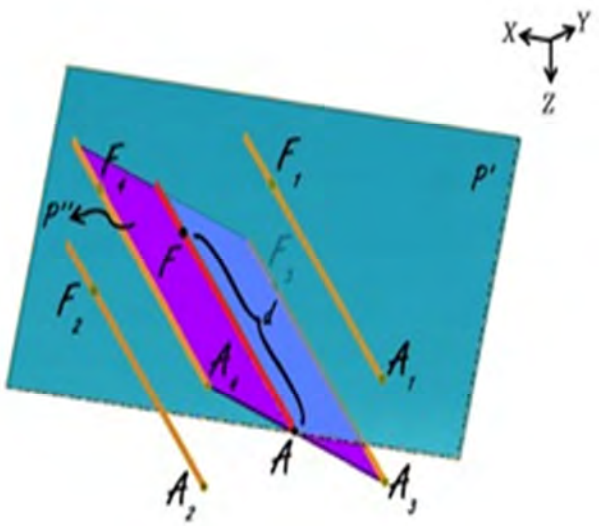

Figure 3. Anatomical and functional targets

According to figure 3, plane P'' is orthogonal to plane P' and AF is the intersection of these two planes.

By using the cross product of direction vector of line AF and normal vector of plane P', the normal vector of plane P'' would be determined as:

$$\begin{vmatrix} i & j & k \\ -\cos\beta & \sin\beta\cos\alpha & -\sin\beta\sin\alpha \\ 0 & -\sin\alpha & -\cos\alpha \end{vmatrix} = (-\sin\beta)\hat{i} + (-\cos\beta\cos\alpha)\hat{j} + (=\cos\beta\sin\alpha)\hat{k} \quad (5)$$

By using normal vector of plane P'', equation of plane P'' passing through point A could be expressed as: $(-\sin\beta)(x-x_A) + (-\cos\beta\cos\alpha)(y-y_A) + (+\cos\beta\sin\alpha)(z-z_A) = 0$ (6)

Coordinates of points A_1 and A_2 are considered as:

$$A_i = \left(X_{A_i}, Y_{A_i}, Z_{A_i}\right),\ i = 1, 2$$

The distance between points A_1 and A_2 to point A is 2 mm, so,

$$\left(x_{A_i} - x_A\right)^2 + \left(y_{A_i} - y_A\right)^2 + \left(z_{A_i} - z_A\right)^2 = 2^2 \quad (7)$$

Points A, A_1, A_2, A_3 and A_4 are on the same plane. Plane P' passes through points A_1 and A_2, thus:

$$-z_{A_i}\cos\alpha - y_{A_i}\sin\alpha = iz_A\cos\alpha - y_A\sin\alpha \quad (8)$$

Direction vector of line AA_i is perpendicular to normal vector of line AF:

$$(X_{A_i} - X_A)(-\cos\beta) + (Y_{A_i} - Y_A)(\sin\beta\cos\alpha) + (Z_{A_i} - Z_A)(-\sin\beta\sin\alpha) = 0 \quad (9)$$

By solving simultaneous equations 7, 8 and 9, parametric values of A_1 and A_2 could be expressed as:

$$\begin{cases} x_{A_1} = x_A - 2\sin\beta \\ y_{A_1} = y_A - 2\cos\beta.\cos\alpha \\ z_{A_1} = z_A + 2\cos\beta.\sin\alpha \end{cases} \quad (10)$$

$$\begin{cases} x_{A_2} = x_A + 2\sin\beta \\ y_{A_2} = y_A + 2\cos\beta.\cos\alpha \\ z_{A_2} = z_A - 2\cos\beta.\sin\alpha \end{cases} \quad (11)$$

Coordinates of points A_3 and A_4 are considered as:

$$A_i(X_{A_i}, Y_{A_i}, Z_{A_i}),\ i = 3, 4$$

The distance between points A_3 and A_4 to point A is 2 mm, plane P'' passes through points A_3 and A_4 and direction vector of line AA_i is perpendicular to normal vector of line AF.

Similarly to A_1, A_2, parametric values of A_3, A_4 could be expressed as:

$$\begin{cases} x_{A_3} = x_A \\ y_{A_3} = y_A + 2\sin\alpha \\ z_{A_3} = z_A + 2\cos\alpha \end{cases} \quad (12)$$

$$\begin{cases} x_{A_4} = x_A \\ y_{A_4} = y_A - 2\sin\alpha \\ z_{A_4} = z_A - 2\cos\alpha \end{cases} \quad (13)$$

Note that direction vectors of all trajectories A_iF_i (i = 1, 2, 3, 4) are equal to direction vector of line AF and their length is 1 mm and also all points F_i (i = 1, 2, 3, 4) are on the respective lines A_iF_i (i = 1, 2, 3, 4), so to clarify coordinates of points F_i:

$$\begin{cases} \overrightarrow{A_1F_1} \parallel \overrightarrow{N_2} \\ \left|\overrightarrow{N_2}\right| = 1 = \left|\overrightarrow{AF_1}\right| = d\left|\overrightarrow{N_2}\right| \end{cases} \rightarrow \overrightarrow{A_1F_1} = d\overrightarrow{N_2} \rightarrow$$
$$\begin{cases} \left(X_{F_i} - X_{A_i}\right) = d\cos\beta \\ \left(Y_{F_i} - Y_{A_i}\right) = +d\sin\beta\cos\alpha \\ \left(Z_{F_i} - Z_{A_i}\right) = -d\sin\beta\sin\alpha \end{cases} \rightarrow$$
$$\begin{cases} X_{F_i} = X_{A_i} - d\cos\beta \\ Y_{F_i} = Y_{A_i} + d\sin\beta\cos\alpha \\ Z_{F_i} = Z_{A_i} - d\sin\beta\sin\alpha \end{cases} \quad (14)$$

Using all of equations 10, 11, 12 and 13 in equation 14 we determined parametric values of F_1, F_2, F_3 and F_4 respectively:

Right lateral trajectory and left medial trajectory:

$$\begin{cases} x_{F_1} = x_{A_1} - 2\sin\beta - d\cos\beta \\ y_{F_1} = y_{A_1} - \cos\alpha\,(2\cos\beta - d\sin\beta) \\ z_{F_2} = z_{A_2} + \sin\alpha\,(2\cos\beta - d\sin\beta) \end{cases} \quad (15)$$

Right medial trajectory and left lateral trajectory:

$$\begin{cases} x_{F_2} = x_{A_2} + 2\sin\beta - d\cos\beta \\ y_{F_2} = y_{A_2} + \cos\alpha\,(2\cos\beta + d\sin\beta) \\ z_{F_1} = z_{A_1} - \sin\alpha\,(2\cos\beta + d\sin\beta) \end{cases} \quad (16)$$

Right or left anterior trajectory:

$$\begin{cases} x_{F_3} = x_{A_3} - d\cos\beta \\ y_{F_3} = y_{A_3} + 2\sin\alpha + d\sin\beta\cos\alpha \\ z_{F_3} = z_{A_3} + 2\cos\alpha - d\sin\beta\sin\alpha \end{cases} \quad (17)$$

Right or left posterior trajectory:

$$\begin{cases} x_{F_4} = x_{A_4} - d\cos\beta \\ y_{F_4} = y_{A_4} - 2\sin\alpha + d\sin\beta\cos\alpha \\ z_{F_4} = z_{A_4} - 2\cos\alpha - d\sin\beta\sin\alpha \end{cases} \quad (18)$$

Right or left central trajectory:

$$\begin{cases} x_F = x_A - d\cos\beta \\ y_F = y_A + d\sin\beta\cos\alpha \\ z_F = z_A - d\sin\beta\sin\alpha \end{cases} \quad (19)$$

Finally the spatial distance between anatomical (A) and functional (F_i) targets (delta) was calculated as:

$$\Delta = \sqrt{\left(x_{F_i} - x_A\right)^2 + \left(y_{F_i} - y_A\right)^2 + \left(z_{F_i} - z_A\right)^2} \quad (20)$$

To determine the significance of the difference between the anatomical and functional targets along the three axes (X, Y, and Z) an analysis was carried out using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). We used Wilcoxon and paired t-tests for analyzing this difference. Pearson's correlation coefficient defined the strength of linear dependence between coordinates of two targets on each axes for comparing accuracy of targeting between different methods. Furthermore, independent t-test and analysis of variance (ANOVA) compared the "delta" between right and left sides on the five different trajectories (anterior, central, medial, lateral and posterior).

