Iranian Journal of Neurology

Official Journal of Iranian Neurological Association

Original Articles

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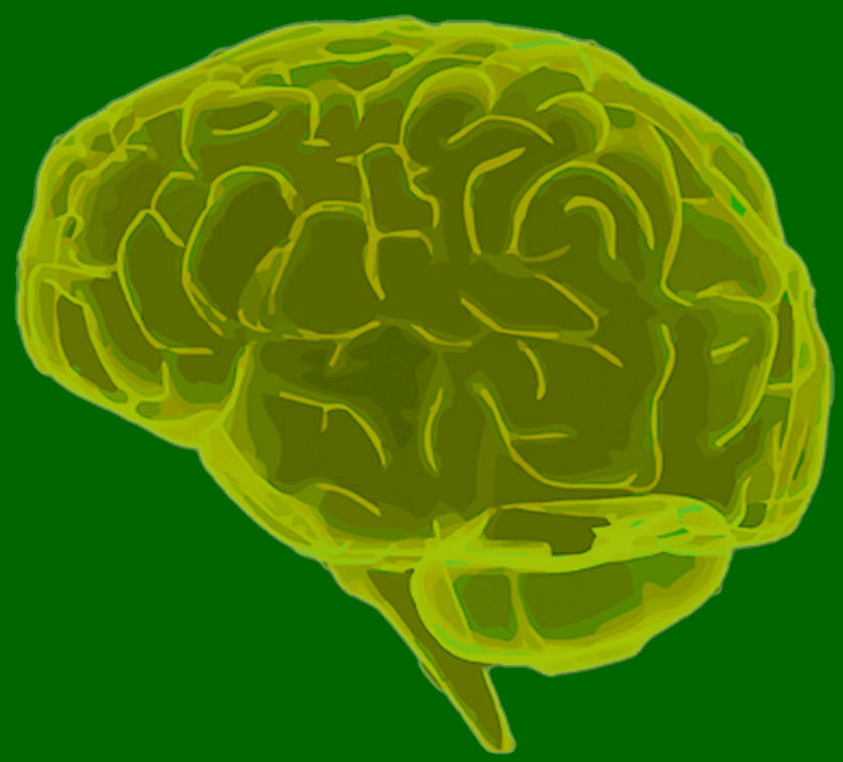

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Iranian Journal of Neurology

INFORMATION FOR AUTHORS

Aim and Scope

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

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Cover Letter:

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

(1) The paper has not been published to date (except for abstracts of conference materials).

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

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

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The Editorial Board reserves the right to reject a paper without seeking reviewers' opinion provide the content or the form of the paper does not meet minimum acceptance criteria or if the subject of the paper is beyond the aims and scope of the journal.

Everyone listed as the author of a paper is responsible for the reliability and completeness of data presented in the paper.

Do not submit papers that copy fully or partially previously published papers.

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Where available, URLs for the references have been provided.

The text is double-spaced; uses an Arial 12-point font; and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.

The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.

If the Editorial Board is not notified in advance and the paper is found to have been copied during editorial work, the paper shall be rejected.

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Manuscripts

The journal publishes:

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

Details

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

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

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

Neurological images or videos: Interesting cases as

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.

Clinical notes: Refer to important interesting observations which are imperative for reminders in clinical practice. The maximum number is 1000 words with maximum 5 references, 1 table and 1 figure with no abstract.

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

Structure of Articles

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 manuscript type, see above):

1. **Introduction:** The introduction should be as concise as possible and introduce the context of the paper to the reader; the paper should clearly state the research hypothesis and the objective of the study.

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.

3. **Results:** Present results directly related to the topic of the paper only; tables and/or figures are recommended.

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

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In the paper references should be given in **superscripts** with no space between the comma and the consecutive number.

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Give names of first ***six*** authors; if there are more authors, add "et al.". Use Index Medicus abbreviations for journal titles. Then mention the volume and the issue of the journal.

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

Review process: All papers submitted for publication in the journal are assessed by two independent reviewers with the mutual anonymity rule as to the names of reviewers and authors observed.

Plagiarism policy: According to the plagiarism policy of Iranian Journal of Neurology, plagiarism is defined as a paper which replicates another publication with as a minimum 25% resemblance and devoid of citation.

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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Iranian Journal of Neurology

Original Paper

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A combined exercise model for improving muscle strength, balance, walking distance, and motor agility in multiple sclerosis patients: A randomized clinical trial

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Keywords
Multiple Sclerosis; Exercise Therapy; Aerobic Exercise; Resistance Training

Abstract

Background: Multiple sclerosis (MS) is a neurological disease with a variety of signs and symptoms. Exercise therapy has been shown to improve physical functions in MS. However, questions about an optimal exercise therapy remain. In this regard, we suggest a combined exercise therapy including aerobic and resistance exercises for MS patients. The study is designed to observe, test and compare the effects of proposed combined exercises on strength, balance, agility, fatigue, speed, and walking distance in people with mild to moderate MS [0 < expanded disability status scale (EDSS) < 5].

Methods: A total of 40 people with relapse-remitting MS (16 male, 0 < EDSS < 5) were randomized into one of the four groups (3 intervention and one control). The intervention consisted of various combinations of aerobic and resistance exercises with different repetition rates. Pre- and post-intervention scores of fatigue severity scale (FSS), timed up and go (TUG) test, 6-minute walk test (6MWT), 10- and 20-MWT, Berg balance scale (BBS), and one repetition maximum (1RM) test were recorded and analyzed.

Results: For most tests, post-intervention values of the group 1, with 3-aerobic and 1-resistance exercises, were significantly higher compared to control group ($P < 0.050$). However, no significant progression was observed in the other two intervention groups.

Conclusion: A combination of three aerobic exercises with one resistance exercise may result in improved balance, locomotion, and endurance in MS patients.

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system with both inflammation and neurodegeneration outcomes such as inflammatory attacks.[1] Adults between 18 and 40 are commonly affected by MS with a relapsing-remitting and sometimes a steady progression course.[2,3] The most common symptoms of MS include weakness, fatigue, and imbalance.[2,3] Balance impairment, which can lead to falls and injuries, is reported in 78% of people with MS.[4] There is no uniform and/or well-established pharmacologic method to resolve imbalance, fatigue and weakness in MS. However, rehabilitation methods may be helpful.[5,6] A number of studies have reported the benefits of exercise and physical activity.[7] On one hand, power exercises can ameliorate muscle weakness and improve coordination which, in turn, can improve balance, agility and decrease muscle spasticity.[7-10] Further, studies have reported increased muscle strength and functional capacity, using different power exercises in people with MS.[11-13] On the other hand, aerobic exercise has been shown to significantly decrease fatigue[14] and increase walking distance[15] or speed.[16]

Although several studies have approved the efficacy of exercise to improve balance in people with MS, each has followed a different exercise protocol and yielded different results. A gradual progression from simple exercises such as stationary biking or weight lifting, to a combination of exercises has been reported to be beneficial.[6] For instance, combined exercises improved patients' balance[17-19] as well as endurance.[20-22]

Although combined exercises have proved effective,[19,23] their complexity may force patients and professionals to do them in well-equipped centers. Besides, these types of interventions were conducted on patients with mild relapsing-remitting MS, with an expanded disability status scale (EDSS) of < 3.5. To best of our knowledge, there are no studies on the effects of exercise in MS patients with moderate to severe disability and in progressive type.[5,8] Hence, the objective of this study is to observe, test and compare the effects of proposed combined exercises on strength, walking speed, walking distance, balance, agility and fatigue, in mild to moderate people with MS (0 < EDSS < 5).

Materials and Methods

This is a case-control randomized clinical trial. Due to obvious limitations, only those assessing the outcomes were blinded to group assignment. Members of Iranian MS Society (IMSS) were referred to IMSS physiotherapy center in Tehran, Iran, by their neurologists for rehabilitation program from September until November 2012. Demographic information of all patients was recorded in the center database, and those met the inclusion/exclusion criteria were advised to participant in the study. Finally, 40 people with MS were recruited and randomly assigned to four groups: three experimental and one control group. To avoid confounding effects, the four groups were matched on group characteristics [namely age, gender, body mass index (BMI), and social status].

Inclusion/exclusion criteria

The inclusion criteria include:

1. Definite relapse-remaining MS (RRMS)
2. Adults between 18 and 50 years of age
3. An EDSS level of 0-5
4. Right-handed
5. No history of systemic disease, concomitant neurological disorders, epilepsy, heart diseases, anemia, or severe depression.

The exclusion criteria include:

1. Under treatment with corticosteroid (in relapse time), or a history of recent attack (< 3 months)
2. Participants who completed < 30 sessions of exercise for any reason.

Participants were randomly assigned to four groups:

1. Group 1, which performed 1 aerobic exercise training and 3 resistance exercise training sessions per week
2. Group 2, which performed 2 aerobic exercise training and 2 resistance exercise training sessions per week
3. Group 3, Group 1, which performed 3 aerobic exercise training and 1 resistance exercise training session per week
4. Control group: All participants voluntarily filled the informed consent. Baseline scores were recorded within 5 days before the intervention and post-test scores were recorded exactly 72 hours after the end of the protocol for each group.

Outcome measures evaluated in this study are defined and measured as below:

1. One repetition maximum (1RM) test: To

measure strength (heaviest weight a person can lift using quadriceps and hamstring muscles at first attempt)[24,25]

2. Berg balance scale (BBS): To measure balance[26]

3. Timed up and go (TUG) test: To measure agility[27,28]

4. 10-minute walk test (10MWT) and 20MWT: To measure speed of movement[29]

5. 6MWT: To measure the endurance and functional capacity[30,31]

6. Fatigue severity scale (FSS): To measure fatigue[30,31]

7. BMI: Weight in kilograms divided by the square of height in centimeters.[32]

A JEXERS® exercise machine with a tolerance of 1 kg was used to measure the quadriceps and hamstring strength based on 1RM. Furthermore, a metal meter was used to measure the height of subjects in centimeters and a G200 BEURER® (China) digital scale with 100 g tolerance to measure the weight of cases.

In addition, BBS test was based on the Farsi version, which is a standard device in the IMSS rehabilitation center.[26] To test for the walking speed, a running track in the gymnasium of rehabilitation center was measured and marked exactly at 10 and 20 m.[33] For the TUG test, as mentioned in the manual, a chair, and a digital chronometer were used. The 6MWT was performed in a big gymnasium out of rehabilitation center.

Participants in the intervention groups performed exercises in groups. However, due to space and time limitations, it was not possible for all the groups to do the exercises simultaneously.[34] Each group had four exercise sessions per week for 8 weeks (32 sessions). The interventions consisted of three stages per session: Stage 1: Warm up, Stage 2: main intervention and Stage 3: cool down.

- Stage 1: in this stage, one of the trainers demonstrated simple stretches for the neck, upper/lower extremities, and the trunk. Subjects were asked to follow.
- Stage 2: during the main interventional stage, each group followed their own program. For example, group 1 patients practiced individually tailored resistance exercises one session each week. For the next three sessions of the week, participants did two aerobic exercises: stationary bike and treadmill. Table 1 illustrates the workout routine for both resistance and aerobic exercises. For groups 2 and 3, the exercise sessions changed to 2 resistance/2 aerobic and 3 resistance/1 aerobic sessions per week, respectively. Maximum heart rate (MHR) of each person was tracked to prevent exhaustion while biking or using treadmill. During the 1st week, the aerobic exercise begun with about 40% of MHR and 10 minutes per each device, then it gradually increased up to 70% of MHR and 20 minutes for each aerobic exercise. In addition, strength exercises started with 50% of 1RM with 10 repetitions of 3 sets and increased up to 70% of 1RM with 10 repetitions and three sets of exercise for each flexor or extensor of both knees.[24,25]
- Between two aerobic activities, bike and treadmill, and resistance sessions, extensors and flexors of the both knees, patients had a 10-minute and 5-minute inactive rest, respectively. If a patients' heart rate reached above the limit, the exercise was stopped and the participant had to rest until the heart rate decreased (Tables 1 and 2).

Table 1. Endurance exercises mode

Exercise types	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Cycling	10 minutes 40% MHR	10 minutes 50% MHR	15 minutes 50% MHR	15 minutes 55% MHR	15 minutes 55% MHR	20 minutes 55% MHR	20 minutes 60% MHR	20 minutes 70% MHR
Rest	10 minutes Inactive	10 minutes Inactive	10 minutes Inactive	10 minutes Inactive	10 minutes Inactive	10 minutes Inactive	10 minutes Inactive	10 minutes Inactive
Walking on treadmill	10 minutes 40% MHR	10 minutes 50% MHR	15 minutes 50% MHR	15 minutes 55% MHR	15 minutes 55% MHR	20 minutes 55% MHR	20 minutes 60% MHR	20 minutes 70% MHR

MHR: Maximum heart rate

Table 2. Strength exercises model

Exercise kind	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Knee extension	Intensity 50% 1RM	Intensity 55% 1RM	Intensity 60% 1RM	Intensity 60% 1RM	Intensity 65% 1RM	Intensity 65% 1RM	Intensity 70% 1RM	Intensity 70% 1RM
	3 times'	3 times'	3 times'	3 times'	3 times'	3 times'	3 times'	3 times'
	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time
Rest time	5 minutes	5 minutes	5 minutes	5 minutes	5 minutes	5 minutes	5 minutes	5 minutes
	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Knee flexion	Intensity 50% 1RM'	Intensity 55% 1RM'	Intensity 60% 1RM'	Intensity 60% 1RM'	Intensity 65% 1RM'	Intensity 65% 1RM'	Intensity 70% 1RM'	Intensity 70% 1RM'
	3 times'	3 times'	3 times'	3 times'	3 times'	3 times'	3 times'	3 times'
	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time	10 repetitions each time

1RM: One repetition maximum

- Stage 3: one of the trainers demonstrated some simple stretching movements to ensure that all participants cooled down at the end of exercise sessions. Participants were further encouraged to take some fruit juice, date, biscuits, and milk.[35]

Ethical issues (including plagiarism, informed consent, research misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors. The Ethics Committee of Sport Science Research Institute of Iran approved the study protocol with Code No: S/93/398. For ethical reasons, at the end of the study the control group also received combinational exercises. All participants gave informed consent (both oral and written) in accordance with the declaration of Helsinki.

The normality of data was tested and confirmed by Kolmogorov-Smirnov test. Homogeneity of the four groups at baseline was confirmed using one-way ANOVA. Values from pre- (5 days before the intervention) and post-test (3 days after the intervention) were compared based on paired t-test. All data were analyzed using SPSS software (version 22, SPSS Inc., Chicago, IL, USA). An α-level of < 0.05 was considered significant.

Results

IMSS referred 97 RRMS patients to our rehabilitation center. According to the inclusion/exclusion criteria, 40 patients (24 female and 16 male) participated in the study; with mean disease duration of 2 years and BMI range of 18.5-25 kg/m^2. All the patients successfully completed the procedure (Figure 1). There were 4 men and 6 women in each group. Table 3 gives descriptive statistics for age, height, weight, BMI and EDSS variables, separately for each group.

Test results

6MWT: 6MWT score of the control group and the intervention group 1 did not change significantly comparing pre- and post-intervention values, whereas both intervention group 2 and 3 showed significant changes ($P < 0.050$) (Table 4). A comparison of post-test scores changes between groups declared a significantly higher score for groups 1 and 2 compared to the control group ($P < 0.050$).

10MWT: For 10MWT, all the three experimental groups showed a significant decrease in time taken to walk after the intervention ($P < 0.050$) (Table 4). The decreases in groups 1 to 3 were 2.4, 1.5 and 1.9 seconds, respectively. An average change in time taken to walk for group 1 was significantly different from control group ($P = 0.030$) (Table 5).

20MWT: In the 20MWT, time taken to walk significantly decreased after the intervention in experimental groups 1 ($P = 0.045$), 2 ($P = 0.012$) and 3 ($P = 0.014$) compared to the baseline values (day-0) (Table 4). In the control group, however, no significant change was observed (Table 4). An average change in time taken to walk for group 1 was significantly different from control group ($P = 0.020$) (Table 5).