Results

Of the 50 bilaterally implanted patients in this study, 9 were females and 41 were males. The mean age was 50.45 ± 9.17 years. We recorded STN signals in 1 and 5 trajectories in 1 and 22% of STNs respectively (Figure 4). Table 2 shows the mean lengths of STN recorded on various trajectories on the right and left sides.

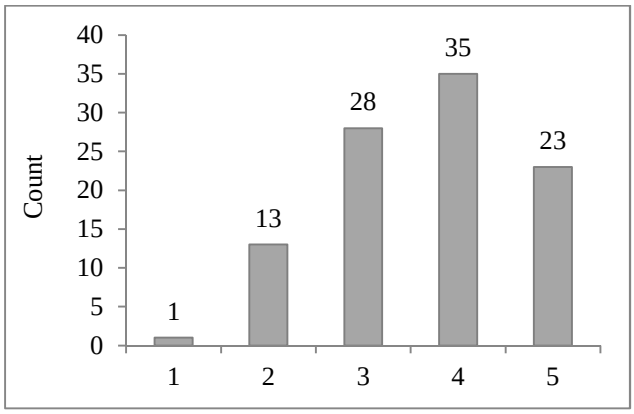

Figure 4. Number of trajectories in which subthalamic nucleus signal was recorded

In each case, we selected one of the five trajectories (anterior, central, medial, lateral or posterior) for placement of the permanent DBS lead on either sides and most frequently it was the central trajectory (Figure 5).

We determined the anatomical target (by six different methods) and the functional target along the three axes(X, Y, and Z). We evaluated the normal distribution of the parameters with one-sample Kolmogorov-Smirnov along each coordinate axes. Parameters of Y and Z coordinates had normal distributions and for X coordinate, the distribution was not normal.

For the X coordinate, using non-parametric Wilcoxon test, we compared the statistical difference between anatomical and the functional targeting methods. Only in the atlas-based method, we found a statistical difference between them along the X axis (Table 3).

Table 2. Mean lengths of subthalamic nucleus recorded on various trajectories on right and left sides

Trajectory (mm) / Target	Central	Anterior	Posterior	Medial	Lateral
Right STN (mean length ± SD)	4.02 ± 2.30	3.10 ± 2.72	3.44 ± 2.16	3.16 ± 2.34	2.43 ± 2.53
Left STN (mean length ± SD)	4.20 ± 2.06	3.61 ± 2.81	2.65 ± 2.42	2.08 ± 2.18	2.42 ±2.22

SD: Standard deviation; STN: Subthalamic nucleus

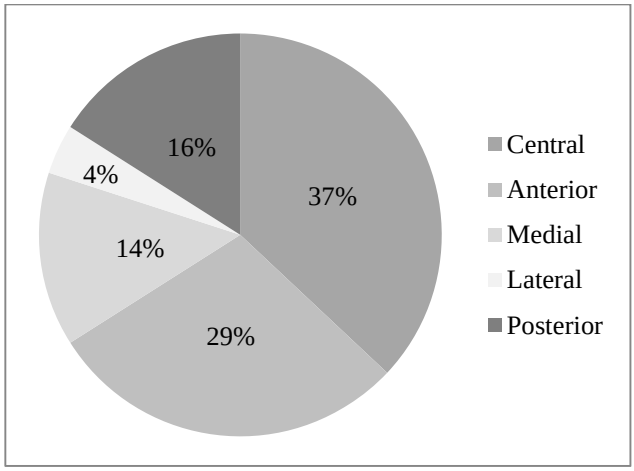

Figure 5. Trajectory selection distribution

Using paired t-test, there was a statistical difference between functional and all six anatomical targeting methods on Y axis; but on the Z axis, just in the manual/axial plane we found a statistically significant difference (Table 2).

Comparing the distances between functional and anatomical targets in six methods on three coordinates which can show the accuracy and partial error of targeting between these anatomical methods (Table 4 and Figure 6).

The less the mean distance and the range of confidence interval, the more accurate is the targeting method, so we also defined the correlation between coordinates of functional and anatomical targets in six methods on each axis (Table 5).

Table 3. Significance of difference between position of functional and anatomical targets on X, Y and Z coordinate axes

Coordinate axis		Combined	Manual coronal	Manual axial	Stereonauta coronal	Stereonauta axial	Atlas based
Significance (two-tailed)	X (Wilcoxon)	0.950	0.340	0.190	0.580	0.720	0.047
	Y (paired t-test)	0.010	< 0.001	0.037	0.002	< 0.001	0.001
	Z (paired t-test)	0.710	0.180	0.040	0.920	0.290	0.650

Table 4. Distance between functional and anatomical targets in six different methods on X, Y, and Z coordinate axes

Coordinate axes	Combined	Manual coronal	Manual axial	Stereonauta coronal	Stereonauta axial	Atlas based
X						
Mean	0.66	2.63	2.65	2.87	2.68	3.4
Range of 95% CI	0.51-0.81	1.35-3.9	1.39-3.9	1.54-4.2	1.4-3.9	2-4.8
SE	0.07	0.64	0.63	0.66	0.62	0.7
Y						
Mean	1.07	2.06	1.52	1.50	1.60	1.84
Range of 95% CI	0.91-1.23	1.75-2.37	1.2-18	1.21-1.78	1.29-1.92	1.53-2.1
SE	0.08	0.15	0.16	0.14	0.15	0.15
Z						
Mean	1.01	1.55	1.48	1.26	1.53	1.76
Range of 95% CI	0.85-1.18	1.17-1.92	1.13-1.82	0.98-1.54	1.05-2.01	1.16-2.37
SE	0.08	0.18	0.17	0.13	0.24	0.30

SE: Standard error; CI: Confidence interval

The mean difference between combined method of anatomical targeting and functional target chosen is defined as "delta" was 1.84 ± 0.88 mm (range: 0-4.25 mm). Using the independent t-test, we compared delta on the right and left sides (1.83 ± 0.91 and 1.75 ± 0.86 mm, respectively) and found no statistical difference between them (P = 0.680).

Identifying delta for each trajectory separately (Table 6), the central trajectory was the least (0.98 ± 0.74 mm) with an interesting statistical difference with others (using least significant difference-post-hoc test of ANOVA, P < 0.001).

The pre-operative unified PD rating scale III scores OFF and ON medication was 54.52 ± 5.40 and 18.22 ± 2.88, respectively. Post-operative score yielded was 12.80 ± 3.14 in stimulation ON and medication ON (with a 40% decrease in L-dopa equivalent dosage) state that showed significant difference comparing with both pre-operative scores (P < 0.001).

This study was conducted to evaluate the accuracy and precision of six anatomical targeting methods in comparison with intra-operative localization using MER and MES. This is arranged according to Pearson's correlation coefficient between coordinates of two targets along each axes in table 7.

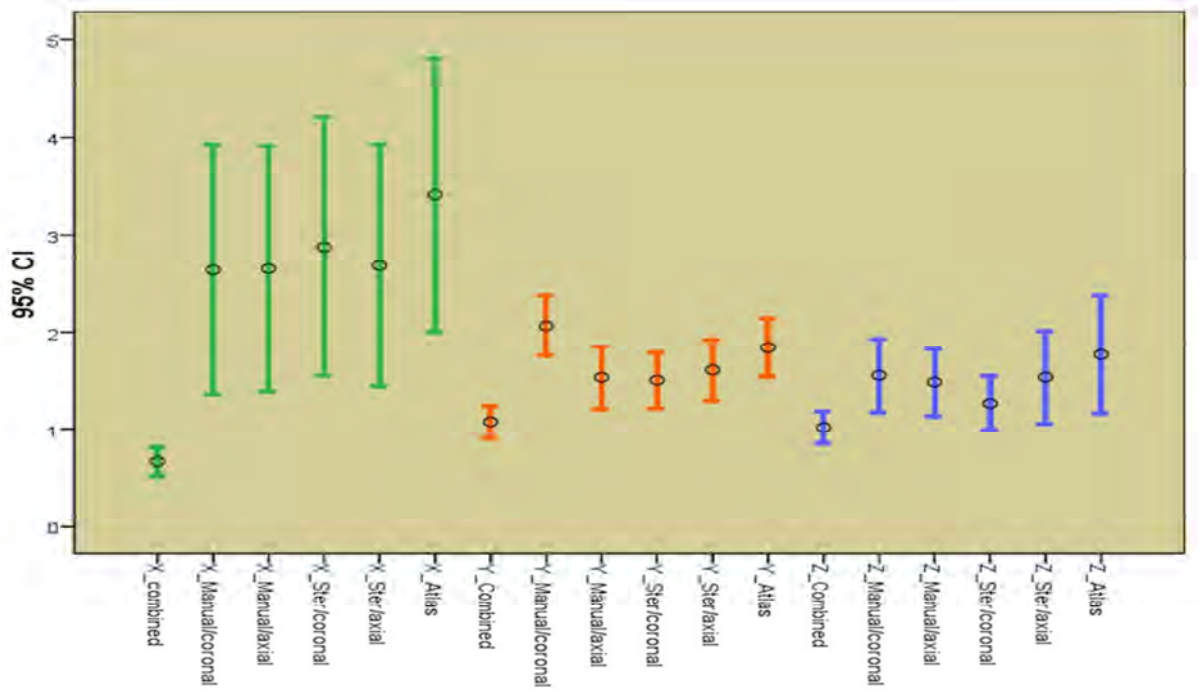

Figure 6. Comparing distances between anatomical and functional targets

Table 5. Pearson's correlation coefficient between coordinates of two targets on each axes for six different methods

Axes	Combined	Manual coronal	Manual axial	Stereonauta coronal	Stereonauta axial	Atlas based
X	0.990	0.790	0.800	0.780	0.82	0.760
Y	0.920	0.814	0.751	0.792	0.818	0.775
Z	0.970	0.820	0.839	0.857	0.856	0.775

Table 6. Descriptive analysis of "delta" on five different trajectories

Electrode	Mean ± SD	SE	95% CI for mean		Minimum	Maximum
			Lower bound	Upper bound		
Posterior	2.551 ± 0.629	0.157	2.216	2.886	2.00	4.25
Central	0.986 ± 0.743	0.122	0.739	1.234	0.00	2.50
Anterior	2.292 ± 0.322	0.060	2.169	2.415	2.00	3.40
Medial	2.315 ± 0.491	0.131	2.032	2.599	2.00	3.61
Lateral	2.160 ± 0.228	0.114	1.797	2.522	2.02	2.50
Total	1.848 ± 0.879	0.088	1.674	2.023	0.00	4.25

SD: Standard deviation; CI: Confidence interval; SE: Standard error

Table 7. Relative accuracy of six targeting methods on each axis

Different methods	X	Y	Z
The most accurate	Combined	Combined	Combined
2nd	Stereonauta/axial	Stereonauta/axial	Stereonauta/coronal
3rd	Manual/axial	Manual/coronal	Stereonauta/axial
4th	Manual/coronal	Stereonauta/coronal	Manual/axial
5th	Stereonauta/coronal	Atlas based	Manual/coronal
The least accurate	Atlas based	Manual/axial	Atlas based

Discussion

The most accurate targeting method on each coordinate axes was a combination of all six methods by an experienced functional stereotactic neurosurgeon and the second most accurate method was using the Stereonauta software in coronal plane for Z and in axial plane for Y and X coordinates. Overall the combination of all methods is the closet anatomical estimate of the physiological target. The spatial position of the functional target is calculated later in this section.

Several prior studies using atlases for targeting are known to be not accurate enough and have remarkable limitations, as they are extracted from limited brain specimens and also with degeneration antero-supero-lateral transposition of the STN

occurs with aging chronologically and in the disease life cycle itself.[11,15-17]

On the other hand, in a study performed by Zonenshayn et al.[18] to compare different anatomical targeting methods, the most precise was a combined approach and followed by an mid-commissural point based method using the Schaltenbrand and Wahren Atlas. Interestingly MRI-guided targeting had the least accuracy.

In the current study, anatomical atlas-based indirect targeting presented among the two least accurate methods on three axes. Direct targeting using T2 MRI was the second most accurate method.

In some other studies, MER and MES were reported to be time-consuming procedures, which were associated with complications such as ICH and infection. They were not helpful in improving accuracy of targeting either.[3,6]

Foltynie et al.[19] studied different targeting methods on 79 patients and emphasized that the ideal method remains unknown but MER may lead to increased complications and even death. They attribute increase in surgery time, dural opening and consequently prolonged cerebrospinal fluid leakage may itself exacerbate brain shift; however precise anatomical targeting without dural opening is sufficient to obtain optimal results.

In the current study, the time required for five simultaneous MER trajectories and subsequent MES per STN was about 60 minutes. In a 1-year follow-up after surgery, no superficial or deep infection was observed. During the procedure, a semi-sitting position was used (as close as possible to the MRI acquisition position), placement of the frontal burr holes on the uppermost part of the skull and also continuous irrigation with normal saline minimized intracranial air penetration and possible brain shift.[17]

In addition, it merits consideration that comparison of anatomical-functional target distances on each coordinate axes revealed statistical difference on Y coordinate between all six pre-operative localization methods and on X and Z coordinates, in Atlas and manual/axial methods respectively.

It is worthwhile noting that among our 100 STN DBS procedures, non-central trajectories were chosen for permanent stimulation as the functional target in 63%. Thus, although accurate pre-operative anatomical targeting may reduce the need for invasive intra-operative exploration and thereby decrease the surgical duration and procedure-related complications, certain intra-operative electrophysiological measurements are still required to compensate for the possible inadequacy of these targeting methods.

A review article, which was published by Benabid,[20] emphasizes on efficacy of MER despite the presence of some potential complications. In a study by Molinuevo et al.[3], on 15 PD patients who underwent bilateral STN DBS, a significant difference between location of pre-operative anatomical target and final surgical target was found (2.1 ± 1.3 mm, more than 4 mm in 10% of patients). In the current study, the difference between these two targets in 100 procedures was 1.84 ± 0.88 mm (more than 3 mm in 7% of cases).

In the current study, we determined the mean "delta" for each trajectory and found a significant difference between the central trajectory (0.99 mm) and other trajectories which might be due to a measurement bias. In fact, "delta" on the central trajectory could be any value but the least it could be on other trajectories is 2 mm, as the distance between central and other four parallel trajectories is 2 mm.

Many previously published studies emphasize on beginning the procedure on the contralateral side of the patient's dominant symptoms because between the two STN (left and right) procedures, targeting accuracy may significantly decrease on the second side due to brain shift and even perform more comprehensive MER on this side.[21] Despite beginning the surgical procedure on the left side in all patients at our center, we found no statistically significant difference between "delta" on both sides which were 1.75 ± 0.86 and 1.83 ± 0.92 mm on right and left STN's respectively (P = 0.680).

Finally, we used the following formulae as a mathematical model for composition of inaccuracy of anatomical targeting and probable intra-operative brain shift to identify X, Y, and Z coordinates of the final (functional) target for the right/left STN according to the coordinates of the anatomical target, depth at which the permanent DBS lead was placed (distal end of the distal most electrode) and arc and ring angles on the Leksell stereotactic system.

Right lateral trajectory and left medial trajectory:

$$\begin{cases} x_{F_1} = x_{A_1} - 2\sin\beta - d\cos\beta \\ y_{F_1} = y_{A_1} - \cos\alpha\left(2\cos\beta - d\sin\beta\right) \\ z_{F_2} = z_{A_2} + \sin\alpha(2\cos\beta - d\sin\beta) \end{cases}$$

Right medial trajectory and left lateral trajectory:

$$\begin{cases} x_{F_2} = x_{A_2} + 2\sin\beta - d\cos\beta \\ y_{F_2} = y_{A_2} + \cos\alpha\left(2\cos\beta + d\sin\beta\right) \\ z_{F_1} = z_{A_1} - \sin\alpha\left(2\cos\beta + d\sin\beta\right) \end{cases}$$

Right or left anterior trajectory:

$$\begin{cases} x_{F_3} = x_{A_3} - d\cos\beta \\ y_{F_3} = y_{A_3} + 2\sin\alpha + d\sin\beta\cos\alpha \\ z_{F_3} = z_{A_3} + 2\cos\alpha - d\sin\beta\sin\alpha \end{cases}$$

Right or left posterior trajectory:

$$\begin{cases} x_{F_4} = x_{A_4} - d\cos\beta \\ y_{F_4} = y_{A_4} - 2\sin\alpha + d\sin\beta\cos\alpha \\ z_{F_4} = z_{A_4} - 2\cos\alpha - d\sin\beta\sin\alpha \end{cases}$$

Right or left central trajectory:

$$\begin{cases} x_F = x_A - d\cos\beta \\ y_F = y_A + d\sin\beta\cos\alpha \\ z_F = z_A - d\sin\beta\sin\alpha \end{cases}$$

We could not identify any formulae for calculating these parameters according to pre- and intra-operative findings during the literature review. These could easily be incorporated in a simple program like Microsoft Excel (version 2010). In studies that used post-operative MRI for determining the exact location of permanent electrode to compare it with pre-operative target, magnetic artifact of the electrode itself, represented as the origin of errors in this process.[22-25]

Limitations in the above study can be addressed in future research. It would have been more purposeful to perform a post-operative conditionally safe MRI brain scan to compare the anatomical location with the final lead location as guided by the intra-operative electrophysiology. This would be relevant to identify systematic errors that can be corrected by a dynamic correction factor which can be used to recalculate the stereotactic coordinates.