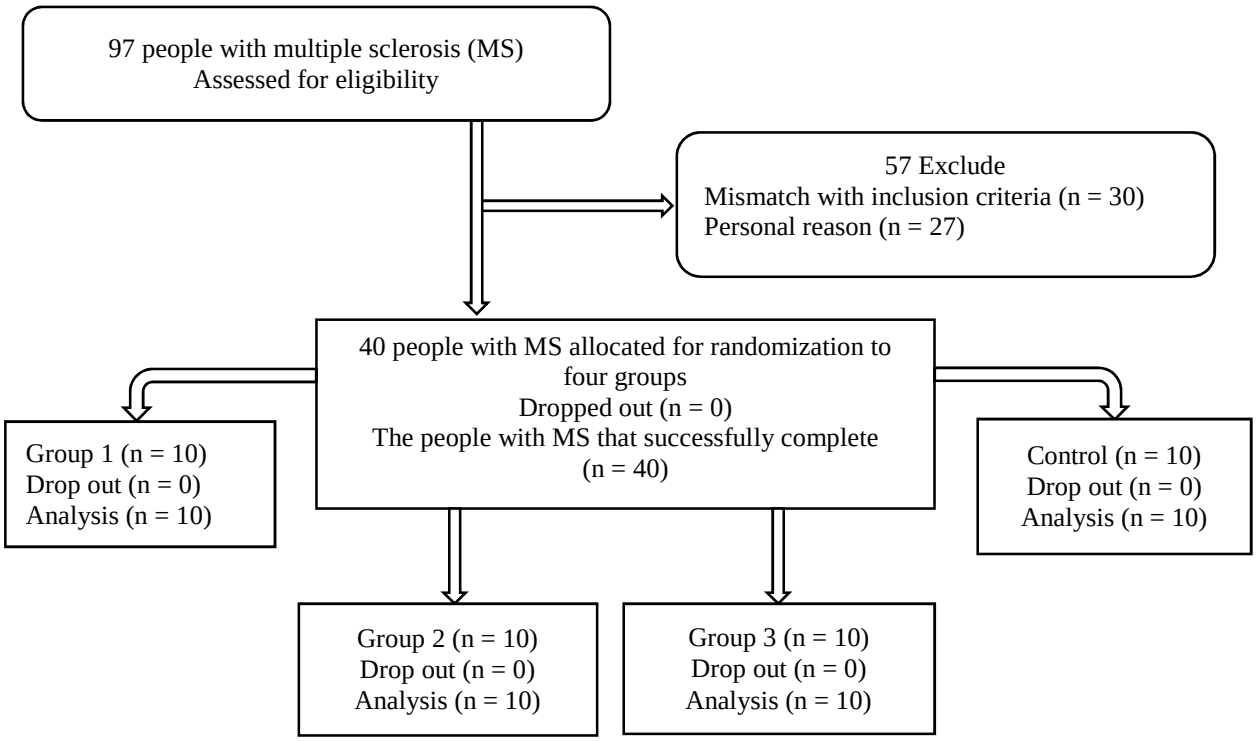

Figure 1. Consort flowchart

Table 3. Mean of age, height, weight, body mass index (BMI), and expanded disability status scale (EDSS) for all groups

Groups	Age (years)	Length (cm)	Weight (kg)	BMI (kg/m^2)	EDSS (score)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Experimental 1 (n = 10)	35.80 ± 8.42	166.48 ± 6.99	68.13 ± 9.48	24.92 ± 2.76	1.33 ± 0.66
Experimental 2 (n = 10)	31.33 ± 8.21	164.97 ± 7.90	63.55 ± 13.65	23.99 ± 5.78	2.06 ± 0.86
Experimental 3 (n = 10)	33.91 ± 7.94	165.06 ± 8.56	66.92 ± 12.35	24.01 ± 3.35	1.95 ± 1.12
Control (n = 10)	33.63 ± 6.92	165.12 ± 7.59	63.00 ± 11.25	24.44 ± 4.78	1.81 ± 0.53

SD: Standard deviation; BMI: Body mass index; EDSS: Expanded disability status scale

BBS: BBS score significantly raised (about 6 points) after the intervention only for group 1 (P = 0.010) (Table 4). Group 1 score change was also significantly higher compared to the control group (P < 0.001) (Table 5).

Right knee extension and flexion strength (dominant leg): Right knee extension strength significantly increased in experimental groups 1 and 3 (P < 0.050). However, only group 3 showed a significant improvement of flexion strength (P = 0.012) (Table 4). A comparison of mean score change (post- and pre-score) indicated that flexion strength changes for intervention groups were significantly different from control group (P = 0.020, P = 0.040 and P = 0.010, respectively) (Table 5).

Left knee extension and flexion strength (non-dominant leg): Extension strength score significantly changed in all the intervention groups (P < 0.050). Average scores increased 8.4, 5.7 and 8.6 kg in groups 1 to 3, respectively. Moreover, flexion strength significantly changed in groups 1 and 3 (P = 0.015 and P = 0.001, respectively) (Table 4). A comparison of mean change in flexion and extension strength between groups showed that in groups 1 and 3, changes were significantly different from that of the control group (P = 0.010) (Table 5).

TUG test and FSS: A statistical analysis of both TUG test and FSS values did not indicate any significant change within groups.

In addition, based on post-hoc analysis of mean score change, none of the pair-wise comparisons of intervention groups were significantly different in 6MWT, 10MWT, 20MWT, right and left knee extension/flexion (P > 0.050).

Table 4. Descriptive statistics for four studied groups' variables before and after test

Variable	Group	n	Average before test	SD	Average after test	SD	Difference between average after test and average before test	Difference percentage	P
10MW speed (s)	Control	10	15.217	18.94777	15.122	19.02946	−0.095	−0.624281255	0.758
	Group 1	10	9.828	4.89645	7.422	2.42591	−2.4056	−24.47750259	0.040*
	Group 2	10	8.109	2.08783	6.567	1.29852	−1.5413	−19.00774467	0.037*
	Group 3	10	9.874	5.56309	7.949	5.55153	−1.925	−19.49564513	0.014*
20MW speed (s)	Control	10	29.085	32.02146	28.985	32.13234	−0.1	−0.343819838	0.908
	Group 1	10	19.953	10.04469	14.876	5.00254	−5.0777	−25.4479209	0.045*
	Group 2	10	17.124	4.31811	13.306	2.03388	−3.8175	−22.29353298	0.012*
	Group 3	10	17.248	5.31164	13.919	3.99213	−3.329	−19.3007885	0.014*
Balance (score)	Control	10	45.000	10.04277	45.000	9.74500	0	0	0.214
	Group 1	10	43.111	4.96096	49.000	2.34521	5.8889	13.65982311	0.010*
	Group 2	10	49.375	3.06769	50.625	1.84681	1.25	2.53164557	0.080
	Group 3	10	45.400	8.93433	48.500	4.99444	3.1	6.828193833	0.060
Left knee extension strength (kg)	Control	10	10.667	5.04645	11.333	6.43946	0.6666	6.249355471	0.146
	Group 1	10	12.000	5.3619	20.444	6.12599	8.4444	70.37	0.004*
	Group 2	10	19.000	10.01428	24.750	10.93814	5.75	30.26315789	0.029*
	Group 3	10	14.580	7.16377	23.200	8.70249	8.62	59.12208505	0.001*
Right knee extension strength (kg)	Control	10	14.667	3.26599	16.667	7.44759	2	13.63633264	0.458
	Group 1	10	12.111	5.1099	19.000	6.61438	6.8889	56.88087787	0.002*
	Group 2	10	21.375	9.31876	25.000	10.91526	3.625	16.95906433	0.340
	Group 3	10	16.000	6.8313	24.300	8.53815	8.3	51.875	0.001*
Left knee flexion strength (kg)	Control	10	5.346	2.761	4.917	2.61566	−0.42897	−8.024625538	0.2390
	Group 1	10	7.422	3.50955	13.000	4.03113	5.5778	75.150225	0.015*
	Group 2	10	12.375	4.89716	15.500	5.47723	3.125	25.25252525	0.151
	Group 3	10	7.060	2.49275	12.600	2.79682	5.54	78.47025496	0.001*
Right knee flexion strength (kg)	Control	10	8.205	3.55624	7.750	2.80624	−0.4555	−5.551154713	0.100
	Group 1	10	7.722	3.64958	12.333	4.74342	4.6111	59.71225816	0.080
	Group 2	10	13.375	5.15302	17.250	5.94619	3.875	28.97196262	0.098
	Group 3	10	8.850	2.80921	12.900	3.38132	4.05	45.76271186	0.012*
6MWT	Control	10	361.500	238.86757	367.500	258.75692	6.0000	1.659751037	0.249
	Group 1	10	380.222	136.77790	461.444	139.61206	81.2222	21.36177674	0.057
	Group 2	10	422.500	106.39012	491.500	108.79338	69.0000	16.33136095	0.034*
	Group 3	10	363.000	159.48319	396.500	154.32739	33.5000	9.228650138	0.043*

*Significant at α level less than 0.05

SD: Standard deviation; 6MWT: 6 minute walking test; 10MW: 10 m walk

Table 5. The groups compare to control group

The tests	Groups	Mean difference	SE	P
Left knee flexion	Control group			
	Group 1	−5.57	2.09	0.010*
	Group 2	−3.12	2.14	0.150
	Group 3	−5.54	2.04	0.010*
Right knee flexion	Control group			
	Group 1	−4.61	1.89	0.020*
	Group 2	−3.87	1.94	0.040*
	Group 3	−4.05	1.85	0.010*
Left knee extension	Control group			
	Group 1	−7.77	2.73	0.010*
	Group 2	−5.08	2.80	0.080
	Group 3	−7.95	2.68	0.010*
Right knee extension	Control group			
	Group 1	−4.88	3.48	0.170
	Group 2	−1.62	3.56	0.650
	Group 3	−6.30	3.41	0.070
Balance	Control group			
	Group 1	−5.88	1.80	< 0.001*
	Group 2	−1.25	1.85	0.500
	Group 3	−3.10	1.75	0.090
6MWT	Control group			
	Group 1	−75.22	28.21	0.010*
	Group 2	−63.00	29.03	0.040*
	Group 3	−27.50	27.54	0.330
10MW test	Control group			
	Group 1	2.31	1.04	0.030*
	Group 2	1.45	1.07	0.190
	Group 3	1.83	1.01	0.080
20MW test	Control group			
	Group 1	4.98	2.05	0.020*
	Group 2	3.72	2.11	0.090
	Group 3	3.23	2.00	0.120

Significant at α level less than 0.05, SE: Standard error; 6MWT: 6 minute walking test; 10MW: 10 m walk

Discussion

Our study was a randomized clinical trial to evaluate the effects of proposed combined exercises to improve muscle strength, balance, walking distance, and motor agility in patients with MS. We can divide the result into four sub-categories to discuss; the first part relates to tests that evaluated the strength of flexor and extensor muscles of the knees. The second part includes the tests that evaluated features of walking. The third and fourth parts are balance and fatigue scales.

Our findings showed a significant improvement of measures in intervention group 1, for which the dominant activity was aerobic exercise. Furthermore, they were in accordance with the studies of Dalgas et al.,[5] Le Page et al.,[8] Kjolhede et al.,[9] Motl et al.,[36] and Sangelaji et al.,[19] However, Hansen et al.[37] reported ineffectiveness of combined exercises, which may be due to application of different methods and measures as he used heart rate and blood examination. Significant strength improvements were observed in almost all knee flexor and extensor muscles in groups 1 and 3, but not group 2. These findings are in concordance with those of DeBolt and McCubbin,[38] Kjolhede et al.,[9] Le Page et al.[8] and Medina-Perez et al.[39] Although one would expect increase in muscle strength through resistance exercises, it was remarkable to note the increase in muscle strength with endurance exercises for group 1. A reason could be the fact that exercises such as stationary bike and treadmill walking may strengthen people with MS who lack regular exercise. This may also be a reason why significant improvement was detected for the non-dominant leg (left) and not the dominant leg (right).

Walking features, namely duration and speed were tested by 10MW and 20MW tests as well as

6MWT. The results showed a pattern of effectiveness for aerobic exercises. For all three tests, group 1 showed a greater improvement compared to control group. In addition, a significant change was observed for group 2 in 6MWT. These results are in agreement with those of other studies including Cakt et al.,[40] Rampello et al.,[16] Geddes et al.,[41] Motl et al.,[36] Sangelaji et al.,[19] and van den Berg et al.,[42] which showed an improvement in walking endurance and speed after combined exercises. In addition, a systematic review by Citaker et al.[43] showed a small significant change in mobility after exercise therapy. Hansen et al.,[37] however, showed that combined exercises have no effects on endurance. The discrepancy between results could be explained by the differences in employed exercises and mobility measures. It seems that aerobic exercises such as treadmill can improve the gait style of the people with MS as well as their endurance and strength. With respect to our study design, no specific balance exercise was performed by the patients but the results showed a significantly greater post-intervention balance score for group 1 compared to both baseline and control group. The difference in the scores of two groups which reached nearly 6 points (P = 0.001) is noteworthy. This is in line with a study by Donoghue and Stokes[44] that investigated the changes in Berg test corresponding to real changes in patients.

In addition, our results matches, other studies like Paltamaa et al.,[21] Kjolhede et al.,[9] Sangelaji et al.,[19] and Tarakci et al.[23] In a study by Tarakci et al., the main reason for a significant difference between intervention and control groups was the odd point decrease of BBS in the control group in just 12 weeks and no increase in intervention group. It seems that treadmill as an aerobic exercise has some collateral effect such as balance improvement. Due to the nature of this kind of physical activity, some muscles that are effective in balance such as erector spinal muscles,[23] may have strengthen and this phenomena may lead to improve balance in group 1 only and no the other groups. Studies by DeBolt and McCubbin[38] and Rietberg et al.[7] were in line with this concept. Some recent studies have focused on more specific muscles, such as Cakt et al.,[40] Cattaneo et al.[20] and Citaker et al.[43] they all confirmed the effectiveness of resistance exercise on balance. Our results did not show any significant effect on fatigue.

Fatigue is one of the most complicated symptoms in MS and the results of various studies on fatigue are contradicting. For instance, Sangelaji et al.,[19] Cakt et al.,[40] Schmidt and Wonneberger[45] and Tarakci et al.[23] reported a mild to moderate effect of aerobic, resistance and combined exercises on fatigue; however, van den Berg et al.,[42] Rietberg et al.,[7] Hansen et al.,[37] and Geddes et al.[41] did not find any significant effect of various type of exercise on fatigue. In addition, Surakka et al.[46] reported a significant effect of aerobic activities on fatigue just in females. This discrepancy may be a result of varying interventions, insufficient intervention periods and examined population. Although TUG test score changes in groups 1 and 3 were significantly before and after the intervention, no significant change was detected in comparison with control group. Motl et al.,[36] and Golzari et al.,[17] however, showed that combined exercises have a significant effect on TUG test. This paradox could be due to the small sample size of intervention groups.

Main highlights of the present study are the choice of accessible exercises, use of a randomized controlled trial (RCT) study design and collaboration of various professionals (e.g., neurologist, physiotherapist, physical educator and epidemiologist).

Two major limitations were inability to control for diet attitude or sleep-wakefulness schedule of the participants. Furthermore, mood state of the participants was not controlled during the study course. In addition, because of space and time limitations, groups did their exercises in different sessions, so we could not match the groups based on the exact time of physical activity.

Conclusion

Our study showed that a combined exercise schedule with a predominant aerobic component was more effective. The proposed model may help people with MS and can lead to improved balance skills, better walking abilities, and enhanced muscle strength. Furthermore, all modalities used in this model are simple, convenient and feasible. Hence, the proper combination of aerobic exercises with smaller portions of resistance exercises may be much more suitable for patients with MS. On the other hand, we showed a tangible improvement in test scores and scales after the intervention, specifically for groups 1 and 3; so we may speculate that rehabilitation and exercise therapy can help people with MS even in short-term. Finally, RCTs with

large sample size and various exercise combinations are recommended to select the best rehabilitation regimen for people with MS.

Conflict of Interests

The authors declare no conflict of interest in this study.

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The correlation between dietary fat intake and blood pressure among people with spinal cord injury

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Keywords
Hypertension; Spinal Cord Injury; Dietary Fats; Blood Pressure

Abstract

Background: Studies have demonstrated the effect of different dietary fats on blood pressure (BP) in general population. However, these associations have not yet been described in people with spinal cord injury (SCI).

Methods: Referred patients to Brain and SCI Research Center between 2011 and 2014 have been invited to participate. Only paraplegic individuals were recruited and patients with injury at cervical or higher thoracic sections were excluded to omit the bias effect of autonomic dysreflexia. Dietary intakes were assessed by recording consumed foods by 24-hour dietary recall interviews using Nutritionist IV 3.5.3 modified for Iranian foods. Systolic BP (SBP) and diastolic BP (DBP) were measured 3 times and the mean values entered analysis.

Results: Higher intakes of cholesterol were related to higher BP (P = 0.010 and 0.011 for SBP and DBP, respectively). Similarly, intake of saturated fat was positively correlated to both SBP (P = 0.016, r = 0.21) and DBP (P = 0.011, r = 0.22). The effect of eicosapentaenoic acid (EPA) on BP was insignificant (P = 0.760 and 0.720 for SBP and DBP, respectively). However, intake of docosahexaenoic acid (DHA) was related to lower BP among people with SCI.