Conclusion

The most physiologically accurate method for anatomical targeting is a combination of multiple independent methods with experience of a stereotactic neurosurgeon and it is ideal to refine the same with intra-operative neurophysiological recording (MER) and stimulation (MES) to identify the optimal functional target in real time.

A question to be answered in future studies is the significance of a number of recording trajectories (single sequential vs. multiple simultaneous) and whether a correlation is present between intra-operative neurophysiological monitoring and better clinical outcome?

Conflict of Interests

The authors declare no conflict of interest in this study.

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Review Article

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Myotonic disorders: A review article

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Myotonia; Myotonic Dystrophy; Myotonia Congenita; Paralysis Periodica Paramyotonia; Hyperkalemic Periodic Paralysis

Abstract
The myotonic disorders are a heterogeneous group of genetically determined diseases that are unified by the presence of myotonia, which is defined as failure of muscle relaxation after activation. The presentation of these disorders can range from asymptomatic electrical myotonia, as seen in some forms of myotonia congenita (MC), to severe disability with muscle weakness, cardiac conduction defects, and other systemic features as in myotonic dystrophy type I (DM1). In this review, we describe the clinical features and pathophysiology of the different myotonic disorders, their laboratory and electrophysiologic findings and briefly review the currently available treatments.

Introduction

The myotonic disorders are a group of rare, genetically heterogeneous syndromes presenting with clinical and/or electrical myotonia. Clinical myotonia is characterized by the failure of muscle relaxation after activation.[1] Electrical myotonia is the spontaneous discharge of muscle fibers that waxes and wanes in both amplitude and frequency on electromyography (EMG). Myotonia is thought to be due to increased excitability of muscle fibers, leading to discharge of repetitive action potentials in response to stimulation.[2] Electrical myotonia can also be seen with certain drugs (cholesterol lowering agents, cyclosporine, and colchicine, among others), in inflammatory myopathies, Pompe disease, hypothyroidism, myotubular myopathy, and chronic denervation (usually as brief runs).[1]

Clinical myotonia manifests with painless muscle stiffness, although some forms can be associated with pain.[2,3] The typical location of stiffness varies depending on the underlying disorder but commonly seen in the eyelids, mouth, hands, and proximal legs.[3-6] Common triggers include cold, stress and exercise, and symptoms can worsen during pregnancy and menstruation.[3] Most demonstrate a "warm-up" phenomenon, where myotonia improves with repeated action.[3,5,6] In contrast, paradoxical myotonia or paramyotonia worsens with repeated use. Some forms of myotonia are also associated with diffuse muscle hypertrophy.[7]

Myotonia can be brought out by asking the patient to repeatedly grip and relax their hand or open and close their eyes. Alternatively, direct percussion of a muscle can achieve the same effect; including tapping the thenar eminence, forearm extensors, or even tongue.[8]

Typically, myotonias are classified as either dystrophic or non-dystrophic (table 1). The former are characterized by fixed muscle weakness, systemic features, and dystrophic changes on muscle biopsy. Fixed weakness and dystrophic changes are less common, but can be seen in the non-dystrophic myotonias (NDM), and myopathic changes may be noted on muscle biopsy.[9] Recent evidence suggests structural muscles changes on magnetic resonance imaging and ultrasound imaging of some patients.[7,10]

Myotonic dystrophy

The myotonic dystrophies are inherited in an autosomal dominant fashion and classified into type I (DM1) and type II (DM2), also known as proximal

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Table 1. Clinical features of familial myotonic disorders

Conditions	Inheritance	Gene	Myotonia	Episodic weakness	Fixed weakness	Major trigger	Other features
DM							
DM type 1	AD	DMPK	M	Absent	Distal limbs, face	None	Frontal balding, temporal wasting, cataracts, systemic disease
Myotonic dystrophy type 2 (PROMM)	AD	CNBP (ZNF9)	M	Absent*	Proximal limbs	None	Disabling and atypical pain, cataracts, milder systemic disease
NDM							
MC							
AD (Thomsen)	AD	CLCN1	M	Absent	Rare	Rest	Generalized muscle hypertrophy
AR (Becker)	AR	CLCN1	M	Absent*	Proximal LE	Rest	Muscle hypertrophy in LE
PMC	AD	SCN4A	P	Present in some	Proximal LE	Cold, exercise	Most sensitive to cold
Potassium-sensitive periodic paralysis	AD	SCN4A	P, M or absent	Present	Proximal LE	K+, rest after exercise	Potassium levels may be high***
PAM							
Myotonia fluctuans	AD	SCN4A	M**	Absent	Absent	K+, exercise	Have good days and bad days
Myotonia permanens	AD	SCN4A	M**	Absent	Absent	K+, exercise	Continuous muscle stiffness
Acetazolamide-responsive myotonia	AD	SCN4A	M**	Absent	Absent	K+, exercise	Respond to therapy with acetazolamide

*PROMM patients may initially have intermittent or transient weakness; recessive MC patients may have transient weakness after severe bouts of stiffness, **May have eyelid paramyotonia, ***Potassium levels may be normal during attack normokalemic periodic paralysis (normoKPP).
AD: Autosomal dominant; AR: Autosomal recessive; K+: Potassium, LE: Lower extremities; M: Myotonia; P: Paramyotonia; PROMM: Proximal myotonic myopathy; DM: Dystrophic myotonias

myotonic myopathy (PROMM). Both are caused by expansion of DNA tandem repeats, resulting in a toxic gain of function of the resulting mutant RNA and sequestration of RNA-binding proteins.[11] DM1 results from expansion of CTG repeats in the DM protein kinase (DMPK) gene[12,13] whereas DM2 is caused by expansion of CCTG repeats in the ZNF9 gene.[14,15]

DM1

DM1 has an estimated prevalence of 3-15 per 100000[16,17] with higher prevalence reported in Sweden, the Basque area of Spain, and the Saguenay region of Quebec, Canada, were it is up to 20 times higher.[16,18] To our knowledge, disease prevalence has not been reported in Iran, but the incidence of excess DMPK CTG repeats in healthy Iranian controls is reported to be similar to Western Europe and Japan.[19]

DM1 can present at any age and often occurs earlier in successive generations, showing marked anticipation.[20] Larger repeat expansions are associated with earlier onset and more severe forms of the disease in most cases.[20-25] The most severe form, congenital DM, presents at birth with generalized hypotonia, severe weakness, facial diplegia (tent shaped mouth), intellectual disability, hypoventilation, gastrointestinal (GI) dysmotility, and early death.[17,23] Interestingly, myotonia is usually absent in infancy and muscle strength can improve with time if the infant survives.

Classically, DM1 presents in the second to fourth decade with prominent facial weakness, including ptosis, neck extension/flexion weakness, and distal weakness with a predilection for finger flexors/extensors and foot dorsiflexors.[20] Muscle atrophy occurs in line with the progression of weakness and myotonia is common (particularly in the hands).[17,22,25] Temporal muscle atrophy, ptosis and frontal balding result in a characteristic myotonic facies, and dysphagia and dysarthria are often prominent. Weakness tends to progress slowly over time with more than 95.0% of patients remaining ambulatory after a mean disease duration of 16-19 years.[20,26]

Systemic features include cardiac disease, especially conduction defects and possibly cardiomyopathy.[27] Cataracts are seen early (before 50 years in most) with bilateral iridescent (Christmas tree) or posterior cortical lens opacities being highly specific for DM1.[28] GI symptoms have been attributed to smooth muscle dysfunction and include reflux, abdominal pain, bloating, constipation, and diarrhea.[29] Endocrinopathies, in the form of insulin resistance and hypogonadism may also occur.[30] Excessive daytime sleepiness, independent of obstructive sleep apnea,[31] is common. Patients may have mild cognitive impairment and often have an avoidant personality with apathy toward their disease.[32,33] More recently, associations with mild peripheral neuropathy[34] and increased risk of cancer have been suggested.[35] Mild forms, limited to myotonia, frontal balding and early cataracts with normal strength and lifespan also occur, usually in patients with lower number of repeats.[20,22]

DM2

The prevalence of DM2 or PROMM is unclear but reported as even higher than DM1 in some populations in Finland and the Czech Republic.[36,37] Unlike DM1, there is no clear relationship between the number of repeats and disease severity[36] and congenital forms have not been reported. Most patients present in middle age with a mild phenotype of proximal weakness, myalgias, and early cataracts. Weakness characteristically involves neck flexors, elbow extensors, thumb/deep finger flexors, hip flexors and hip extensors. Facial weakness is less common.[38] Marked muscle atrophy is uncommon, and calf hypertrophy can be seen in some.[37] Muscle pain is present in 56-76%[38,39] of patients and occasionally leads to a misdiagnosis of fibromyalgia.[40,41] Clinical myotonia is often absent, and patients can occasionally present with asymptomatic hyperCKemia.[37,38,42]

Systemic features are similar to DM1 but milder.[35,38,43,44] Cognitive function is mostly normal although mild changes have been reported.[45-47] Dysphagia is common but typically mild.[48,49] In addition, there are reports of higher incidence of autoimmune disease compared to controls and DM1.[50]

Diagnosis and treatment of DMs

The evaluation of patients suspected to have myotonic dystrophy should include a thorough family history and physical examination, including testing of strength and myotonia. Definitive diagnosis is through genetic testing, commercially available for both DM1 and DM2. CK levels can be normal to moderately elevated,[38,39] and other laboratory features include mild hypogammaglobulinemia and non-specific liver enzyme abnormalities.[37] Nerve conduction studies are usually normal but can show mild length dependent axonal polyneuropathy. EMG shows myotonic discharges in all patients with DM1 and 90-100% of patients with DM2.[38,51,52] Myopathic units, fibrillation potentials, and positive sharp waves can also be seen but are sometimes obscured by prominent myotonic discharges. Muscle biopsy in DM1 shows atrophy of type I fibers, increased internalized nuclei, ring fibers, sarcoplasmic masses, small angulated fibers, and atrophic fibers with

pyknotic clumps.[16,17] DM2 may show similar features but milder and with atrophy of type II fibers, in contrast.

Treatment of the myotonic dystrophies is symptomatic and should include screening for cardiac arrhythmias, glucose intolerance, obstructive sleep apnea, and cataracts. Limited evidence exists for drug treatment of myotonia with antiepileptic and antiarrhythmia agents.[53] A recent randomized controlled trial demonstrated efficacy of mexiletine in patients with DM1;[54] however, concerns have been raised regarding its long-term safety in DM1 patients due to the potential of cardiac arrhythmias.[55] We use it with caution in patients with DM1 and in consultation with cardiology. It may be started at 150 mg twice daily and slowly increased to a maximum of 300 mg 3 times daily. An electrocardiogram should be performed at baseline and periodically.

Excessive daytime somnolence is sometimes treated with stimulants, although evidence for efficacy is mixed.[56-59] GI complaints can occasionally be due to small intestine bacterial overgrowth and may respond to antibiotic therapy,[60] and prokinetic agents have been used to treat gastroparesis.[61]

Non-Dystrophic Myotonias (NDM)

These are a group of rare disorders caused by mutations in genes coding for sodium (SCN4A) or chloride (CLCN1) channels. Their prevalence is estimated at ~1/100000 with higher rates (7-9/100000) in Northern Finland and Norway.[62-65] CLCN1 mutations are the most common form of NDM (0.52/100000) followed by paramyotonia congenita (PMC) (0.17/100000).[65]

The muscle chloride channel was previously thought to be important in stabilizing the resting membrane potential, with mutations leading to a lower threshold for muscle membrane firing.[66] More recent studies bring this into question.[67] Sodium channel mutations lead to poor inactivation of the channel, which results in repetitive discharges, with mild depolarization, or weakness, with severe depolarization.[68,69]

Myotonia congenita (MC)

MC is a chloride channelopathy, typically divided into dominant (Thomsen disease) and recessive (Becker disease) forms. Over 150 mutations in the CLCN1 gene have been reported,[70] with the recessive form of the disease classically presenting earlier in life with a more severe phenotype, although mild or late presentations have been reported.[71,72]

Thomsen disease was initially described by Thomsen himself in 1876, through a detailed description of his own disability and that of his family members.[73] It typically presents in the first decade with stiffness in legs more than arms, hands, and face.[3,6,72] Penetrance is incomplete, and disease severity can vary widely in family members.[74] Classically, stiffness is worse after rest, and patients often complain of leg stiffness that improves with walking. Myotonia can also affect muscles of mastication and swallowing. Some patients describe pain associated with their stiffness.[3,6] Warm-up phenomenon is usually present, and the stiffness can worsen with cold exposure, pregnancy, menses, hypothyroidism, and stress.[3,6,17,75,76] Examination demonstrates generalized muscular hypertrophy, action myotonia more pronounced in the hands than eyelids,[3,6] and percussion myotonia. Thomsen disease is not associated with systemic features, and patients have normal lifespans.

Becker disease usually presents between the ages of 4 and 12 years, although onset in adulthood is also seen.[72,73] Symptoms are similar to Thomsen disease, but myotonia tends to be more severe in the lower limbs and proximal muscles, and men tend to be more severely affected than women.[72] Transient weakness, lasting seconds to minutes, is sometimes seen after sustained bouts of myotonia and patients often have difficulty moving if startled suddenly.[6,73] Patients may develop mild fixed distal weakness and a "dystrophic" variant with severe atrophy and weakness, contractures and myopathic changes on muscle biopsy.[77] Similar to Thomsen disease, no systemic features are seen, and lifespan is normal.

Laboratory investigations are usually normal in both dominant and recessive MC although mild elevations in CK can be seen.[73] EMG shows widespread myotonic discharges and myopathic motor units can be seen in weak muscles if not obscured by myotonia. Given the commercial availability of genetic testing, muscle biopsy is rarely done and shows non-specific changes or mildly increased variability in fiber size and increased number of internalized nuclei.[73]

Paramyotonia Congenita (PMC)

PMC is an autosomal dominant condition caused by mutations in the SNC4A gene. It is highly penetrant and typically presents in the first decade with stiffness that is most pronounced in the face and hands. In contrast to other forms of myotonia, the patients have paramyotonia.[3,6] It commonly worsens with cold and patients can develop severe weakness with the prolonged exposure that can take hours to improve despite rewarming.[17,78,79] Patients may complain of hand stiffness while shoveling snow or in the frozen food section of the supermarket. Parents will occasionally report that affected infants are unable to

open their eyes after a crying spell, presumably due to the eyelids being "exercised" while crying.

Myotonia can worsen with pregnancy, menstruation, ingestion of potassium-rich food, and anesthetics.[3,78] Muscle hypertrophy is less common than in MC, and some patients develop progressive weakness with time.[78] This disorder is allelic with potassium-sensitive periodic paralysis, and some patients demonstrate features of both disorders with episodes of generalized weakness.[9,79,80] Lifespan is unaffected and systemic involvement is not a feature of PMC.[81]

Examination of affected patients shows eyelid and grip paramyotonia in most patients,[78] but percussion myotonia is not prominent. Immersing a limb in cold water can worsen myotonia and result in weakness. Laboratory investigations show mild elevations in CK, and potassium levels can be high or normal during episodes of weakness.[79,82] EMG shows diffuse myotonic discharges, which can worsen with cooling of the affected limb, as well as eventual electrically silent contractures with progressive cooling.[83] Genetic testing is commercially available, and muscle biopsy demonstrates non-specific myopathic changes with occasional vacuoles.[9,82]

Potassium aggravated myotonia (PAM)

These are a group of autosomal dominant NDMs characterized by sensitivity to potassium ingestion without episodic weakness. They are caused by mutations in SCN4A and include myotonia fluctuans, myotonia permanens, and acetazolimide responsive myotonia. CK levels can be normal or mildly elevated, and EMG shows diffuse myotonic discharges and fibrillation potentials. Commercial genetic testing is available, and changes on muscle biopsy are not well-described.[84-87]

Myotonia fluctuans typically presents in the first to the second decade of life, with myotonia that fluctuates from day-to-day. Patients can be asymptomatic 1 day and have severe myotonia affecting the limbs, extraocular muscles, muscles of mastication, and swallowing on other days. Myotonia is accompanied by "warm-up" phenomenon and increases with potassium ingestion and with a short delay (usually minutes) after exercise. Patients do not develop fixed weakness, and there is no increase in myotonia with exposure to cold.[84,85,88] Eyelid paramyotonia is frequently seen on examination while grip myotonia is less common.