Conclusion: This study has demonstrated that higher intakes of cholesterol and saturated fat are associated with increased BP, whereas DHA is an antihypertensive agent. Dietary modifications with reduction of cholesterol and saturated fat along with intake of additional DHA supplements may help to reduce BP in spinal cord injured-individuals with hypertension.

Introduction

Hypertension is a well-known risk factor for cardiovascular diseases (CVDs).[1-4] Therefore, identification of the determinants of blood pressure (BP) has always been a major clinical goal. In this regard, the role of diets in prevention and treatment of hypertension has attracted attentions.[5] Thus, the importance of determination of dietary components that are associated with BP is obvious. There is conflicting evidence about the effect of dietary fat intake on BP. Some investigations have shown a positive correlation between dietary cholesterol intake and BP,[6,7] whereas McCarron et al.[8] revealed no significant

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effect of cholesterol intake on BP. Due to the existence of inconsistent evidence, the contributory role of dietary fat intake in determining BP still needs to be clarified.

Reducing the proportion of saturated fat in diets is recommended to prevent CVDs and increased consumption of unsaturated fat has been shown to be associated with decreased BP.[9] Furthermore, dietary omega-3 polyunsaturated fatty acids (ω-3 PUFAs) have been shown to positively affect hypertension in animal models.[10,11] The BP reducing effect of ω-3 PUFAs has also been demonstrated in human,[12] which shows that the components of dietary fat have a significant influence on BP and dietary modifications play an important role in prevention and treatment of hypertension.

Up to now, the relationship between dietary fat intakes and BP among people with spinal cord injury (SCI) has not yet been described. People with SCI are susceptible to orthostatic hypotension and paroxysmal hypertension[13] and maintenance of BP in the normal range is a clinical challenge among affected individuals. The prevalence of traumatic SCI in Tehran, Iran, has been shown to range from 1.2 to 11.4 per 10000 people.[14] The high burden of SCI measured by disability-adjusted life years has been shown in Iran.[15] Hypertension as a treatable complication of SCI requires attention and prevention of hypertension among people with disability is closely related to the dietary modifications. In the present investigation, we aimed to assess the correlation between dietary fat intakes and BP among people with SCI. Whether dietary fat components can be determinants of BP among individuals with SCI has been discussed in this study.

Materials and Methods

Participants were people with SCI who were referred to Brain and SCI Research Center between 2011 and 2014. Inclusion criteria were: traumatic SCI and post injury duration longer than 1 year. Depressive mood, which is mostly prevalent in the 1st year after SCI,[16] may contribute to induction of changes in dietary intakes. Therefore, we only recruited those individuals with time since injury longer than 1 year. Exclusion criteria were pregnancy, amputation, non-traumatic SCI etiology, history of chronic diseases (e.g., diabetes, rheumatologic diseases, cancer, endocrine diseases, and etc.), use of special medications such as glucocorticoid, hormones, thyroid hormones, anticonvulsive drugs, heparin, lithium, blood glucose reducing agents, atorvastatin, gemfibrozil (serum lipid reducing medications), ω-3 fatty acids, or other nutrients supplements. Since the aim of this study was to evaluate the role of diet in determining BP, those participants with were under treatment with nutrient supplements were excluded. Addiction, smoking, and alcoholism were also considered as exclusion criteria. Since patients with injury at the cervical level or higher thoracic levels are susceptible to autonomic dysreflexia,[17] we excluded individuals with high injury level and quadriplegia. Informed consents were obtained from each individual before enrollment. The participation was voluntarily. The protocol of the study was approved by Ethics Committee of Tehran University of Medical Sciences.

Dietary intakes were assessed by recording consumed foods by 24-hour dietary recall interviews with participants in 3 non-consecutive days using Nutritionist IV 3.5.3. (N-Squared Computing, Salem, OR, USA) modified for Iranian foods.[18] This software enables the user to analyze single foods, recipes, meals, and complete diets for nutrient values. It has been shown by Crawford et al.[19] that 3-day dietary record is an appropriate and reliable choice for dietary measurements, and the agreement between observed and reported intakes are admissible. According to Cox et al.,[20] people with SCI need daily energy intake of about 23 kcal/kg. In this study, the percentage of patients with inadequate energy intake (below 23 kcal/kg/day) has also been estimated.

Body weight was measured using a digital wheelchair scale, and body height was obtained measuring the supine length. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters) squared. Systolic BP (SBP) and diastolic BP (DBP) were measured with appropriate tools as well. BP was measured 3 times and the mean values entered analysis. Participants' age and gender were also recorded.

An injury level was determined by clinical examination performed by a neurosurgeon and was confirmed by magnetic resonance imaging. Those patients with injury at the cervical level or higher thoracic levels (above T4) were excluded because of susceptibility to autonomic dysreflexia. Completeness was classified as either complete (no preserved sensory or motor function) or incomplete (variable preserved motor function).[21,22]

All statistical analysis was performed using SPSS software (version 21, SPSS Inc., Chicago, IL, USA). Categorical variables were described be numbers and percentages, whereas mean ± standard deviation (SD) was used to describe continuous variables. Comparison of means between groups was used by t-test and one-way analysis of variance. The correlation between dietary fat intakes and BP was assessed using partial correlation test with controlling for demographic confounders (age, weight, BMI) and injury related variables (completeness, quadriplegia vs. paraplegia). Dietary sodium intake is known as a major factor contributing to increase BP, and all the analysis were performed with adjustment for dietary sodium intake.

Results

A total of 157 paraplegic individuals with mean age of 37.19 ± 11.64 years old entered this investigation. The majority of patients were men (n = 124, 79.0%) and only 33 women participated. Mean weight and BMI were 68.92 ± 14.39 kg and 23.63 ± 4.54 kg/m^2, respectively. The majority of participants had a complete injury (n = 100, 63.7%). Table 1 illustrates the baseline demographic characteristics of participants along with mean dietary fat intakes. Although the most patients were receiving adequate daily energy intake (n = 100, 63.7%), the percentage of people with SCI with inadequate daily calorie intake (lower that 23 kcal/kg/day) was still noticeable (n = 57, 36.3%). Mean total energy intake was 1846.7 ± 589.3 kcal. Mean total fat and cholesterol intakes were 75.07 ± 34.24 g and 256.29 ± 159.50 mg. Mean intake of saturated, polyunsaturated fat and monounsaturated fats were 20.58 ± 9.67, 22.57 ± 14.39 and 24.20 ± 15.93 g, respectively. Intakes of linoleic acid, oleic acid, alpha-linolenic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are shown in table 1.

Table 1. Baseline characteristics and mean intake of dietary fats in participants with spinal cord injury (SCI) (n = 157)

Variable	Mean ± SD
Age (year) (mean ± SD)	37.19 ± 11.64
Gender [n (%)]	
Male	124 (79.0)
Female	33 (21.0)
Weight (kg) (mean ± SD)	68.92 ± 14.39
BMI (kg/m^2) (mean ± SD)	23.63 ± 4.54
Completeness of the injury [n (%)]	
Complete	100 (63.7)
Incomplete	57 (36.3)
Total energy intake (kcal) (mean ± SD)	1846.70 ± 589.30
Carbohydrate intake (g) (mean ± SD)	238.00 ± 82.92
Total protein intake (g) (mean ± SD)	71.18 ± 25.52
Fat intake (g) (mean ± SD)	75.07 ± 34.24
Cholesterol intake (mg) (mean ± SD)	256.29 ± 159.50
Energy intake per kg body weight [n (%)]	
≤ 23 kcal/kg/day	57 (36.3)
> 23 kcal/kg/day	100 (63.7)
Intake of saturated fat (g) (mean ± SD)	20.58 ± 9.67
Intake of polyunsaturated fat (g) (mean ± SD)	22.57 ± 14.39
Intake of linoleic acid (g) (mean ± SD)	19.73 ± 13.22
Intake of EPA (g) (mean ± SD)	0.07 ± 0.03
Intake of monounsaturated fat (g) (mean ± SD)	24.20 ± 15.93
Intake of oleic acid (g) (mean ± SD)	19.53 ± 13.45
Intake of alpha linolenic acid (g) (mean ± SD)	0.33 ± 0.29
Intake of DHA (g) (mean ± SD)	0.09 ± 0.05
SBP (mmHg) (mean ± SD)	77.80 ± 50.60
DBP (mmHg) (mean ± SD)	38.90 ± 31.60

DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SCI: Spinal cord injury; BMI: Body mass index

Table 2. The effect of demographic variables (and probable confounders) on blood pressure (BP) in patients with spinal cord injury (SCI)

Variable	SBP		DBP	
	P*	R	P*	R
Age	0.022	0.20	0.019	0.24
Gender	0.860	-	0.950	-
Completeness of the injury	< 0.001**	-	< 0.001***	-
BMI (kg/m^2)	0.300	-	0.350	-
Total energy intake	0.007	0.23	0.003	0.25
Dietary sodium intake	0.001	0.42	0.040	0.38

*P values stand for correlation analysis for the assessment of relationship between continuous variables (age, BMI, total energy intake and dietary sodium intake) and BP. P values for the effect of categorical variables (gender, completeness of injury) has been obtained by comparison of means between groups using t-test. **SBP was significantly higher in patient with incomplete injury (92.7 ± 40.2 vs. 41.18 ± 36.13). ***DBP was significantly higher in patients with incomplete injury (58.5 ± 25.5 vs. 26.09 ± 28.60).
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SCI: Spinal cord injury; BMI: Body mass index

We assessed the effect of probable confounders on BP in patients with SCI. Older ages were associated with higher SBP and DBP (P = 0.022 and P = 0.019, respectively). Gender was not a significant determinant of BP. SBP was significantly higher in patient with incomplete injury (92.7 ± 40.2 vs. 41.18 ± 36.13; P < 0.001). Similarly, DBP was significantly higher in patients with incomplete injury (58.5 ± 25.5 vs. 26.09 ± 28.60; P < 0.001). As expected, dietary sodium intake was correlated to higher BPs (P = 0.001 and 0.040 for SBP and DBP, respectively). Although BMI was not significantly related to BP, higher total calorie intake was associated with increased SBP (P = 0.007, r = 0.23) and DBP (P = 0.003, r = 0.25). These results showed that age, completeness of injury, dietary sodium intake, and total calorie intakes were confounders that influence BP among people with SCI (Table 2). At the next stage of analysis, we performed partial correlation analysis with controlling for these confounders to evaluate the relationship between dietary fat intakes and BP in SCI.

There was no significant relationship between dietary intakes of polyunsaturated fat, monounsaturated fat, linoleic acid, oleic acid and alpha-linolenic acid, and SBP (P = 0.080, P = 0.490, P = 0.100, P = 0.690 and P = 0.280, respectively). Similarly, no significant effect of dietary intakes of polyunsaturated fat, monounsaturated fat, linoleic acid, oleic acid and alpha-linolenic acid was detected (Table 3). Total fat intake was not correlated with SBP (P = 0.060) and DBP (P = 0.080). On the other hand, higher intakes of cholesterol were related to higher BP (P = 0.010 and P = 0.011 for SBP and DBP, respectively). Similarly, intake of saturated fat was positively correlated to both SBP (P = 0.016, r = 0.21) and DBP (P = 0.011, r = 0.22). The effect of EPA on BP was insignificant (P = 0.760 and P = 0.720 for SBP and DBP, respectively). However, intake of DHA was related to lower BP among people with SCI.

Table 3. The effect of dietary intake of fats on blood pressure (BP) after adjustment for confounders (age, gender, BMI, total energy intake and dietary sodium intake) in patients with Systolic blood pressure (SCI)

Dietary fat	SBP	DBP
Cholesterol intake (mg)	0.010 (r = 0.23)	0.011 (r = 0.27)
Fat intake (g)	0.060	0.080
Intake of saturated fat (g)	0.016 (r = 0.21)	0.011 (r = 0.22)
Intake of polyunsaturated fat (g)	0.080	0.130
Intake of linoleic acid (g)	0.100	0.160
Intake of DHA (g)	0.010 (r = -0.22)	0.012 (r = -0.23)
Intake of EPA (g)	0.760	0.720
Intake of monounsaturated fat (g)	0.490	0.480
Intake of oleic acid (g)	0.690	0.660
Intake of alpha-linolenic acid (g)	0.280	0.220

DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SCI: Spinal cord injury; BMI: Body mass index

Discussion

Our study showed that increased dietary intake of cholesterol is related to higher BP in patients with SCI. Similar to our results, Sakurai et al.[23] showed that there is a positive relationship between dietary cholesterol intake and SBP after controlling for possible confounders in general population of Japan. Our investigation is comparable with Sakurai et al.' study[23] since the methodology in the assessment of dietary intakes in both researches is 24-dietary recall. In line with Sakurai et al.,[23] our outcomes have confirmed that higher cholesterol intake increases BP. To our knowledge, this is the first study illustrating the BP-raising effect of high cholesterol intake in patients with SCI. There are limited researches that have investigated the effect of cholesterol on BP.[24]

Most studies have focused on the influence of dietary cholesterol intake on serum lipids and cardiovascular risk. According to Stamler,[25] cholesterol intake is one of the many factors that affect BP. Here, we identified the probable confounders and the association between cholesterol intake and BP were assessed with controlling for these confounders. Previously, a clinical trial showed that vegetarian diets that contain less total fat, saturated fat and dietary cholesterol, lowered BP[26] which is in line with our findings among people with SCI. However, clinical trials are required to confirm the effect of dietary cholesterol intake on BP to support cholesterol-lowering dietary modifications for spinal cord injured-individuals with hypertension.

Previously, Theobald et al.[27] demonstrated that low-dose DHA lowers DBP in middle-aged men and women. Here, we found that dietary intake of DHA has BP-lowering effect on both SBP and DBP in patients with SCI. Similarly, Mori et al.[28] reported that DHA (but not EPA) reduces BP and therefore, the BP-lowering effects of fish oil can be assigned to DHA influence. These findings are consistent with our outcomes in population of people with SCI. Similar with Mori et al.,[28] the relationship between dietary intake of EPA and BP was insignificant in our study whereas DHA intake was negatively correlated to BP. These results suggest that DHA can be considered as a BP-lowering agent in dietary modification for spinal cord injured-individuals with hypertension.

Our study showed that increased intake of saturated fat is associated with higher SBP and DBP. It has been previously demonstrated by Salonen et al.[29] that there is a consistent relationship between the mean arterial pressure and intake of saturated fat which is in line with our findings. The disadvantageous effects of diets which contain high levels of saturated fat on risk of hypertension have been well-documented.[30] Here, we have found that saturated fat increases BP in patients with SCI which is similar to previous findings on general population.[29,30]

The relationship between dietary linoleic acid intake and BP has been previously investigated by Miura et al.[31] in general population. Miura et al.[31] showed that the correlation between dietary intake of linoleic acid and BP is insignificant which is consistent with our study. On the other hand, Takeuchi et al.[32] reported that alpha-linolenic acid have an antihypertensive effect among individuals with mild hypertension. Our study does not approve the BP-reducing effect of alpha-linolenic acid in patients with SCI. One reason for this discrepancy can be traced back in the differences of study subjects. In fact, Takeuchi et al.[32] assessed patients with hypertension and here, we investigated spinal cord injured-individuals. It seems that the effect of alpha-linolenic acid on BP is more prominent with background increased BP exists. In this regard, further investigations with the recruitment of patients with coincidental SCI and hypertension should be performed to clarify the influence of dietary intake of alpha-linolenic acid on BP.

Previously, Terés et al.[33] showed that oleic acid has BP-reducing effect and in fact the antihypertensive effect of olive oil is mediated thorough oleic acid. These findings contradict with our study since we did not observe any significant association between dietary intake of oleic acid and BP among people with SCI. Oleic acid is known to have also beneficial effects in reducing cardiovascular risk and improving blood lipids favorably.[34] However, the advantageous influences of oleic acid in SCI have been poorly documented, and the most studies support the positive effects of oleic acid on health in general population.[33,34] People with SCI are susceptible to metabolic syndrome, dyslipidemia and obesity,[35] and therefore, the metabolism pathways through which oleic acid may influence BP could be affected. Thus, the antihypertensive effect of oleic acid may be camouflaged in population with SCI. Altogether, here we did not detect any BP-reducing effect of oleic acid in patients with SCI. However, future clinical trials should be designed to assess the effect of diets

enriched with oleic acid on BP among individuals with SCI.

The estimation of inadequate calorie intake was performed in our study based on the threshold of 23 kcal/kg/day suggested by Cox et al.[20] However, a recent investigation by Nevin et al.[36] showed that the factors affecting resting energy expenditure (REE) in patients with SCI are numerous and therefore, indirect calorimetry is the only accurate assessment of REE. An assessment of the prevalence of inadequate energy intake in patients with SCI is very important. Thus, further investigations with performing of indirect calorimetry are required to estimate the accurate prevalence of insufficient calorie intake in SCI.