Myotonia permanens is characterized by constant, generalized myotonia that can affect respiration and even lead to hypoxia and respiratory acidosis.[68,86] It has been reported with neonatal episodic laryngospasm,[89] and to worsen with potassium ingestion, fever, pregnancy and after exercise,[86,87] without associated weakness or exacerbation with cooling.

Acetazolimide responsive myotonia presents as painful muscle stiffness in childhood that can involve proximal limbs, muscles of mastication, and extraocular muscles. It worsens with potassium and fasting but may improve with carbohydrate ingestion. Examination shows variable muscle hypertrophy, easily elicitable action and percussion myotonia and paradoxical myotonia in the eyelids.[90,91]

Potassium-sensitive periodic paralysis

This disorder, also called hyperkalemic periodic paralysis (HyperPP), is associated with autosomal dominant mutations in SCN4A. It can present as a pure periodic paralysis syndrome or as periodic paralysis with clinical/electrical myotonia or paramyotonia.[17] Myotonia is usually mild, often involving the eyelids, hands, and tongue. The attacks of weakness can occur at any time and are commonly triggered by rest the following exercise, fasting, ingestion of food high in potassium or stress.[92] Some patients may develop progressive myopathy.[93]

Other sodium channel myotonias

Severe neonatal episodic laryngospasm is a recently described entity consisting of recurrent laryngospasm which results in apnea and apparent life-threatening events in neonates. This has been associated with multiple mutations in SCN4A.[89,94,95] It remains unclear if this is a de novo disorder or represents a neonatal presentation of NDM.

Diagnosis and treatment of NDM

Clinical examination and electrodiagnostic studies are helpful in narrowing down the differential before ordering commercially available genetic tests. Pronounced sensitivity to cold is most suggestive of PMC, although mild cold intolerance is present in other forms. Myotonia tends to be more prominent in the legs in MC, leading to difficulty standing up quickly, while more prominent in the arms and face in PAM. Eye closure myotonia, as well as grip and eye closure paramyotonia, are more common with SCN4A mutations and warm-up phenomenon with MC.[3,6] Patients with recessive MC,[96] PMC, and HyperPP are more likely to report episodes of transient paresis.

The degree of myotonic discharges does not seem to differ greatly between MC and sternocleidomastoid on EMG, but may be less in DM2.[3,97]

The use of the short exercise test, in particular with cooling, has proven useful in differentiating various forms of myotonia.[98,99] The long exercise test can also be helpful, but typically used for diagnosing periodic paralysis.[97]

Treatment of NDM includes the avoidance of triggers and, if necessary, symptomatic treatment of myotonia. PMC patients should be counseled to avoid cold exposure, and HyperPP, PMC or PAM patients to avoid foods rich in potassium (banana, papaya, mango, beans, and dried fruits). Mexiletine use for treatment of myotonia has been supported by a recent randomized control trial.[100] The most common side effect is GI distress[101] that may improve if taken with food. Serious side effects include ventricular arrhythmias and patients should have regular EKG monitoring. Other medications, mostly affecting sodium channels, have shown varying success, including carbamazepine, phenytoin, procainamide, and flecainide.[87] Acetazolimide may work well in acetazolamide-responsive myotonia[91] but rarely reported to cause paralysis in PMC.[102,103]

Conclusion

The myotonic disorders are a heterogeneous group of diseases that result in clinical and/or electrical myotonia. The resulting severity can range from asymptomatic electrical myotonia, as in some cases of dominant MC, to severe disability as in advanced DM1 or myotonia permanens. Correct diagnosis is important for genetic counseling, treatment and proper screening for systemic features. Currently, treatment remains symptomatic, but research in therapies that target the genetic or molecular pathophysiology of these diseases is ongoing.[104-10]

Conflict of Interests

The authors declare no conflict of interest in this study.

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Letter to Editor

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Reversible pulmonary artery hypertension in association with interferon-beta therapy for multiple sclerosis

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The patient was a 32-year-old woman referred to a neurologist in 2008 for walking difficulty and easy fatigue. Physical examination revealed spastic paraparesis. The patient had history of some neurological symptoms since 2003 which were neglected because of little functional impairment and self-limitation. Brain and cervical magnetic resonance imaging (MRI) fulfilled Barkhof criteria for multiple sclerosis (MS). A thorough paraclinical investigation was done and was negative for any other possible explanation for her clinical and MRI presentation. Treatment with subcutaneous interferon beta 1a (IFN-β1a, REBIF@) three times a week began with the diagnosis of relapsing-remitting MS (RRMS). She developed weakness of lower extremities after two months that partially responded to intravenous (IV) corticosteroids.

She was referred to our center due to increased disability score during eight months period despite regular subcutaneous IFN-β1a injections without any obvious relapse. She also suffered from tachycardia, palpitation and easy fatigue. The treatment regimen changed to mitoxantrone with the impression of secondary progressive course, also propranolol started for palpitation. Baseline echocardiography before mitoxantrone injection showed an ejection fraction of 62% for left ventricle, with moderate tricuspid regurgitation and moderate pulmonary artery hypertension (PAH) with pulmonary artery pressure (PA pressure) of 61 mmHg. At that time, she had normal cardiopulmonary physical examination.

A workup for PAH started which revealed tachycardia in electrocardiogram (ECG), and normal chest X-ray, spirometry and ventilation-perfusion scan of lungs. Laboratory investigations for vasculitis were negative. She had low level of thyroid stimulating hormone (TSH), normal total T4 level and increased T3 resin uptake (T3RU) at this time. These findings interpreted as thyroiditis due to IFN-β1a treatment discontinued 7 days before. Her thyroid function returned to normal levels about 10 days later and her palpitation disappeared; propranolol gradually discontinued. She received 20

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mg of mitoxantrone and also advised to perform right-heart catheterization (RHC) but she refused. So the cardiologist decided to follow up her.

In 2010, before the third dose of mitoxantrone and 6 months after stopping IFN-β1a injections, she had no cardiopulmonary symptom, and normal physical examination of cardiopulmonary system. The second echocardiography done by the same cardiologist showed an ejection fraction of 58% for left ventricle, mild tricuspid regurgitation and PAH (PA pressure of 43 mmHg). No specific treatment was done for her PAH. She received 5 doses of 20 mg mitoxantrone every three months. The last echocardiography performed in 2012 (2 years after IFN-β discontinuation) showed normal PAP (25 mmHg). She has still normal cardiopulmonary function and examination, although her Expanded Disability Status Scale (EDSS) has increased to 6.5.

Since the initial discovery of interferon in 1957 as an integral part of innate immunity, many different molecules in this family have been recognized. All three classes of IFNs have been developed as pharmaceuticals and they have clinical indications in many medical specialties.[1]

IFN-β1b was the first disease-modifying therapy for treatment of RRMS approved in 1993 by the United States Food and Drug Administration (USFDA). Subsequently, intramuscular (IM) IFN-β1a (1997) and IFN-β1b (2002) were approved.[1] IFN treatment is accompanied by a variety of adverse events. Relatively, frequent side effects include flu-like symptoms, menstrual disorders, transient laboratory abnormalities, injection-site reactions and psychiatric disorders. A number of possible rare side effects were reported after commercial application of the drugs which were not reported in pivotal trials. These include development and exacerbation of other autoimmune diseases (thyroiditis, immune thrombocytopenia, and anemia), capillary leak syndrome, anaphylactic shock and polyneuropathy.[1] There are also reports of livedoreticularis and Raynaud phenomenon, renal thrombotic microangiopathy and malignant arterial hypertension in patients with MS receiving IFN-β treatment.[2]

Since 1993, there are reports of PAH associated with IFN-α injections.[3] The first report of PAH following IFN-β treatment was in 2009;[4] after that, other cases of patients with MS were detected who developed this serious condition after IFN-β treatment,[3-7] but this side effect has been remained rare among IFN-β users. In most of the IFN-α associated PAHs, there are also other risk factors of PAH; although some patients has not any other risk factors and in some, PAH has developed before IFN-α therapy, but progressed with this treatment to more severe disease.[3]

In the few reported cases of IFN-β-associated PAH, only one had a definite risk factor of PAH (atrial septal defect) which resolved after surgical repair.[3] In other cases, PAH was severe and making combination treatment of was necessary, leading to death in 2 cases.[3] In all previous cases, PAH was developed after more than 3 years of IFN-β injections. Our case is the first asymptomatic, incidentally detected PAH which was also self-limited after discontinuing the treatment. The interval time between starting IFN-β treatment and PAH detection was less than one year.

Many experimental studies have investigated the effect of IFN on pulmonary vascular systems. Stimulation of thromboxane cascade, endothelin release, and "sensitizing" effect of tumor necrosis factor (TNF) on IFN responsiveness are all presumed mechanism according to the studies.[3] But, the exact mechanism is to be determined.

Although in many cases of IFN-α related PAH there are other risk factors for development of PAH, and IFN treatment seems to be a "trigger", but as mentioned, there are some "pure" cases of PAH after IFN-β therapy, and IFN is now considered as a "possible" risk factor for PAH.[3] As PAH is a serious condition, it seems reasonable to conduct well designed, clinical and experimental research to better understand the underlying mechanism of IFN-related PAH.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Neurological Image/Video

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Neurofibromatosis type 1, presenting as a rare widespread neurofibromas with cord compression

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Keywords
Neurofibromatosis type 1; Neurofibroma; Spinsl Cord Compression

Neurofibromatosis type 1 (NF1) is a genetic disorder that disturbs cell growth in nervous system, causing tumors to form on nerve tissue.

A 26-year-old man was brought to Ali-Ebn Abitaleb Hospital, Rafsanjan, Iran, with asymmetric quadriplegia more in left side. He was a known case of NF1. He first had a paraparesia two weeks before admission that progressed to quadriparesia. There was no family history of neurofibromatosis.

Hyperpigment lesions were revealed in variable sizes. Multiple nodular lesions and inguinal freckles were seen on his body surface. Babinski sign, hyperreflexia and spasticity were detected in lower limbs examination. Decreased sensation was revealed more in left side. Sphincter function was normal. In cervical spine magnetic resonance imaging (MRI), there were multiple mass lesions in paraspinal, intradural extramedullary and extradural region with cord compression from C1 to C6. Several neurofibromas were extraordinary in orbital cavity, neck, whole paraspinal tissues, mediastinum, para-aortic region, presacral, and pelvis with widening of neural foramina (dumbbell shaped lesions), also in perianal and sacral region (Figures 1-3).

Three months later, he was admitted to the surgery ward for an extensive laminectomy and reconstruction procedures.

As the most common symptom in other reports, our presenting case symptom was quadriparesis but asymmetric. In our case, there was multi-level involvement of cervical cord, not only C2 or C3 as in most reported cases.[1]

In a retrospective study on 97 patients with NF1, spinal curvature abnormality was present in 50/97 patients.[1] In another case report, a 43-year-old man with history of NF1 presented with signs and symptoms of myelopathy and severe cervical kyphotic deformity.[2] Our case was unique according to absence of deformity with widespread and plexiform neurofibromas.

In literature, there were some reported extensive neurofibromas that were less widespread than ours; and also there were 9 reported cases between the age of 3 to 15 years old with voluminous plexiform neurofibromas in neck region that were not as widespread as our case.[3]

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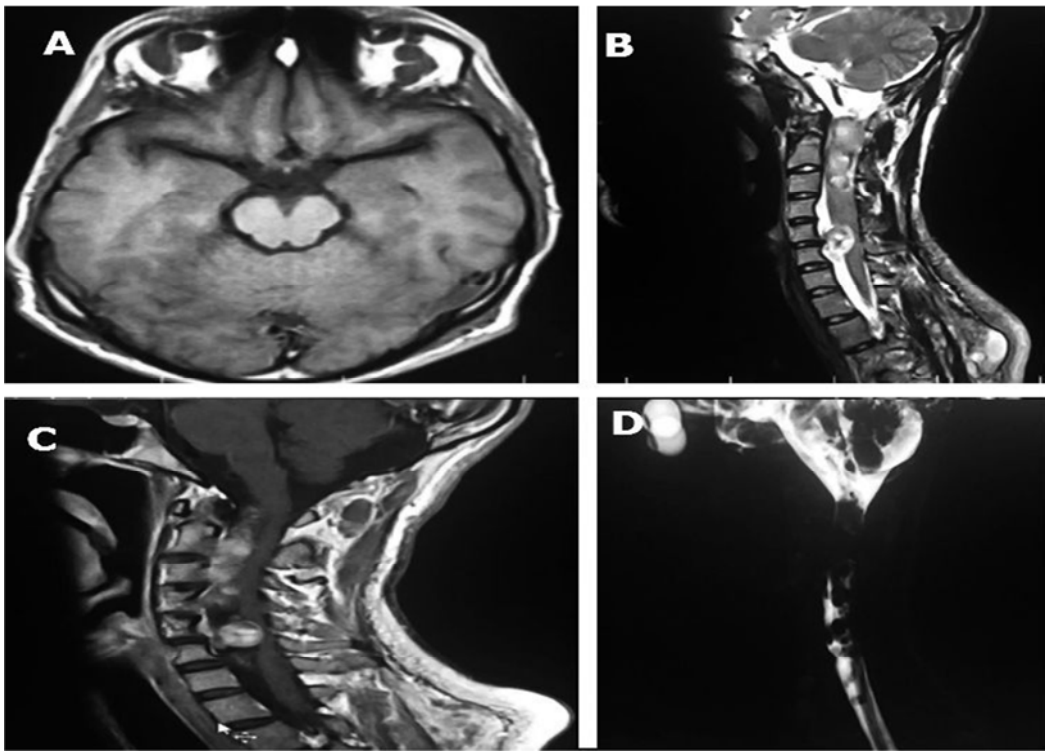

Figure 1. Widespread neurofibromas of orbital and cervical spine. Axial noncontrast T1-weighted image of brain reveals bilateral supra-orbital neurofibromas (A), Sagittal T2-weighted magnetic resonance imaging (MRI) of cervical spine reveals multiple intradural extramedullary neurofibromas, causing cord compression, widening of upper thoracic neural foramen and subcutaneous neurofibromas (B), Sagittal post-contrast T1-weighted image of cervical spine demonstrates multiple enhancing intradural extramedullary lesions causing cord compression (C), Sagittal cervical magnetic resonance myelogram shows multiple intradural filling defects (D).

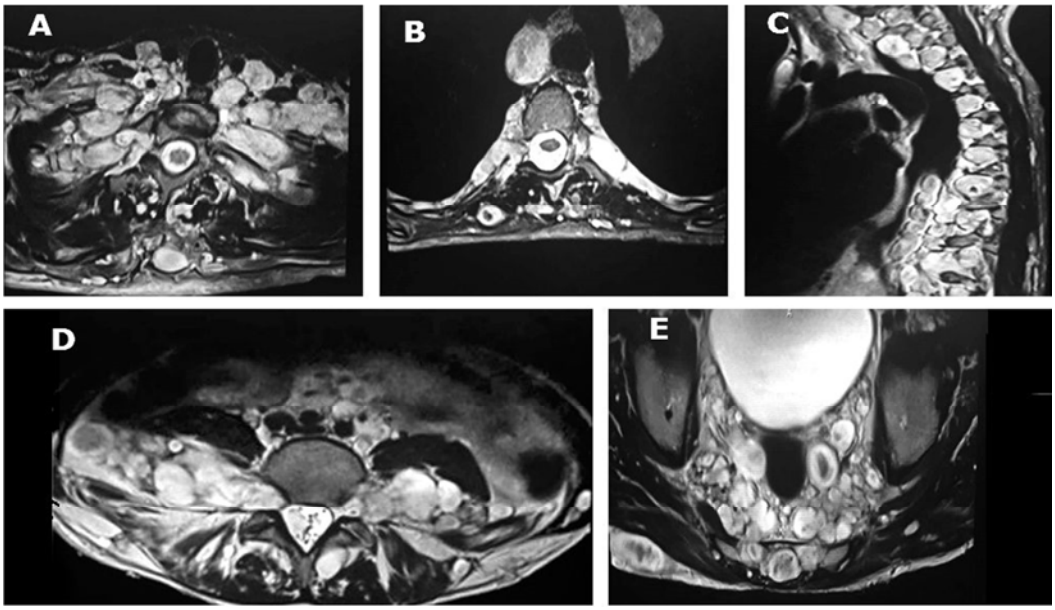

Figure 2. Widespread neurofibromas in neck, thorax, abdomen and pelvis; Axial T2-weighted image demonstrates widespread plexiform neurofibromas in the neck (A), Axial and parasagittal T2-weighted magnetic resonance imagings (MRI) demonstrate widespread cervical and thoracic paravertebral and mediastinal neurofibromas arising from cervicothoracic nerve roots (B and C), Axial T2-weighted MRI demonstrates multiple neurofibromas in the lumbar paravertebral, neural foraminal, para-aortic and retroperitoneal regions. Anterior displacement of bilateral psoas muscles is seen (D), Axial T2-weighted MRI demonstrate widespread pelvic neurofibromas in the perirectal and presacral spaces (E).