Limitation

This study assessed the correlation between dietary fat intake and BP in people with SCI in a cross-sectional design. Future clinical trials are required to compare this relationship between people with SCI and healthy individuals. Moreover, further studies with measurement of indirect calorimetry are needed to estimate the prevalence of inadequate calorie intake in patients with SCI.

Conclusion

This study is the first investigation illustrating the effects of dietary intake of fats on BP in patients with SCI. Our results have demonstrated that higher intakes of cholesterol and saturated fat are associated with increased BP, whereas DHA is an antihypertensive agent. Dietary modifications with reduction of cholesterol and saturated fat along with intake of additional DHA supplement may help to reduce BP in spinal cord injured-individuals with hypertension.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Validation of the Persian version of the dysphagia handicap index in patients with neurological disorders

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Keywords
Dysphagia; Disability Evaluations; Persian; Iran; Reliability and Validity; Neurologic Disorders; Reproducibility of Results; Questionnaire Design

Abstract

Background: Dysphagia as a common condition affecting many aspects of the patient's life. The Dysphagia Handicap Index (DHI) is a reliable self-reported questionnaire developed specifically to measure the impact of dysphagia on the patient's quality of life. The aim of this study was to translate the questionnaire to Persian and to measure its validity and reliability in patients with neurogenic oropharyngeal dysphagia.

Methods: A formal forward-backward translation of DHI was performed based on the guidelines for the cross-cultural adaptation of self-report measures. A total of 57 patients with neurogenic dysphagia who were referred to the neurology clinics of Tehran University of Medical Sciences, Iran, participated in this study. Internal consistency reliability of the DHI was examined using Cronbach's alpha, and test-retest reliability of the scale was evaluated using intraclass correlation coefficient (ICC).

Results: The internal consistency of the Persian DHI (P-DHI) was considered to be good; Cronbach's alpha coefficient for the total P-DHI was 0.88. The test-retest reliability for the total and three subscales of the P-DHI ranged from 0.95 to 0.98 using ICC.

Conclusion: The P-DHI demonstrated a good reliability, and it can be a valid instrument for evaluating the dysphagia effects on quality of life among Persian language population.

Introduction

Oropharyngeal dysphagia is defined as a difficulty in moving bolus from the mouth to the stomach due to neurologic, structural, or other medical conditions. It commonly occurs in 30-84% of individuals with neurological disorders [i.e., stroke, Parkinson's, amyotrophic lateral sclerosis (ALS), and multiple sclerosis

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(MS)].[1] The abnormal swallowing can lead to malnutrition and weight loss, dehydration, aspiration pneumonia, and even death.[2-5] Furthermore, the inability to eat represents a social handicap that not only affects the patient physically but also mentally.[6] Dysphagia can interfere with many aspects of one's life including work, leisure, social interactions, and self-esteem. It ultimately leads to reduced quality of life for the patient and those around him or her.[6-9]

In recent years, several questionnaires were designed to assess quality of life in the patients with dysphagia, but most of them are disease-specific. In 2001, Chen et al.[10] created the M. D. Anderson Dysphagia Inventory to evaluate quality of life-related to dysphagia in the patients with head and neck cancer. Woisard et al.,[11] in 2005, developed the Deglutition Handicap Index, which is a patient-reported 30-item questionnaire that measures the deglutition-related aspects in daily life and is a valid tool. The dysphagia-goal-handicap (DGH) was developed to examine the handicapping effect of esophageal dysphagia in 1991. It was indicated that dysphagia affects quality of life.[12] One of the comprehensive patient-reported tools for dysphagia is the swallowing quality of life questionnaire which has more popularity in research areas of this regard. However, the completion of this test is time-consuming and understanding some of its items is difficult for the patient. Thus, its application is limited to clinical practice.[13]

In 2012, Dysphagia Handicap Index (DHI) was developed by Silbergleit et al.[7] The purpose of creating DHI was to provide a tool that can measure dysphagia disabling effects on the physical, functional and emotional aspects of individual's life in a wide variety of swallowing disorders.

DHI is a new and efficient tool that has excellent psychometric characteristics and can be used in planning or modifying treatment approaches.[7] It has been translated into Arabic. An Arabic translation and validation of this questionnaire have shown good psychometric properties;[14] however, this test has not been translated to Persian. Regarding the high prevalence of oropharyngeal dysphagia following stroke and other neurological disorders,[1] the purpose of this study was to translate DHI into Persian and to evaluate its validity, internal consistency and test-retest reliability in neurogenic oropharyngeal dysphagia.

Materials and Methods

Persian-DHI (P-DHI) translation process

The process of developing P-DHI was performed based on the guidelines for the cross-cultural adaptation of self-report measures in five steps.[15] First, the original version of DHI was translated separately by two translators into Persian. Second, a meeting was held with speech pathologists and translators to investigate Persian translations of DHI and prepare preliminary Persian version of the index. In the third stage, the preliminary Persian version of the index was back-translated into English by two other translators and was approved by the original author. In the fourth stage, a meeting was held to prepare pre-final Persian version of DHI (P-DHI). In the fifth step, the pre-final Persian version of the index was completed tentatively by patients with dysphagia, and finally after considering the views of experts and participants, the final P-DHI was developed. All of the items on the DHI were directly translated into Persian and received no changes.

Participants

This study was performed in teaching hospitals of Tehran University of Medical Sciences, Iran, in 2014. 57 consecutive adult Persian patients with oropharyngeal dysphagia were included in this study. Patients participated in this study based on the diagnosis of their specific neurological disorders including stroke, Parkinson's disease, ALS, brain tumors, MS, and myasthenia gravis. All patients were evaluated by the Northwestern Dysphagia Patient Check Sheet[16] and provided that the results of this test showed that the patient had at least one of the disorders of deglutition phase (oral phase or pharyngeal phase) or, aspiration, or pharyngeal delay could enter this study. Exclusion criteria were (1) inability to understand written or spoken Persian, (2) evidence of purely esophageal dysphagia, (3) evidence of cognitive problems as screened by the Mini-Mental State Examination (MMSE) (a score of < 23).[17] And finally, to measure the reliability of test-retest, the P-DHI was completed by 14 patients twice in a period ranging from 1 to 2 weeks. During this period, the patients received no medical, surgical or behavioral intervention for swallowing disorders.

DHI questionnaire[7]

The DHI is composed of 25 items and three physical, functional, and emotional subscales. The

Table 1. Features of Dysphagia Handicap Index (DHI) subscale distributions of the patient group

DHI scale	Number of items	Possible range	Observed range	Mean ± SD
Physical	9	0-36	32-2	13.28 . 6.90
Functional	9	0-36	32-0	11.47 . 7.61
Emotional	7	0-28	0-26	9.75 . 5.11
Total	25	0-100	10-78	34.51 . 16.35

DHI: Dysphagia Handicap Index; SD: Standard deviation

physical subscale includes 9 items that represent the individual's perception of physical discomfort caused by dysphagia. The emotional subscale is composed of 7 items that examine patient's emotional reactions to his dysphagia and functional subscale includes 9 items which are related to the impact of dysphagia on daily activities of a person's life. For each question, three answers are considered (never, sometimes and always) that are scored (0, 2 and 4, respectively). After completing the test by the patient, subjects are asked to measure their severity of dysphagia by a 7-point equal-appearing interval scale. On this scale, number 1 represents no problem as number 7 represents a serious one and number 4 shows moderate dysphagia.

Validation and statistical testing

The P-DHI was validated using content validity. The P-DHI and the back translated version presented to five swallowing therapist. They scored each question based on the quality of translation, fluency, understandability, and the cultural context.

Internal consistency of the P-DHI was examined using Cronbach's alpha, and test-retest reliability of the scale was evaluated using intraclass correlation coefficient (ICC). To compare mean P-DHI subscales and total scores with the self-reported dysphagia severity, one-way ANOVA and Duncan post-hoc test were used. Spearman's correlation coefficient was also used to evaluate the relationship between the total P-DHI scores, P-DHI subscale scores, and the self-reported dysphagia severity scores. Data were analyzed using SPSS software (version 17, SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed and a $P < 0.050$ was considered statistically significant. The data are presented as a mean ± standard deviation (SD).

Results

A total of 57 patients with neurological disorders, 21 males and 36 females participated in this study (mean age 54.96 . 14.81 years). Table 1 shows a range of the total P-DHI and its subscales scores in patients under the study (Table 1). The mean total P-DHI score of the patients was 34.51 . 16.35.

The content validity of the P-DHI was also evaluated; the fluency, understandability and cultural adaptation of the P-DHI confirmed by swallowing therapists and patients.

To assess the internal consistency of the scale, Cronbach's alpha coefficient was calculated for each subscale and also the total (Table 2). Cronbach's alpha coefficient was ($\alpha = 0.88$) for the total scale and demonstrated good internal consistency of the scale items The ICC for the total P-DHI and physical, functional and emotional subscales were between 0.95 and 0.98 (Table 2).

Table 2. Internal consistency and test-retest reliability of the Persian Dysphagia Handicap Index (P-DHI)

DHI scale	Cronbach's alpha (n = 57)	ICC (n = 14)
Physical	0.73	0.95
Functional	0.83	0.97
Emotional	0.71	0.96
Total	0.88	0.98

DHI: Dysphagia Handicap Index; ICC: Intraclass correlation coefficient

Adapted from the original version of DHI, the self-reported severity of dysphagia scale was grouped into four categories: 1: normal; 2 and 3: mild; 4 and 5: moderate; 6 and 7: severe. The mean scores of total P-DHI and its subscales for the severity groups are presented in table 3. Data analysis showed that there is a significant difference between the four severity groups considering the P-DHI and the three subscales ($P < 0.001$).

The results of post-hoc analyses of the severity groups showed that all the pairwise comparisons were significant, except for the normal and mild severity groups ($P > 0.050$). Spearman's correlation coefficient was calculated to assess the relationship between P-DHI scores and the self-reported dysphagia severity scores. The results indicated that there is a significant relationship between the total score ($r = 0.67$, $P < 0.001$) and the subscales (physical, $r = 0.59$, $P < 0.001$; functional, $r = 0.49$, $P < 0.001$; and emotional, $r = 0.52$, $P < 0.001$).

Table 3. Dysphagia Handicap Index (DHI) subscales and total DHI for the self-reported dysphagia severity scales

DHI	Normal (n = 6)	Mild (n = 7)	Moderate (n = 39)	Severe (n = 5)	F(3,53)	P
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Physical	6.33 ± 2.34	8.43 ± 4.47	13.95 ± 6.13	23.20 ± 6.57	9.74	< 0.001
Functional	4.00 ± 0.00	5.43 ± 3.78	12.46 ± 6.59	21.20 ± 10.06	9.09	< 0.001
Emotional	5.00 ± 2.10	6.57 ± 3.41	9.90 ± 4.13	18.80 ± 5.22	12.84	< 0.001
Total	15.33 ± 3.27	20.43 ± 6.92	36.31 ± 12.00	63.20 ± 18.14	19.41	< 0.001

SD: Standard deviation; DHI: Dysphagia Handicap Index

To determine the correlation between the subscales and the total P-DHI scale, Pearson's correlation coefficient was calculated. There was a significant correlation between the total scale and the physical ($r = 0.82$, $P < 0.001$), functional ($r = 0.87$, $P < 0.001$) and emotional ($r = 0.77$, $P < 0.001$) subscales. Furthermore, a significant correlation was observed between the physical and functional subscales ($r = 0.53$, $P < 0.001$), physical and emotional subscales ($r = 0.46$, $P < 0.001$), and the functional and emotional subscales ($r = 0.57$, $P< 0.001$).

Discussion

In recent years, much attention is given to the application of patient-centered measures for evaluating voice and swallowing disorders.[14] Focusing on the patient's self-perception of dysphagia with their medical diagnosis, the therapist can have a broad picture of the patient's health status which is useful for planning the treatment protocols.[7] Hence, making such tools to assess various aspects of a disorder is very important and valuable. DHI is a new tool which evaluates physical, functional and emotional aspect of dysphagia and it has excellent validity and reliability.

The purpose of this study was to evaluate the validity and reliability of the P-DHI in neurological disorders. The results of this study revealed that the P-DHI like other DHI versions has a good content validity.[7,14] There were no problems during translation and cross-cultural adaptations as P-DHI had simple and clear items. This indicates the clinical use of the P-DHI as an easy-to-complete tool for assessing dysphagia consequences on the quality of life.

The Cronbach's alpha coefficient for the total P-DHI and physical, functional and emotional subscales was between 0.71 and 0.88, indicating a good internal consistency of the P-DHI. These findings are in agreement with the original study and with the Arabic version of the DHI.[7,14] ICC for original DHI and the Arabic version of DHI were 0.83 and 0.90, respectively.[7,14] Similarly, the results of our study indicated that P-DHI has strong test-retest reliability (ICC = 0.98). Based on these findings, it can be stated that the P-DHI has good validity and reliability among patients with neurological disorders.

The subjects in this study gained the highest mean scores, respectively, on physical, functional, and emotional subscales, in accordance with previous reports.[7,14] It is probable that the physical subscale contained items easier to understand by the patients. Another possible explanation would be that they might be more concerned with the physical aspects of their oropharyngeal dysphagia than the other ones.

In this study, we had no comparison between P-DHI and other tools that evaluated quality of life in the patients with dysphagia. Hence, it is recommended that in the future studies concurrent validity should be considered.

Conclusion

The results of our study indicate that P-DHI is a valid and reliable tool among patients with neurological disorders; as a result, it could be used to evaluate disabling effects of dysphagia on quality of life of these patients.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Prevalence of intracranial artery stenosis in Iranian patients with acute ischemic stroke using transcranial Doppler ultrasonography

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Keywords
Ischemic Stroke; Intracranial Arteries; Transcranial Doppler Ultrasonography; Atherosclerosis

Abstract

Background: The aim of this study is to determine the frequency of intracranial artery stenosis in patients with acute ischemic stroke in Iran.

Methods: A total of 169 patients with acute ischemic stroke were eligible to participate and were enrolled in this study from January 2012 to February 2013. All the patients were admitted to the Nemazee Hospital, affiliated to Shiraz University of Medical Sciences, Iran. They underwent transcranial Doppler (TCD) ultrasonography. Mean flow velocity (MFV) of basilar artery, vertebral artery, middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) were evaluated.

Results: A mean of patients' age was 67.80 ± 8.14 years. There were 83 men (49.1%) and 86 women (50.9%). Overall, 43 patients (25.4%), with a mean age of 66.7 ± 6.2 years, had intracranial stenosis. The number of men and women with intracranial stenosis was comparable (52.4% men vs. 47.6% women). Hypertension ($P < 0.001$), hyperlipidemia ($P < 0.001$), and diabetes mellitus (DM) ($P < 0.001$) were major risk factors for intracranial stenosis.

Conclusion: The prevalence of intracranial artery stenosis in patients with acute ischemic stroke is 25.4% which is comparable with previous reports from Iran and other Middle East countries.

Introduction

A stroke, sometimes referred to as a cerebrovascular accident (CVA), is among the most common causes of mortality and morbidity in developed and developing countries. The incidence of stroke is increasing in developing countries in the Middle East.[1,2] The age-adjusted incidence rate of ischemic stroke in Iranian population was 4.5 per 1000 residents.[2] Currently,

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stroke is the third cause of mortality worldwide.[3] Several factors are responsible for this increase, including modernization and lifestyle changes, smoking, and increased the prevalence of hypertension and diabetes mellitus (DM).[4]

The previous studies have reported that intracranial etiologies are responsible for the majority of stroke cases, i.e., disturbances in intracranial circulation cause most strokes.[4] Approximately 10% (12.9%) of ischemic strokes occur secondary to atherosclerotic intracranial arterial stenosis.[5] It has been demonstrated that the risk of developing ischemic stroke in those with middle cerebral arteries stenosis in about 24% in 6-year follow-up.[6] As the investigation of intracranial artery stenosis is highly important, some studies have evaluated cerebral hemodynamics and the cerebral blood flow to predict ischemic CVAs.[7] It has been suggested that the patients with more than 50% intracranial arteries stenosis should undergo more rigorous prevention strategies.[8]

Several methods including transcranial Doppler (TCD) ultrasonography, cerebral angiography, computed tomography angiography (CTA), and magnetic resonance angiography (MRA) have been introduced to evaluate the intracranial blood flow in asymptomatic patients.[9] Among these methods, TCD is an available, simple and non-invasive method for the assessment of the intracranial blood flow and hemodynamic changes.[10,11] This non-invasive technique can be used for follow-up and continuous monitoring, can be performed in a bedside setting, and also can be applied for targeted thrombolysis.[12] The European Federation of Neurological Sciences (EFNS) summarized that TCD is very useful for assessing stroke risk of children between 2 and 16 years of age with sickle cell disease, detection and monitoring of vasospasm after subarachnoid hemorrhage, evaluation of the intracranial artery stenosis and blood flow, diagnosis of the right-to-left shunts and for monitoring the cerebral reperfusion after thrombolysis therapy of middle cerebral artery (MCA) after acute ischemic stroke.[13] The results of TCD can assist physicians to determine preventive and therapeutic strategies.[14]

Several reports have indicated that the prevalence of intracranial artery stenosis varies between different geographical regions and is higher in blacks and Asians compared with Caucasians.[15] Although many studies have documented that the intracranial artery stenosis can lead to ischemic stroke, some others have shown that the stenosis of extracranial arteries in thrombotic stroke is more prevalent.[16] Caucasian patients with ischemic stroke have a higher prevalence of intracranial stenosis compared to other ethnic groups.[15] There are few studies reported from the Middle East which have addressed intracranial arteries blood flow in ischemic stroke.[17,18] The aim of this study is to determine the frequency of intracranial artery stenosis in patients with acute ischemic stroke in Iran.

Materials and Methods

This prospective cross-sectional study was performed in the Neurology Section of Nemazee Hospital, affiliated to Shiraz University of Medical Sciences, Iran, from January 2012 to February 2013. The medical research ethics committee as well as Institutional Review Board of … approved the study protocol. All the patients provided their informed written consents before inclusion in the study. A total of 169 adult patients with definite diagnosis of ischemic stroke were included. The Recognition of Stroke in the Emergency Room scale (ROSIER) was used to confirm cerebral infarction, also known as ischemic stroke, as a focal neurological deficit of sudden onset that persisted beyond 24 hours in surviving patients and documented by a brain CT or an MR imaging.[19] The patients with condition confounding the clinical presentation including previous brain injuries, the patients with tumor or other conditions mimicking stroke, and those with a cardioembolic source of stroke were excluded.

Cerebrovascular risk factors such as cigarette smoking, hypercholesterolemia [history of hypercholesterolemia and/or fasting total cholesterol level > 200 mg/dL or total triglyceride (TG) level > 200 mg/dL or low-density lipoprotein (LDL) > 130 mg/dL], hypertriglyceridemia (history of hypertriglyceridemia and/or fasting triglycerides level > 180 mg/dL), arterial hypertension [history of hypertension and/or systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg, out of the acute phase, treated or not], DM [diagnosis according to the criteria of the National Diabetes Data Group (NDDG)],[20] and associated medical diseases were assessed. The patients were also evaluated regarding the cardiovascular diseases and comorbidity, such as arrhythmias and impulse conduction disorders, mitral and/or aortic valve

disease, left ventricular hypertrophy, and coronary heart disease (CHD).

We used odd/even day randomization technique to select the patients randomly. The demographic data of all the patients including age, gender, place of residence, educational status, and risk factors were recorded at the time of admission. CT scans of the brain were performed for the patients and the findings were reported based on the territory of the involved artery.

All patients underwent TCD in the following days of admission. All TCD examinations were performed at maximum 5 days after ischemic stroke. TCD studies of intracranial arteries were performed via temporal and occipital windows using a DWL Multi-Dop T unit with a 2-MHz probe. The anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA) were evaluated bilaterally through the temporal window. The vertebral and basilar arteries were assessed via the occipital window. The depth, peak systolic velocity (PSV), mean flow velocity (MFV), end diastolic velocity, and pulsatility index (PI) were measured for each artery separately. In this study, we considered the focal MFV (increased focal velocity in the normal range of depth for each artery) of arteries for the diagnosis of intracranial stenosis according to previously published data.[21] Therefore, we considered MFV of ≥ 80 cm/s for MCA as abnormal in favor of stenosis. In the same way, MFV of ≥ 80 cm/s for ACA was considered as stenosis.[18] For vertebral artery, MFV of ≥ 70 cm/s was considered as abnormal while MFV ≥ 80 cm/s was considered as stenosis for basilar.[22] For PCA, MFV of ≥ 60 cm/s was considered as stenosis.[18] The patients, who were not evaluated due to technical problems, were regarded as poor window and the frequency was reported. Extracranial arteries were not evaluated in this study.

SPSS software (version 16, SPSS Inc., Chicago, IL, USA) was used for data analysis. Descriptive data are presented as mean ± standard deviation (SD). Chi-square test was used to compare the proportional data between those with and without intracranial artery stenosis. Independent t-test was used to compare parametric data between corresponding categories. Multivariate logistic regression analyses were carried out to control the potentially confounding effect of different risk factors. A two-sided $P < 0.050$ was considered statistically significant.

Results

A total of 169 patients with acute ischemic stroke were eligible for participation and were included to undergo TCD during a 13-month period. A mean of patients' age was 67.80 ± 8.14 (ranging from 29 to 92) years. There were 83 men (49.1%) and 86 women (50.9%). Table 1 represents the demographic data of all the patients.

Table 1. Baseline characteristics of the 169 patients with acute ischemic stroke

Variable	Value (n = 169)
Age (years) (mean ± SD)	67.80 ± 8.14
Sex [n (%)]	
Men	83 (49.1)
Women	86 (50.9)
Education [n (%)]	
Illiterate	145 (85.8)
Primary school	10 (5.9)
Diploma	9 (5.3)
Elementary school	4 (2.4)
Associate degree	1 (0.6)
Place of residence [n (%)]	
Village	123 (72.8)
City	24 (14.2)
Large city	22 (13.0)
Risk factors [n (%)]	
Hypertension	93 (55.0)
Hyperlipidemia	57 (33.7)
DM	54 (32.0)
Smoking	47 (27.8)

DM: Diabetes mellitus; SD: Standard deviation

The quality of the procedure was adequate in 139 patients (82.2%) but it was inadequate in 30 patients (17.8%) (poor window). Intracranial vessels could not be evaluated by TCD in 17.8% of the patients (poor window). No significant difference in the frequency of intracranial stenosis was observed between the two genders (Table 2). There is no significant difference between the right and the left MCA had stenosis in 27 patients (16.0%) and 16 patients (9.5%), respectively. 43 patients (25.4%) had stenosis in at least one of the intracranial arteries. The number of stenosis intracranial vessels was 1 in 20 patients (11.8%), 2 in 8 (4.7%), 3 in 10 (5.9%), 4 in 3 (1.8%), and 6 in 1 patient (0.6%). The anterior circulation (MCA + ACA) was involved in 64 patients (37.8%) in our study while the posterior circulation (PCA + vertebral + basilar) was involved in 17 patients (8.2%). ACA and MCA were stenosis bilaterally in 6 patients (3.5%), but only 1 patient (0.6%) had bilateral vertebral

Table 2. The characteristics of patients with and without intracranial stenosis

Variable	Stenosis (n = 42)	Normal (n = 92)	P
Age (years) (mean ± SD)	66.7 ± 6.2	67.4 ± 9.1	0.635
Sex [n (%)]			
Men	22 (52.4)	50 (54.3)	0.854
Women	20 (47.6)	42 (45.7)	
Education [n (%)]			0.718
Illiterate	37 (88.1)	76 (82.6)	
Primary school	3 (7.1)	5 (5.4)	
Diploma	1 (2.4)	3 (3.3)	
Elementary school	1 (2.4)	7 (7.6)	
Associate degree	0 (0.0)	1 (1.1)	
Place of residence [n (%)]			0.700
Village	7 (16.7)	13 (14.1)	
City	5 (11.9)	16 (17.4)	
Large city	30 (71.4)	63 (68.5)	
Risk factors [n (%)]			
Hypertension	32 (76.2)	43 (46.7)	< 0.001
Hyperlipidemia	25 (59.5)	23 (25.3)	< 0.001
DM	23 (57.8)	23 (25.0)	< 0.001
Smoking	13 (31.0)	25 (27.2)	0.795
Controlled risk factors [n (%)]			
Hypertension	9 (21.4)	39 (42.3)	0.032
Hyperlipidemia	7 (16.6)	26 (28.2)	0.026
DM	4 (9.5)	18 (19.5)	0.041
Transient ischemic attack	6 (14.3)	21 (22.8)	0.354

DM: Diabetes mellitus; SD: Standard deviation

stenosis. Table 3 demonstrates the frequency of intracranial stenosis using TCD ultrasonography.

The frequency of poor window was significantly higher among the women (compared with men (26.7 vs. 8.4%; P = 0.002). The patients with intracranial stenosis had significantly higher prevalence of hypertension (76.2 vs. 46.7%; P < 0.001), hyperlipidemia (P < 0.001), and DM (P < 0.001) compared with the patients who had no stenosis (Table 2).

Table 3. Frequency of intracranial stenosis using transcranial Doppler (TCD) ultrasonography in 169 patients with acute ischemic stroke

Variable	Unilateral	Bilateral
ACA [n (%)]	27 (15.9)	6 (3.5)
MCA [n (%)]	37 (21.9)	6 (3.5)
PCA [n (%)]	2 (1.2)	0 (0.0)
Vertebral [n (%)]	6 (3.5)	1 (0.6)
Basilar [n (%)]	5 (2.9)	-

ACA: Anterior cerebral artery; MCA: Middle cerebral artery; PCA: Posterior cerebral artery; TCD: Transcranial Doppler

Discussion

This study suggests that the hypertension is the most common risk factor for cerebrovascular diseases as it was found in 55.0% of our patients following hyperlipidemia, DM and smoking. TCD findings revealed that MCA and ACA are two most common arteries which are stenosis in patients with acute ischemic stroke.

Intracranial artery stenosis is considered among the most common causes of ischemic stroke worldwide. The incidence and prevalence of intracranial artery stenosis varies between geographical regions and ethnicities even in Asian countries.[23] Some part of this variation may be due to different modalities and different criteria used in these studies. The pattern of its epidemiology and distribution is similar to ischemic strokes.[24] It is more common among the Hispanics, people of African descent, and among Asians compared to Caucasians.[25] Several studies have addressed the prevalence of intracranial artery stenosis in patients with acute ischemic stroke.[24,25] Our findings replicate the findings of a study conducted by Zarei et al.[17] that showed stenosis of intracranial arteries was detected in 29% of the patients with acute ischemic stroke in Iran. However, in our study, the prevalence of intracranial artery stenosis was significantly lower than the results of other previously published studies from other countries in the Middle

East.[17,18,26-30] Gujjar et al.[18] reported a prevalence of 79% for intracranial artery stenosis in patients with ischemic stroke in Oman.

The previous studies have reported that Asian populations have a higher prevalence of intracranial artery stenosis.[17,18,31] Wityk et al.[15] conducted a study in 672 patients with ischemic stroke in Pakistan and reported that the prevalence of intracranial arteries stenosis was only 12%. However, Iranmanesh et al.[16] reported that intracranial artery diseases in Caucasians are as high as 16-25%. Wasay et al.[31] reported a low prevalence of intracranial vessels in ischemic stroke in Pakistan that is similar to the low frequency of carotid artery disease in patients with stroke in Southeast Asia.[32,33] They also reported that there is a correlation between carotid atherosclerosis and risk factors such as hypertension, smoking status, and DM that is consistent with previous studies.[32,33] It has been reported that the prevalence of intracranial stenosis in patients with ischemic stroke is 33-50% in China, 47% in Thailand, 48% in Singapore, and 10-25% in Korea.[19] O'Leary et al.[34] conducted a study in the USA and showed that the prevalence of intracranial stenosis in patients with stroke and transient ischemic attack is similar to asymptomatic population.[34] In their study, 1189 members of the Framingham cohort (asymptomatic), aged 66-93 years, were examined that showed there were no diseases in 30%, < 50% stenosis in 62%, 50-74% stenosis in 5%, 75-99% stenosis in 2%, and 100% stenosis in 1%.[34] These results are comparable with our results in which only 25.4% of our patients with ischemic stroke had intracranial artery stenosis. In the present study, hypertension, hyperlipidemia, and DM were major risk factors for intracranial stenosis, but smoking was not. Controlling risk factors were protective against developing intracranial stenosis. The risk factors reported in this study is comparable with other previous studies.[32-34]

Zarei et al.[17] reported that multiple intracranial stenosis were more common that single artery stenosis. Suh et al.[35] also reported a prevalence of 21% for single stenosis, 79% for multiple stenosis, 52% for intracranial lesions, and 48% for the extracranial area in patients with ischemic stroke. Their results also showed that anterior circulation was involved in 59%, but posterior circulation was involved in 41% of the patients.[35] In our study, the MCA was the most common site of stenosis followed by ACA. Right MCA was involved in 16% but left MCA was involved in 9.5% of our patients. In the same way, the right ACA was involved in 11.5% and the left in 7.7%. Zarei et al.[17] showed that MCA was the most common involved artery with a prevalence of 11% bilaterally and 5% unilaterally. Gujjar et al.[18] reported the involvement of anterior circulation in 22 patients (11.8%) and posterior circulation in 22 patients (11.8%). The anterior circulation (MCA + ACA) was involved in 64 patients (37.8%) in our study while the posterior circulation (PCA + vertebral + basilar) was involved in 17 patients (8.2%) that are higher than any other previously reported incidence rates.[18] The prevalence of ACA and MCA stenosis was higher in our study than what has been reported by Baumgartner et al.,[36] however, the incidence of vertebral and basilar stenosis was comparable.

It has been shown that the accuracy of TCD is the highest for the evaluation of MCA compared with other intracranial arteries which adds to the value of TCD as a non-invasive technique.[37] When applying TCD results especially for MCA, we should keep in mind that there are other causes which can increase MFV of MCA other than atherosclerosis such as recanalization of an occluded MCA.[38] Therefore, it is recommended that the patients with intracranial stenosis diagnosed in TCD to be followed so that they could be differentiated form recanalization of the MCA.[38] The diagnostic accuracy of TCD should be regarded when applying it. The sensitivity and specificity for TCD have been reported 90 and 88%, respectively.[39]

Gujjar et al.[18] reported a moderate accuracy for TCD in determining the pathology of the intracranial vessels. They reported some abnormality in about two-thirds of their study population when using TCD, while only 56% of those patients had changes in arteries corresponding to infarct location. The findings of these studies are in consistence with other studies.[36,40] The incidence of poor window in our study was 18.3% that is comparable to previous studies from Western countries (11-20%).[36,40,41] However, it is less than the East Asian populations (37%).[42] Gujjar et al.[18] reported a moderate sensitivity of TCD compared with MRA, with a relatively higher specificity. Alexandrov et al.[21] compared the results of TCD with conventional angiography in a group of 84 patients with acute ischemic stroke. They reported high sensitivity (87.5%) and specificity (88.6%),

together with high positive (87.5%) and negative (88.6%) predictive values.[21]

A study compared the MRA and transcranial color-coded Doppler sonography in 135 MCAs among 120 patients with acute stroke and reported that angle-corrected velocities correlated well with different grades of stenosis on MRA (P = 0.006). An angle corrected MCA PSV of > 120 cm/s correlated with MRA evidence of intracranial stenosis with high specificity (90.5%) and positive predictive value (93.9%), but relatively low sensitivity (66.7%; 95% confidence interval = 61.2-69.5%) and negative predictive value (55.1%).[31]

We note some limitations to our study. First, Doppler studies are operator-dependent, and the skill of the operator plays an important role in TCD results. To solve this problem, we had one single neurology resident interpret all the TCDs. Second, we did not record the outcome of the patient to correlate the TCD results with the severity and outcome of the ischemic stroke. In addition, we did not get the follow-up data of the patients and thus the predictive value of TCD could not be interpreted. Third, we performed conventional CT-scans of the brain at the time of admission and did not repeat the imaging in the following hours. This might lead to the high frequency of not formed ischemic region in brain CT-scans. Fourth, we did not perform any other vascular imaging of the brain other than TCD. Thus, the results of TCD could not be correlated with other neuroimaging techniques such as MRA or CTA. Because we used only MFV for the diagnosis of stenosis and MFV may not increase in severe stenosis so we may not detect some cases with very severe stenosis.

Conclusion

The prevalence of intracranial artery stenosis in patients with acute ischemic stroke diagnosed by TCD is 25.4% which is comparable with previous reports from Iran and other Middle East countries.

Conflict of Interests

The authors declare no conflict of interest in this study.

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A single-subject study to evaluate the inhibitory repetitive transcranial magnetic stimulation combined with traditional dysphagia therapy in patients with post-stroke dysphagia

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Keywords
Stroke; Dysphagia; Rehabilitation; Combined Modality Therapy; Transcranial Magnetic Stimulation; Deglutition Disorders

Abstract

Background: Post-stroke dysphagia is common and is associated with the development of pneumonia. To investigate the effects of repetitive transcranial magnetic stimulation (rTMS) combined with traditional dysphagia therapy (TDT) on swallowing function in patients with post-stroke dysphagia.