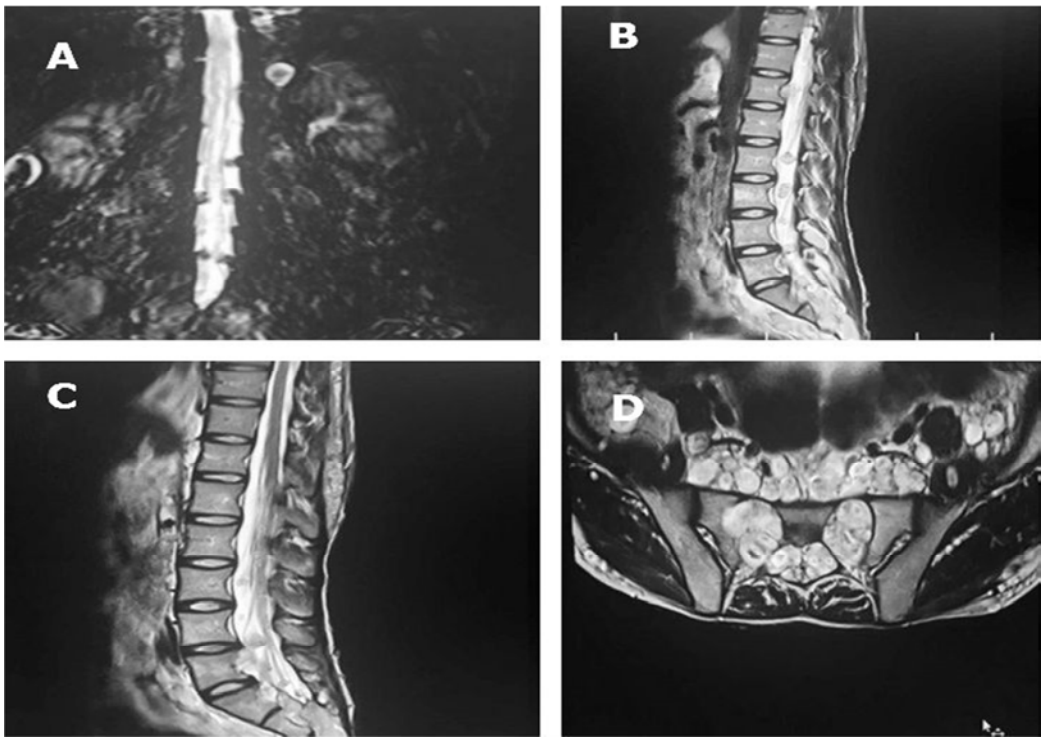

Figure 3. Widespread neurofibromas in lumbosacral nerve roots; In coronal magnetic resonance myelogram, multiple intradural neurofibromas arising from lumbosacral nerve roots are seen (A), Sagittal T2- weighted magnetic resonance imaging (MRI) of lumbosacral spine shows neurofibromas arising from nerve roots (B and C), Axial T2-weighted MRI demonstrates innumerable neurofibromas in the presacral space and in the sacral neural foramina causing enlargement of corresponding neural foramina (D).

Our case had diffuse involvement from orbital to sacral region and such extent of involvement has not been reported in related articles about patients with neurofibromatosis.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

We acknowledge our patient who accepted to participate in this study.

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Iranian Neurological Events

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Iranian International Headache Congress, 2015

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Keywords
Congresses; Headache; Migraine; Iran

The 4th Iranian International Headache Congress was held in Tehran, Iran, from September 16 to 18, 2015. The congress was supported by Iranian Neurological Association under the auspicious of International Headache Society. 340 physicians and researchers participated in the congress among them Professor A. Rapoport, Professor R. Cowan, Professor H. Bolay, Dr. F. Maniyar, and Dr. H. Ansari were the international guests.

The congress was managed by Professor M. Togha and nicely supported by the president of the Neurological Association, Professor H. Pakdaman. The main aim of the congress was to familiarize neurologists and other specialists with the latest scientific achievements in the field of "Headache".

The interesting characteristic of this congress was that abstracts and most of the full texts of lectures were available online on our website from the first day of the congress. In addition, the hard copies of the abstract were offered to the participants on registration.

Accordingly, several scientific programs were held during 3 days. The programs were divided into the following five categories:

1. Main Lectures

Totally, 35 lectures were presented by headache specialists and physicians who were considered expert in a specific field related to primary or secondary headaches.

Accordingly, we can refer to the basic lectures, like pathophysiology of migraine [CGRP (calcitonin gene-related peptide)] presented by Professor A. Rapoport, and basic science (how we could use in animal model) presented by Professor H. Bolay. Besides, different speeches on updates in the field of diagnosis and treatment of primary headaches were given, like non-cephalic migraine equivalents by Professor R. Cowan, optimizing treatment of acute migraine attack by Dr. F. Maniyar, and cluster headache by Dr. H. Ansari.

Different speeches were offered on migraine variants, secondary headaches and related subjects such as metabolic headache by Professor M. Ghafarpoor; ictal epileptic headache by Professor M. Motamedi; migraine and vertigo by Professor M. Togha, and drug interactions in headache treatment by Dr. L. Kuti.

2. Case Presentation

This part was one of the popular sections of the congress moderated by Dr. M. Nabavi, and five challenging cases were discussed in an interactive presentation.

3. Workshops

In this section, two workshops were provided, in the first of which mainly younger neurologists were trained on techniques of botulinum toxin injection

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for chronic migraine; and the techniques of nerve blocks in headaches were touched in the second workshop. These workshops were nicely moderated by Dr. H. Ansari.

4. Panels

Two panels were held during the congress. The first panel discussed different aspects of idiopathic intracranial hypertension and idiopathic intracranial hypotension, and the other one reviewed different unapproved but effective treatment modalities on headaches including migraine surgery, nutritional aspects on headache, the effect of exercise on headaches, and the suggestions of Iranian traditional medicine for headaches.

5. Residents Scientific Competition

This was nicely conducted by Dr. A. Okhovat with cooperation of Dr. S. Ahmadi-Karvrigh and Dr. E. Hesami. In this part, the competition was between the selected neurology residents from 13 universities of different cities of Iran in the primary and final sections and the first, second and third winners were received valuable presents.

The valuable assistance of Dr. S. Baghizadeh and Mr. H. Ghasemi and nice cooperation of Dr. H. Paknejad, Dr. A. Okhovat, Dr. S. Haghighi, Dr. N. Yamani, Dr. F. Vahabi, Dr. Advani, Dr. M. Ghafarpoor, A. Naser Moghadasi, S. Razeghi Jahromi and S. Habibi Moeini as well as, the other members of scientific and organizing committee had an important role in the better management of the congress.

The headache congress could unquestionably play an important role in promoting the status of knowledge in the field of headache in Iran. The positive feedback from the attendees was a good sign of achievement to the goal of the congress that was the presentation of high-quality programs meet their expectations.

Indeed, attendance of distinguished international headache specialist with the cooperation of International Headache Society, and Iranian esteemed neurologists as lecturers and the active participants from different parts of Iran in response to invitation from Iranian Headache Association contributed to establish a good relationship between the Iranian Headache Association and International Headache Society.

Conflict of Interests

The authors declare no conflict of interest in this study.

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From left to right in the front: Dr. N. Beladimoghadam, Professor M. Togha, Dr. J. Adibeig, Professor H. Pakdaman, Professor A. Rapoport, Professor R. Cowan, Professor H. Bolay, Dr. F. Maniyar, and Dr. H. Ansari