Methods: In this single-subject study, four patients with dysphagia post-stroke included. The patients received the rTMS applied to the intact cerebral hemisphere at 1 Hz with train of 1200 for 5 consecutive days combined with TDT 3 days per week for 6 weeks. The main outcome measure was the Mann Assessment of Swallowing Ability (MASA). Measurements were taken before, after the end of 5th, 10th, 15th treatment sessions, and after the end of the treatment (18th session).

Results: The MASA scores improved in all patients following treatment. The maximum and minimum change in level between the baseline phase and treatment phase was +84 and +36. The greatest percentage improvement was observed after 5th treatment sessions ranging between 11 and 35%. The treatment trend was upward shown by the directions of the slopes indicated by positive values (+9.1-+20.7). The dysphagia was resolved after 10th treatment session in all participants. The aspiration

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resolved in two participants after the 5th treatment session and resolved in another 2 participants after the 10th treatment session.

Conclusion: The combination therapy of rTMS plus TDT improved swallowing function in patients with post-stroke dysphagia. Further research with a larger sample size is recommended.

Introduction

Stroke is a leading cause of disability in adult population globally. It can cause various medical and neurological complications such as dysphagia or swallowing problem. Impaired swallowing is a common complication with the prevalence to be approximately between 42 and 67% after stroke.[1-3] Stroke related dysphagia (SRD) as a neuromuscular disorder is important because it can affect the activities of daily living and quality of life of stroke survivors.

The SRD must be treated effectively because it is associated with mortality and increased length of hospital stay.[4] The treatment of SRD include percutaneous endoscopic gastrostomy or nasogastric tube feeding,[5] and rehabilitation techniques of sensory enhancement techniques,[6,7] functional dysphagia therapy,[5] exercise therapy (e.g. Lee Silverman Voice Treatment and the Shaker Head Lift),[8] and compensatory treatment procedures.[9,10]

Recently, the repetitive transcranial magnetic stimulation (rTMS) has been used to treat post-stroke dysphagia.[11-15] However, the authors have reported that the rTMS must be used with rehabilitation techniques to be sufficiently effective.[16] To investigate the safety and feasibility of rTMS combined with swallowing rehabilitation for post-stroke dysphagia, Momosaki et al.[16] treated 4 patients with post-stroke dysphagia with rTMS at 3 Hz applied to the pharyngeal motor cortex bilaterally combined with 20 minutes of swallowing rehabilitation exercises and concluded that the protocol of rTMS plus swallowing rehabilitation exercise seems to be safe and feasible for patients with SRD.

The effects of rTMS plus swallowing rehabilitation treatments are not evaluated in patients with SRD. Therefore, the aim of this study was to investigate the effects of rTMS combined with traditional dysphagia therapy (TDT) in patients with post-stroke dysphagia.

Materials and Methods

This study used an A-B single-subject design with measurements taken on four patients suffering from SRD. The Ethical Committee of Tehran University of Medical Sciences, Iran, approved the study, and all patients gave their written informed consent.

In this study, the Mann Assessment of Swallowing Ability (MASA) was used as the main outcome measure.

Four patients with SRD included in the study. The inclusion criteria were (1) age ≥ 18 years old and (2) first-ever stroke resulted in dysphagia. The patients excluded if they had (1) dementia, (2) other neurological diseases, and (3) history of recurrent stroke.

Patients underwent a baseline interview to collect the demographic data by a speech-language pathologist (SLP). The MASA[17] was administered to assess dysphagia before, after the end of 5th, 10th, 15th sessions, and finally after the end of treatment. Therefore, 1 assessment was performed pre-treatment and 4 assessments were carried out during the treatment phase. Then, the patients received traditional treatment for 6 weeks, 3 days a week combined with rTMS (every day for 5 consecutive days).

The MASA is a simple to use instrument, which has been reported to be reliable and valid to document the swallowing function in patients with stroke.[17,18] This is a 24 clinical item tool arranged from the preparatory oral phase to pharyngeal phase and is comprised 3 components of swallowing: (1) oral motor/sensory, (2) functionality, and (3) recommendations for dietary.[17,18] The MASA scoring system includes a total score out of 200, and an ordinal score for both dysphagia (nil ≤ 178-200; mild ≤ 168-177; moderate ≤ 139-167; and severe ≤ 138) and aspiration (nil ≤ 170-200; mild ≤ 149-169; moderate ≤ 148; and severe ≤ 140).

Treatment consisting of rTMS (5 sessions) combined with TDT were given to each patient. The rehabilitation exercises of TDT included 30 minutes individualized oral motor exercises, swallowing maneuvers, compensatory strategies, and sensory stimuli, 3 days per week for 6 weeks. Table 1 shows the detail of the swallowing exercises provided by a SLP.

The magstim super-rapid stimulator (Magstim, Whitland, Dyfed, UK) and a figure-of-eight coil (Whitland, Dyfed, UK) were used for our low-frequency rTMS protocol. The inhibitory rTMS procedure was targeted the intact cerebral hemisphere with a train of 1200 pulses at 1 Hz,

Table 1. Traditional dysphagia therapy (TDT)

Type of traditional treatment	Examples/Description
Exercise programs	Oral motor control exercises
	Range of motion tongue exercises
	Resistance exercises
	Bolus control exercises
	Bolus propulsion exercises
	Laryngeal elevation
	Shaker exercises
Pharyngeal swallowing maneuvers	Mendelsohn maneuver
	Supraglottic swallow
	Super supraglottic swallow
	Effortful swallow
	Masako maneuver
Compensatory swallowing strategies	Slow rate
	Small bites and sips
	Viscosity changes to food and liquids
	Positional changes (up right, chin tuck, head rotation, head tilt)
	Clear throat or cough after each bite/sip
	No straws
	Place food on right or left side of mouth
	Alternate bite/sip
Sensory stimuli	Changing the taste, volume, temperature, or carbonation of the bolus
	Thermal tactile stimulation
	Additional pressure on the tongue with a spoon

with stimulus strength at 20% above the resting motor threshold for 20 minutes. The optimal point of stimulation was located where the maximum motor evoked potentials (MEP) were obtained for the mylohyoid muscles.[15] The EMG machine (EL258RT, Biopac, Santa Barbara, CA, USA) was used to record MEP using two pairs of shielded bipolar silver-silver chloride surface electrodes was used with bandpass filter at 2-5 kHz, frequency at 20 kHz, and sweep speed at 1 second. A physiatrist applied the rTMS considering the safety recommendations and guidelines.[19] The week 1 treatment protocol included 5 rTMS treatments applied daily plus 3 TDT every other day.

The visual analysis was used for interpreting data. The level was calculated for the differences between the baseline phase and treatment phase data. To quantify the trend, slopes were computed.

Results

Four patients with dysphagia (all male; age range 59-72 years) included and completed the combination therapy. The time between stroke onset and intervention ranged from 1 to 18 months (Table 2).

As shown in table 3, the MASA scores improved in all patients following treatment. The percentage improvement after 5th treatment session was ranged between 11 and 35%.

Participant 1 (26%) and patient 3 (35%), both with subcortical stroke, showed the greatest percentage improvement at this stage. Participants 2 and 4, both with cortex stroke, improved 11% after the 5th treatment session.

Table 2. Demographic characteristics of participants

Participant	Age (year)	Stroke localization	Time stroke onset to intervention (month)
1	59	Subcortical	6
2	60	Cortex	18
3	70	Subcortical	1
4	72	Cortex	10
Mean ± SD	65.2 ± 6.7	-	8.7 ± 7.2

SD: Standard deviation

Table 3. Mann Assessment of Swallowing Ability (MASA) score, severity of dysphagia and severity of aspiration, pre- and post-treatment

Patients	Patient 1	Patient 2	Patient 3	Patient 4
MASA score				
Pre-treatment	119	160	108	153
Fifth session	150	175	146	170
10th session	179	185	178	180
15th session	185	194	185	190
18th session	194	196	192	194
Dysphagia				
Pre-treatment	Yes-Severe	Yes-Moderate	Yes-Severe	Yes-Moderate
Fifth session	Yes-Moderate	Yes-Mild	Yes-Moderate	Yes-Mild
10th session	No	No	No	No
15th session	No	No	No	No
18th session	No	No	No	No
Aspiration				
Pre-treatment	Yes-Severe	Yes-Mild	Yes-Severe	Yes-Mild
Fifth session	Yes-Mild	No	Yes-Moderate	No
10th session	No	No	No	No
15th session	No	No	No	No
18th session	No	No	No	No

MASA: Mann Assessment of Swallowing Ability

The percentage improvement after 10th treatment session compared to the 5th treatment session was 4-22%. Again, the greatest improvement was observed in participants 1 (19%) and 3 (22%). Participants 2 and 4 showed 4 and 6% improvement, respectively, after the 10th treatment session (Table 3).

The maximum and minimum change in level between the baseline phase and treatment phase was +84 and +36 observed in participants 3 and 2, respectively. The treatment trend was upward as shown by the directions of the slopes indicated by positive values (+9.1-+20.7) (Figure 1).

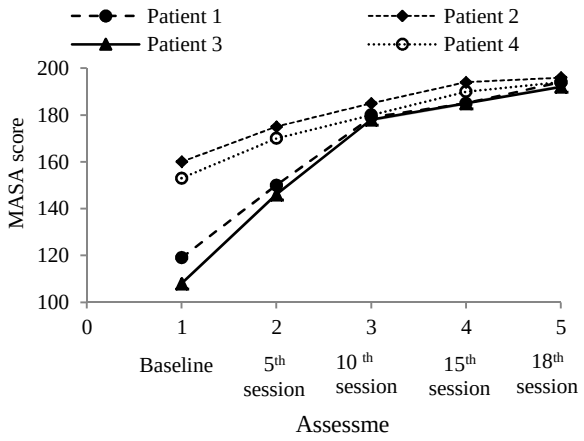

Figure 1. Trend was upward after combined therapy (Slopes values: participant 1: +18.5, participant 2: +9.1, participant 3: +20.7, and participant 4: +10.2)
MASA: Mann Assessment of Swallowing Ability

According to the MASA ordinal scores, the severity of both dysphagia and aspiration improved during the treatment phase. The dysphagia was resolved after 10th treatment session in all participants. The aspiration, however, resolved in participants 2 and 4 after 5th treatment session (cortex stroke) but resolved in participants 1 and 3 (subcortical stroke) after 10th treatment session (Table 3).

Discussion

The results of this single-subject study support the usefulness of combination therapy of rTMS plus TDT for post-stroke dysphagia. The findings of the present study in accordance with Momosaki et al.[16] showed that the combination therapy protocol is safe, feasible, and effective for the treatment of patients with SRD.

The results demonstrated that the patients improved on MASA scores indicating improvements in dysphagia and aspiration post-stroke following rTMS plus TDT protocol.

The greatest improvements were obtained during the first five treatment session where patients received rTMS in combination with TDT. The greatest improvements after 5th treatment session exhibited by patients imply that the addition of rTMS to the TDT had beneficial effects on patients' outcome.

Participants with subcortical stroke who had the lowest scores on MASA pretreatment showed

the greatest improvements after 5th treatment session. This finding indicates that the patients with initially more severe dysphagia may benefit more from combination therapy.

Although patients with initially low scores on MASA exhibited more improvements after 5th treatment session, it is important to note that patients with chronic, cortex stroke (participants 2 and 4) who had initially better scores on MASA achieved complete improvement of aspiration after 5th treatment session. Depending on the severity of the dysphagia post-stroke, however, patients may need more treatment sessions to resolve both the dysphagia and aspiration. Even though, the improvements were found after the end of the treatment (18th treatment session), all participants improved completely after 10th treatment session. This indicates that the 10 treatment sessions of combination therapy may be sufficient to resolve the dysphagia as well as aspiration after stroke. This finding needs to be confirmed with more investigations using high-quality designs with a large sample of patients.

In this study, rTMS was delivered unilaterally to the intact cerebral hemisphere combined with TDT, which resulted in the significant improvement of post-stroke dysphagia.

The improvement may be explained by the inhibitory effects of rTMS that could give rise to the decrease in transcallosal inhibition from the intact hemisphere to the damaged one; this effect might modulate a neural network of cortex associated with the swallowing function.

Previous reports using bilateral rTMS found improvement in dysphagia, as well.[12,16] The improvements obtained in these cases could be also due to the exercises performed using a traditional therapy that has been shown to increase lingual strength with improvements in swallowing function in patients with acute and chronic post-stroke dysphagic.[20] It is possible that the combination effects from rTMS and TDT induced neural plasticity that translated into the improvements in swallowing function. A study is needed to compare the effects of combination therapy with rTMS or TDT.

Conclusion

The results from this single-subject study suggest that that the combination of rTMS plus TDT improved swallowing function in patients with post-stroke dysphagia. This finding that participants with post-stroke dysphagia benefitted from rTMS plus TDT are important because it provides the therapist with a treatment method that is not only effective but also it may improve the post-stroke dysphagia quite quickly. Further research with a larger sample size is needed to confirm the findings.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Study of atherogenic lipid profile, high sensitive C-reactive protein neurological deficit and short-term outcome in stroke subtypes

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Keywords
Stroke; Lipid Profile; Ischemic Stroke

Abstract

Background: Stroke is one of the most frequent causes of death and disability worldwide and has significant clinical and socioeconomic impact. Hyperlipidemia and inflammation play major roles in atherothrombosis and in stroke. This study is conducted to compare the high sensitive C-reactive protein (hs-CRP) levels and the lipid profile parameters between stroke patients and control group and demonstrate correlation between markers, neurological deficit, and short-term outcome.

Methods: We have studied a total 162 patients according to inclusion criteria. Serum level of hs-CRP and lipid profile estimated and correlated with neurological deficit and short-term outcome.

Results: We found stroke patients had significantly higher levels of hs-CRP, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and low level of high-density lipoprotein (HDL) than control. When we compared ischemic and hemorrhagic stroke (HS), data show increased level of triglyceride, LDL and HDL, and decreased the level of hs-CRP in ischemic stroke group than HS group. However, the National Institutes of Health Stroke Scale (NIHSS) score significantly higher in HS as compared to ischemic stroke at the time of admission and on the 7th day.

Conclusion: Thus, continuous clinical observation is necessary for clear differentiation of those changes. Furthermore, the determination of some reliable soluble markers of neuronal damage in blood and cerebrospinal fluid in the early infarction period would be much easier and more useful for tracking the course and prognosis of the disease and for any appropriate therapeutic approach.

Introduction

Stroke is one of the most frequent causes of death and disability worldwide and has significant clinical and socioeconomic impact. While hyperlipidemia and inflammation play major roles in atherothrombosis, there has been controversy regarding the relative contribution of these processes to stroke as compared to coronary

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heart disease.[1] However, the relationship between atherosclerosis and elevated serum lipids is well established and aggressive treatment of dyslipidemia decreases the risk of stroke.[2] Recent studies have shown that distribution of serum triglycerides (TGs) and total cholesterol (TC) within major lipoprotein classes majorly contribute to the development of atherosclerosis, which is the precursor to stroke. Hypercholesterolemia is a moderate risk factor for stroke. Elevated plasma concentration of low-density lipoproteins (LDL) and low high-density lipoprotein concentration (HDL) is associated with an increased risk of atherosclerosis.[3]

High sensitive C-reactive protein (hs-CRP) is a sensitive marker of inflammation and tissue injury in the arterial wall.[4,5] Hs-CRP is a glycoprotein produced by the liver and plays a key role in the development of atherosclerotic disease in cerebral circulation.[6-9] Hs-CRP is now the forerunner in the hunt for inflammatory markers and is subject to intensive research in numerous studies worldwide. Even though both hs-CRP and lipid profile parameters have a key role in initiation and progression of atherosclerosis; however, there is no data is available regarding the correlation of these two entities with respect to the risk stratification of stroke subtypes. Therefore, this study is conducted to compare the hs-CRP levels and lipid profile parameters between stroke patients and control group and demonstrate correlation between biomarkers with neurological deficit or short term outcome.

Materials and Methods

A total of 200 patients with suspected stroke consecutively admitted to emergency department in which 162 patients with confirmed stroke were recruited in the stroke unit of Sri Aurobindo Institute of Medical Sciences, Indore, India. Subsequently, type of stroke identified by trained neurologist on the basis of clinical examination and a computed tomography (CT) scan of the brain and classified them as ischemic and hemorrhagic stroke (HS) subtypes. Criteria for exclusion were stroke more than 72 hours, peripartum stroke, HS or ischemic brain infarctions in the course of cerebral hemorrhage and concomitant major cardiac, renal, hepatic, and tumor diseases potentially interfering with standardized assessment of neurological or neuropsychological status. The inclusion criteria for subjects in the study group were adult stroke (age > 21 years) and within 72 hours of admission. This study was approved by the ethics committee of hospital, and all patients or relatives gave written informed consent.

Biochemical examinations

Serial venous blood samples were collected at admission, at 7th day. To determine serum hs-CRP and lipids levels, blood samples were taken following a 10-12 hour fast. Blood was allowed to clot at room temperature, and serum was obtained immediately by centrifugation at 3500 revolutions per minute (rpm) for 10 minutes. Serum was aliquoted into plastic tubes and stored at -27 °C until assayed. Serum hs-CRP was assayed by turbidimetric test using Roche reagent kit. TC and serum TG were estimated by commercial available standard kits of Roche Diagnostics. HDL-cholesterol (HDL-C) was measured by a reagent kit of Sigma Diagnostics and LDL-cholesterol (LDL-C) by a reagent kit of Accurex diagnostics. All parameters were assayed in Hitachi 917 auto-analyzer, according to the instructions of the manufacturer.

Neurological assessments

All subjects underwent a standardized neurological examination at the time of admission and at 7th day in the stroke unit. The neurological deficit was quantified by the use of the National Institutes of Health Stroke Scale (NIHSS). We performed comprehensive neuropsychological examinations in all patients with a first-ever stroke event and without any clouding of consciousness or severe disorders of attention.

Demographic, clinical and laboratory frequency variables were calculated. Statistical analyses were performed with SPSS for windows (version 17, SPSS Inc., Chicago, IL, USA). Parameters value expressed as a mean ± standard deviation (SD). Statistical significance of the difference between the categorical variables was tested with the chi-square test. Statistical significance for the intergroup difference was assessed by Student's t-test. To study the correlation between quantitative variables, Pearson test was used. A probability value $P < 0.050$ was considered statistically significant. In all cases, a 95% confidence level was used.

Results

The demographic and clinical patient data with cerebral infarction are shown in table 1.

Table 1. Demographic profile

Parameters	Stroke subjects (n = 162)	Control (n = 101)
Sex (Females/Males)	65/97	34/67
Age (year) (mean ± SD)	58.96 ± 12.37	55.54 ± 7.67
Hypertension (mmHg)	118/44	30/61
Smokers (Yes/No)	54/108	26/75
AF (Yes/No)	42/130	21/80
DM (Yes/No)	58/104	27/74
Alcohol (Yes/No)	60/102	26/75

SD: Standard deviation; AF: Atrial fibrillation; DM: Diabetes mellitus

There were no differences in terms of age or sex as shown in table 1. 118 (72%) patients had hypertension, 54 (34%) were smokers, 42 (25%) had atrial fibrillation, 58 (36%) had diabetes mellitus (DM), and 60 (37%) were alcoholic. The study comprised 162 patients that include 100 patients of ischemic stroke and 62 of HS. 101 healthy subjects in the age of 30-58 years were also investigated on similar line and served as control groups. The mean age of the stroke patients were 58.96 ± 12.37 and controls were 55.54 ± 7.67.

Table 2 shows biomarkers and lipid profile status of subject (stroke patients) and control. Stroke patients show significantly elevated level of hs-CRP (4.11 ± 2.00 vs. 0.88 ± 4.90), TC (263.58 ± 38.15 vs. 251.95 ± 35.67), TG (208.13 ± 35.30 vs. 116.65 ± 34.40), LDL-C (191.40 ± 36.40 vs. 88.4 ± 13.6) and significantly decreased level of HDL-C (29.33 ± 5.60 vs. 46.90 ± 12.11) than control.

Table 3 indicates comparison of biomarker and lipid profile status between ischemic and HS group. Data show increased level of TG (229.00 ± 23.07 vs. 99.34 ± 37.17), LDL-C (31.94 ± 5.17 vs. 25.33 ± 3.54) and HDL-C (31.94 ± 5.17 vs. 25.33 ± 3.54) and decreased the level of hs-CRP (2.90 ± 1.70 vs. 5.60 ± 1.10) in ischemic group then hemorrhagic group. However, NIHSS score significantly higher in hemorrhagic group as compared to ischemic group at the time of admission (13.48 ± 7.10 vs. 21.63 ± 1.74) and after 7th day (12.30 ± 7.81 vs. 25.58 ± 3.30), respectively.

We found highly significant positive correlation between hs-CRP and NIHSS score [at the time of admission (Figure 1) (r = 0.923, P < 0.010) and 7th day of admission (Figure 2) (r = 0.982, P < 0.010)]. No statistically significant correlations were found between lipid profile and NIHSS score (at the time of admission and 7th day of admission).

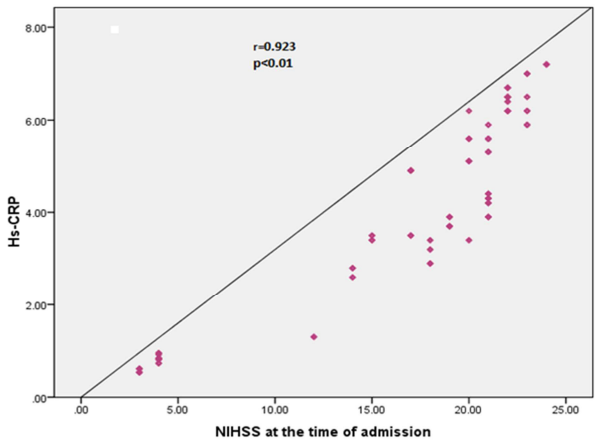

Figure 1. Correlation between high sensitive CRP and neurological deficit

hs-CRP: High sensitive C-reactive protein; NIHSS: National Institutes of Health Stroke Scale

Table 2. Comparison of biomarkers and lipid status between stroke patients and control

Parameter	Subject (n = 162)	Control (n = 101)	t value	P
hs-CRP (mg/L) (mean ± SD)	4.11 ± 2.00	0.88 ± 4.90	7.106	< 0.001***
TC (mg/dL) (mean ± SD)	263.58 ± 38.15	251.95 ± 35.67	14.84	< 0.016**
TG (mg/dL) (mean ± SD)	208.13 ± 35.30	116.65 ± 34.40	20.300	< 0.001***
LDL-C (mg/dL) (mean ± SD)	191.40 ± 36.40	88.4 ± 13.6	27.146	< 0.040*
HDL-C (mg/dL) (mean ± SD)	29.33 ± 5.60	46.90 ± 12.11	15.501	< 0.010**

*Significant, **Highly significant, ***Extremely significant, Degree of freedom (df) = 262

HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; hs-CRP: High sensitive C-reactive protein; TC: Total cholesterol; TG: Triglycerides; SD: Standard deviation

Table 3. Comparison of C-reactive protein (CRP) and lipid profile between ischemic with hemorrhagic stroke (HS) patients

Parameter	Ischemic stroke (n= 100)	HS (n= 62)	t value	P
hs-CRP (mg/L) (mean ± SD)	2.90 ± 1.70	5.60 ± 1.10	14.73	0.001***
TG (mg/dL) (mean ± SD)	229.00 ± 23.07	99.34 ± 37.17	13.55	0.001***
LDL-C (mg/dL) (mean ± SD)	222.17 ± 21.80	84.11 ± 8.63	8.95	0.005**
HDL-C (mg/dL) (mean ± SD)	31.94 ± 5.17	25.33 ± 3.54	17.37	0.001***
TC (mg/dL) (mean ± SD)	296.70 ± 20.54	241.51 ± 30.43	11.83	0.004**
NIHSS score at the time of admission	13.48 ± 7.10	21.63 ± 1.74	13.93	0.050*
NIHSS score at 7th day of admission	12.30 ± 7.81	25.58 ± 3.30	11.83	0.050*

*Significant, **Highly significant, ***Extremely significant, df = 161

HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; hs-CRP: High sensitive C-reactive protein; TC: Total cholesterol; TG: Triglycerides; NIHSS: National Institutes of Health Stroke Scale; HS: Hemorrhagic stroke; SD: Standard deviation

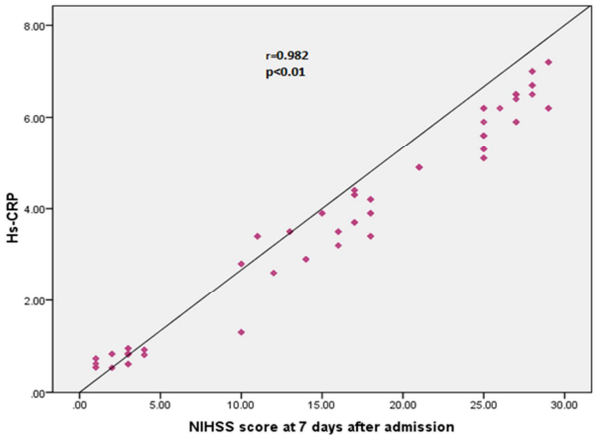

Figure 2. Correlation between high sensitive CRP and neurological deficit

hs-CRP: High sensitive C-reactive protein; NIHSS: National Institutes of Health Stroke Scale

Discussion

Various studies showed that hyperlipidemia and inflammation may accelerate process atherothrombosis and worsening of stroke outcome. In this study, a mean value of inflammatory marker hs-CRP in total stroke patients was higher as compared to control groups. Winbeck et al.,[10] Di Napoli et al.,[11,12] and Eikelboom et al.[13] also reported that the level of hs-CRP, a peripheral marker of inflammation, has consistently been observed to be related to the risk of cerebrovascular and cardiovascular events, and it is systematically elevated in the circulation of patients after acute stroke. Rost et al.[14] recently have shown that elevated hs-CRP levels independently predict the risk of future stroke and transient ischemic attack (TIA) in the elderly. Wakugawa et al.[9] found that hs-CRP may be involved in each of these stages by direct influencing processes such as complement activation, apoptosis, vascular cell activation, lipid accumulation, and thrombosis.

Atherosclerosis, one of the major causes of cerebrovascular disease is considered to involve the inflammatory system. HS-CRP, widely known to be an inflammatory marker, was detected in atherosclerotic plaques. It may be explained by the fact that, inflammation plays a central role in all phases of arthrosclerosis, from the initial recruitment of circulating leukocytes to the arterial wall to the rupture of unstable plaques, which results in the clinical manifestations of the disease. When hs-CRP levels were compared in different subtypes of stroke, the mean hs-CRP level was more in HS than ischemic stroke. Mishra et al.[15] also found significantly increased levels of hs-CRP in HS patients although these results are different from those of Wakugawa et al.[9] in the Hisayama study in which they observed no clear association between hs-CRP levels and HS occurrence. Ridker et al.[16] considered hs-CRP as marker of low-grade vascular inflammation, which is a key factor in the development and rupture of atheromatous plaque. Present data suggested that inflammation plays a key role in the development of brain injury after hemorrhage. HS-CRP is normally absent in the blood. The presence of acute inflammation with tissue destruction within the body stimulates its production, allowing the inflammation to be confirmed.

In present study, total stroke patients showed highly significant rise in TC as compared to control. Stroke is usually caused by a sudden blockage to the arteries carrying blood to parts of the brain. When there is an excess of cholesterol in the artery walls, narrowing of arteries or even a complete blockage can occur in the artery. At narrow points in the arteries, blood clots can form and either block the arteries or break off. Dayton et al.[17] did not find clear correlation between serum cholesterol levels and the risk of stroke. Gorelick and Mazzone[18] showed a U-shaped

relation between the level of serum TC and the risk of stroke of all types, derived from an inverse association with HS and a direct association with ischemic stroke. Konishi et al.[19] found that the possible differences in the effects of cholesterol at different vascular sites could lead to the complex association between serum cholesterol levels and stroke. The origin of the internal carotid artery is probably the most common site of atherosclerosis that leads to TIA or stroke. A highly significant decrease in TC was observed in stroke patients with hemorrhage as compared to ischemic stroke patients.

Iso et al.[20] found an inverse relation between cholesterol level and HS but a positive association with non- HS. Tanizaki et al.[21] in their study found that lower TC was an additional risk factor for cardioembolic infarction in women. Iribarren et al.[22] confirmed a positive association between low serum cholesterol level and intracerebral hemorrhage in elderly men. The mechanisms explaining how low TC could promote HS still remain under investigation. In stroke prone rats, low cholesterol level and abnormal erythrocytes fragility have been reported. It has been hypothesized that such a phenomenon in the endothelial cell could lead to arterionecrosis. Moreover, very low cholesterol could promote cerebrovascular endothelium fragility, which could generate angionecrosis and intracerebral hemorrhage in a context of high pressure.

In total stroke serum, TGs were higher than control in the present study indicating a directly proportional relationship between TH levels and risk of stroke. Hachinski et al.[23] found a positive correlation of serum TG levels with patients suffering from atherothrombotic stroke and TIAs as compared to control subjects. Elevated TGs are markers of elevated levels of lipoprotein remnants [very LDL [VLDL]) which are thought to contribute to plaque build-up. The present study data showed that significant low level of TGs in HS subtypes. Two population-based studies found a positive relationship between low TG and the raised incidents of HS appeared primarily in men and in older age groups, respectively.[22,24] On the basis of data present study hypothesized that the association between low TG level and HS may appear among in individuals with an elevated cerebrovascular risk profile and have particular sensibility to arterial injury.

This study revealed a positive association between LDL-C and the risk of ischemic stroke. Pedro-Botet et al.[25] and Hachinski et al.[23] have found positive correlation between LDL-C levels and risk of ischemic stroke. Treatment with cholesterol-lowering medications and changes in LDL-C level over time may have attenuated the risk in stroke population, and lipid measurements at several points may be a better marker of stroke risk.[26] Kar et al.[27] proved that there was an impressive correlation of increased LDL-C to the atherosclerosis. Varying levels of serum LDL-C are responsible for deferring vascular pathogenesis of underlying stroke. LDL-C is believed to be the most atherogenic lipoprotein. 50% of cholesterol in plasma is found in the form of LDL-C. LDL delivers cholesterol to tissues via a specific high affinity LDL receptor, which controls the uptake of cholesterol by cells. An excess amount of LDL-C in the blood builds up on the inside of the blood vessel walls, making it more difficult for blood to flow freely. This increases the risk of developing stroke. When LDL-C levels were compared in different subtypes of stroke, the mean LDL-C levels were significantly low in HS than ischemic stroke in the present study. Noda et al.[28] report an association between low levels of LDL-C with an increase in the risk of fatal intra-parenchymal intracerebral hemorrhage in a Japanese population-based cohort. Goldstein[29] found that the general population, having low, usual TC and LDL-C appear to be associated with a higher risk of brain hemorrhage. The data of present study are in agreement with the studies of Noda et al.[28] and Goldstein[29] that the low LDL-C appears to be associated with higher risk of brain hemorrhage.

In the present study, it was found that the stroke patients had low level of HDL-C than that of the control group. A study by Kar et al.[27] proved a strong positive correlation of increased LDL-C and decreased HDL-C to the atherosclerosis. Wannamethee et al.[30] reported that higher levels of HDL-C were associated with a significant decrease in the risk of non-fatal stroke. Bloomfield Rubins et al.[31] revealed that gemfibrozil, a fibrate that raises HDL-C levels, reduced the risk of ischemic stroke by 31% in men with congenital heart disease, supporting the idea that HDL-C levels may be important in the pathogenesis of ischemic stroke. Albucher et al.[32] studied 90 young ischemic coronary disease patients and concluded that HDL-C was the only serum lipid index to be associated to an increased risk of stroke. Low HDL-C must be

considered in the care and management of young patients regardless of the detectable presence of atherosclerosis. HDL-C is important for removal of cholesterol from the peripheral tissues to the liver, metabolism of chylomicrons and VLDL-cholesterol. HDL-C affects the metabolism and transport of other lipid fractions. A non-significant alteration in HDL levels was reported in comparison of HS and ischemic stroke patients.

When disability score was compared in different subtypes of stroke, the score was more in HS than ischemic stroke. Andersen et al.[33] and Jorgensen et al.[34] found that strokes are generally more severe in patients with HS and the ratio between HS and ischemic stroke closely related to stroke severity. Corbin et al.[35] figures out those patients with HS are generally considered to be at high risk for mortality compared to patients with infarcts. Franke et al.[36] linked the excess mortality to the generally more severe strokes in patients with HS, whereas stroke type per se was considered to have no influence on mortality-The extent of the injury and initial stroke severity was regarded decisive. Chiu et al.[37] found that intracerebral hemorrhage is an independent predictor of poor neurologic outcome, nearly doubling the odds of long-term disability. However, intracerebral hemorrhage is not associated with higher mortality compared with ischemic stroke after adjusting for initial stroke severity and other baseline characteristics. The present findings supports and extend previous studies on functional outcome after ischemic and HS and concluded that patients with HS patients had a more functional impairment (at the time of admission and 7th day of admission).

Conclusion

In the last decade, multiple techniques were explored and were found useful in the evaluation of the neurological deficit as well as in recovery prediction after the application of therapy in patients with brain ischemia.

Modern neuroradiological techniques, such as CT and nuclear magnetic resonance, are useful in identification of locality and extent of the ischemic lesion, but in the relatively late period, when lesions are mostly formed. Furthermore, in the early period after the onset of a cerebral insult, it is difficult to clinically distinguish and evaluate reversible from irreversible changes in the brain. Thus, continuous clinical observation is necessary for clear differentiation of those changes. Moreover, the determination of some reliable soluble markers of neuronal damage in blood and cerebrospinal fluid in the early infarction period would be much easier and more useful for tracking the course and prognosis of the disease and for any appropriate therapeutic approach.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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Review Paper

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Temporal plus epilepsy: Anatomo-electroclinical subtypes

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Keywords
Temporal Lobe Epilepsy; Insular Cortex; Drug Resistant; Neural Networks; Intracranial Electroencephalography; Positron Emission Tomography

Abstract

Background: Mesial temporal lobe epilepsy (TLE) is a remediable epileptic syndrome. About 40% of patients continue to have seizures after standard temporal lobectomy. It has been suggested that some of these patients could actually suffer from a more complex epileptogenic network. Because a few papers have been dedicated to this topic, we decided to write an article updating this theme.

Methods: We performed a literature search using the following terminology: "temporal plus epilepsy and networks," "temporal plus epilepsy," "orbito-temporal epilepsy," "temporo-insular epilepsy," "temporo-parieto-occipital (TPO) epilepsy," "parieto-temporal epilepsy," "intracortical evoked potential and temporal plus epilepsy," "temporal lobe connectivity and epilepsy," "intracortical evoked potential and epilepsy surgery," "role of extratemporal structures in TLE," "surgical failure after temporal lobectomy," "Diffusion tensor imaging (DTI) and temporal epilepsy," and "positron emission tomography (PET) in temporal plus lobe epilepsy" in the existing PubMed databases. We searched only English and Spanish literature. Only papers that fit with the above-mentioned descriptors were included as part of the evidence. Other articles were used to reference some aspects of the temporal plus epilepsy.

Results: A total of 48 papers from 2334 were revised. The most frequently reported auras in these groups of patients are gustatory hallucinations, vestibular illusions, laryngeal and throat constriction, atypical distribution of somatosensory symptoms (perioral and hands, bilaterally hands paresthesias, trunk and other). The most common signs are tonic posturing, hemifacial twist, and frequent bilateral clonic movements. Interictal electroencephalographic (EEG) patterns exhibit regional and frequently bilateral spikes and/or slow waves. The first ictal electrographic change is mostly regional. It is important to note that the evidence is supported by case series or case reports. Thus, most of the data presented could represent the features on these cases and not actually the totality of the iceberg.

Conclusion: Temporal plus epilepsy is a diagnosis that can be done only after the invasive recordings have been analyzed but an adequate suspicion may arise based on clinical, EEG and imaging data.

Introduction

Temporal lobe epilepsy (TLE) with hippocampal sclerosis may have different semiological, ictal and interictal electroencephalographic (EEG), and

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histopathological features.[1-3] Although more than 60% of patients remained seizure-free after temporal lobectomy, recurrence from an extratemporal, contralateral or neocortical focus are a commonly reported causes of surgical failure.[4-11] Alternately, it has been suggested that some patients with surgically refractory TLE could actually suffer from a more complex epileptogenic network that can encompass the temporal lobe and brain regions to which it is closely related. Ryvlin and Kahane[6] recently introduced the term temporal plus epilepsy (TL+) to designate this form of multilobar epilepsy: an epilepsy in which primary temporal lobe epileptogenic zone is extended to neighbored regions, such as the insula, the suprasylvian operculum, the orbitofrontal cortex (OFC), and the temporo-parieto-occipital (TPO) junction (Figure 1). Until now this, type of epilepsy is only correctly identified using invasive recordings. Because a few papers have been dedicated to this theme and the growing scientific evidence supporting the existence of TL+ epilepsy and the importance of recognize this type of epilepsy to avoid surgical failures, we decided to write an article focused on this topic.

The arrows (from anterior to posterior part of the head) represent some common origins in temporal plus epilepsy (OF, operculum, insular cortex, and TPO junction).

Materials and Methods

We performed a literature search in the PubMed, Medline, and Cochrane databases with the aim of determining the electroclinical and imaging features of temporal plus epilepsy and the white matter (WM) connections underlying the epileptogenic networks studying through intracortical evoked potentials or diffusion tensor imaging (DTI) techniques.

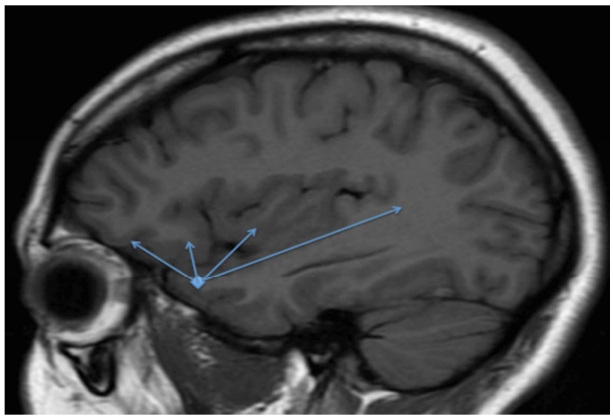

Figure 1. Sagittal magnetic resonance imaging (MRI) of the head

Published case series, case reports, original articles and literature reviews of the temporal plus epilepsy or the epileptogenic networks in TLE were identified using the search terms "temporal plus epilepsy and networks," "temporal plus epilepsy," "orbito-temporal epilepsy," "temporo-insular epilepsy," "TPO epilepsy," "parieto-temporal epilepsy," "intracortical evoked potential and temporal plus epilepsy," "temporal lobe connectivity and epilepsy," "intracortical evoked potential and epilepsy surgery," "role of extratemporal structures in TLE," "surgical failure after temporal lobectomy," "DTI imaging and temporal epilepsy," and "positron emission tomography (PET) in temporal plus lobe epilepsy" in the existing databases. We searched only English and Spanish literature (Figure 2) (Table 1).

Databases: PubMed, Medline, Cochrane

Articles publish under descriptor used for search	Papers found / papers revised
Temporal plus epilepsy and network	(0/0)
Temporal plus epilepsy	(204/7)
Orbito temporal epilepsy	(2/1)
Temporo insular epilepsy	(2/1)
TPO epilepsy	(74/3)
Intracortical evoked potential and temporal plus epilepsy	(1/1)
Intracortical evoked potential and epilepsy surgery	(17/2)
Role of extratemporal structure in temporal lobe epilepsy	(0/0)
Surgical failure after temporal lobectomy	(27/5)
DTI imaging in temporal epilepsy	(123/18)
PET in temporal plus epilepsy	(7/3)
Functional magnetic resonance and focal epilepsy	(1595/4)
Temporal lobe conectivity and epilepsy	(264/3)

Figure 2. Flow of information through the searching of review process
DTI: Diffusion tensor imaging; PET: Positron emission tomography; TPO: Temporo-parieto-occipital

Table 1. Descriptors, papers found and revised, first authors and the title for each search

Descriptors	Papers found/papers revised	Author	Publication
Temporal plus epilepsy and networks	0		
Temporal plus epilepsy	204/7	Thompson et al.[12]	Auditory aura in frontal opercular epilepsy: sounds from afar
		Kahane et al.[13]	The concept of temporal "plus" epilepsy
		Guedj et al.[14]	18FDG-PET in different subtypes of TLE: SEEG validation and predictive value
		Rathore et al.[15]	The utility of 18F-FDG-PET in epilepsy surgery
		Zhu et al.[16]	Temporal plus epilepsies: electrophysiology studied with interictal MEG and intracranial video-EEG monitoring
		Harroud et al.[4]	TLE surgery failures: a review
		Barba et al.[5]	Ictal clinical and scalp-EEG findings differentiating temporal lobe epilepsies from temporal "plus" epilepsies
		Ryvlin and Kahane.[6]	The hidden causes of surgery-resistant TLE: extratemporal or temporal plus?
Orbito temporal epilepsy	2/1	Mesulam and Mufson[17]	Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain
Temporo-insular epilepsy	2/1	de Maeseneire et al.[18]	Musical hallucinations as a presenting manifestation of a left temporo-insular glioma
TPO epilepsy	74/3	Marossero et al.[19]	SEEG and surgery in partial epilepsy with TPO foci
		Williamson et al.[11]	Parietal lobe epilepsy: diagnostic considerations and results of surgery
		Palmini et al.	Occipitotemporal epilepsies: evaluation of selected patients requiring depth electrodes studies and rationale for surgical approaches
Intracortical evoked potential and temporal plus epilepsy	1/1	Enatsu et al.[20]	Connections of the limbic network: A CCEPs study
Intracortical evoked potential and epilepsy surgery	17/2	Almashaikhi et al.[21]	Functional connectivity of insular efferences
		Catenoix et al.[22]	Evoked potential study of hippocampal efferent projections in the human brain
Role of extratemporal structures in TLE	0		
Surgical failure after temporal lobectomy	27/5	Blauwblomme et al.[23]	Prognostic value of insular lobe involvement in TLE: a SEEG study
		Ramos et al.[7]	Failure of temporal lobe resection for epilepsy in patients with mesial temporal sclerosis: results and treatment options
		Jeha et al.[8]	Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy
		Janszky et al.[9]	Failed surgery for TLE: predictors of long-term seizure-free course
DTI imaging and temporal epilepsy	123/18	Labate et al.[24]	WM abnormalities differentiate severe from benign TLE
		Catani and Thiebaut de Schotten[25]	A DTI tractography atlas for virtual *in vivo* dissections

Table 1. Descriptors, papers found and revised, first authors and the title for each search (Continue)

Descriptors	Papers found/papers revised	Author	Publication
		Kemmotsu et al.[26]	Frontolimbic brain networks predict depressive symptoms in TLE
		Liacu et al.[27]	DTI tractography parameters of limbic system bundles in TLE patients
		Bhardwaj et al.[28]	Diffusion tensor tractography detection of functional pathway for the spread of epileptiform activity between temporal lobe and Rolandic region
PET in temporal plus epilepsy	7/3	Guedj et al.[14]	18FDG-PET in different subtypes of TLE: SEEG validation and predictive value
		Rathore et al.[15]	The utility of 18F-FDG-PET in epilepsy surgery
		Boling et al.[29]	FDG-PET imaging for the diagnosis of MTLE
Functional MR and focal epilepsy	1595/4	Avesani et al.[30]	EEG-fMRI evaluation of patients with mesial temporal lobe sclerosis
		Kaiboriboon et al.[31]	Interictal MEG/MSI in intractable MTLE: spike yield and characterization
		Al-Asmi et al.[32]	fMRI activation in continuous and spike-triggered EEG-fMRI studies of epileptic spikes
		Manganotti et al.[33]	Continuous EEG-fMRI in patients with partial epilepsy and focal interictal slow-wave discharges on EEG
Temporal lobe connectivity and epilepsy	264/3	Haneef et al.[34]	Functional connectivity of hippocampal networks in TLE
		Antony et al.[35]	Functional connectivity estimated from intracranial EEG predicts surgical outcome in intractable TLE
		Kemmotsu et al.[36]	Alterations in functional connectivity between the hippocampus and prefrontal cortex as a correlate of depressive symptoms in TLE

TLE: Temporal lobe epilepsy; TPO: Temporo-parieto-occipital; 18F-FDG-PET: 18F-fluorodeoxyglucose-positron emission tomography; MEG: Magnetoencephalography; EEG: Electroencephalographic; CCEP: Cortico-cortical evoked potentials; DTI: Diffusion tensor imaging; WM: White matter; fMRI: Functional magnetic resonance imaging; MSI: Magnetic source imaging

Only papers that fit with the above-mentioned descriptors were included as part of the evidence if it's described the symptomatology, electrographic and imaging features and intracortical evoked potentials in patients with well documented TL+ epilepsy. TL+ epilepsy was considered well documented if in the section "patients and methods" one of the following criteria appeared well described:

1. Seizure freedom after 2 years of surgery in a patient with a wide resection that included temporal lobe structures and one of the following: the insular lobe, OFC, TPO junction or suprasylvian cortices
2. The stereo-electrocorticography (ECoG) showed an ictal onset zone involving insular, OF, TPO junction or suprasylvian cortices during temporal lobe seizures.

From our literature review, we organized the present article into sections detailing the temporal plus network and anatomy, semiology of seizures, features from scalp recording, PET scan, and evoked potentials.

Temporal plus networks and anatomy

Temporal plus neural network encompass different interconnections among many cortical and subcortical structures (parietal lobe, temporal lobe, occipital lobe, temporo-parietal-occipital junction, insular lobe, perisylvian cortex, OF cortical areas, and the cingulate gyrus). Primary and/or secondary epileptogenesis in this broad circuitry explain the different patterns of seizure semiology, interictal or ictal EEG patterns, and hypometabolism in PET images. The knowledge of this circuits can be helpful to understand the temporal plus concept, the planning of invasive studies and finally to decide which should be the epileptogenic zone. Three methods have been of helpful to understand the connectivity among these cortical areas: intracortical evoked potentials, functional resonance images, and post-mortem anatomy dissection. These studies have identified different neural networks: limbic, temporoparietal, TPO, OF, perisylvian, and opercular networks.[24-28,37]

Temporal plus epilepsy: anatomic correlation

The limbic system as a part of the network in temporal lobe epilepsies: Papez[8] proposed a system involved in emotion and episodic memory, which is composed of the hypothalamus, hippocampus, mammillary bodies, thalamus, cingulate gyrus, parahippocampal gyrus (PHG), and the entorhinal cortex (EC). Thereafter, Maclean[39] introduced the neurophysiological and neuroanatomical concept of the "limbic system." He added the OFC and amygdala, and named this group of structures the "limbic system."

Cortico-cortical evoked potentials (CCEP) have demonstrated that a functional connectivity among various components of the human limbic network subserves as a model of epileptogenic network.[20] Data taken from cortical EEG recordings and from right anterior hippocampal stimulation during invasive recordings in patients with focal refractory epilepsy shows that it elicits prominent CCEPs responses in the ipsilateral medial and lateral temporal structures, operculum, medial and lateral OF, medial and lateral prefrontal cortex, supplementary motor cortex (SMA), pre-SMA, anterior cingulated gyrus, and insular cortex.[20,34-36]

The above-mentioned data have some possible implications for the interpretation of the semiology and EEG recordings in patients with suspected TL+ epilepsy. There are strong intra- and interhemispheric connections from these cortical areas to the temporal lobe. This broad intrahemispheric connection can explain the difficulty of interpreting scalp or invasive EEG in epilepsies related with the above-mentioned neural networks.[20]

TPO junction: TPO junction is a complex region of the brain involved in several crucial high-level functions such as language, visuospatial recognition, writing, reading, symbol processing, calculation, self-processing, working memory, musical memory, and face and object recognition.[40] The seizure involvement of this associative cortex gives arise some of the typical symptoms described in TL+ epilepsy (such as auditive, vestibular, and visual auras). The special functional relations in between these cortices could explain emotional changes and postictal amnesia.

At the subcortical level, the WM of the TPO junction represents a crucial node of intralobar and interlobar connectivity that could explain the above-mentioned symptomatology. In fact, the activation of cortical neurons or their axons in TPO junction produces functional changes at both local and distant brain hubs, and the modifications differ based on specific patterns of connectivity.[25,41-45]

The insular lobe: The insular lobe has functional connectivity with the hippocampus,

EC, frontal, temporal and parietal opercula, temporal pole, lateral temporal neocortex, pre-central and post-central regions, perisylvian region, OFC, and amygdala. Most of the connections are reciprocal.[17,21] These connections explain the difficulty to assess insular seizures without invasive recording and the frequency of misleading electrographic patterns when insular seizures are evaluated with scalp electrodes.

The cingulated gyrus: The cingulated gyrus has strong and bidirectional connections with the temporal lobe. The efferent fibers from cingulated cortex reach the hippocampus by the final part of nauta circuitry, throughout the parahippocampal cortex, subiculum, and dentate gyrus.[28,34,35] This circuitry can explain why cingulated seizures can easily mimic temporal seizures.

WM fibers as skeleton of TL+ epilepsy

1. Uncinate fasciculus: this pathway connects the anterior part of the temporal pole, the uncus, amygdala and hippocampal gyrus to the orbital and polar frontal cortex[40]

2. Inferior longitudinal fasciculus connects the anterior part of the temporal lobe to the occipital lobe. Recent DTI studies have demonstrated the existence of both a direct and indirect pathway[40]

3. Inferior occipitofrontal fasciculus: this tract comes from the occipital lobe and postero-lateral temporal areas to the OF and dorso-lateral prefrontal cortices via the anterior floor of the external capsule. The Inferior occipitofrontal fasciculus terminations appears within the superior parietal lobe, superior occipital gyrus, medial occipital gyrus and inferior occipital gyrus, and within the temporo-basal region[40]

4. Superior longitudinal fasciculus (SLF) (or arcuate fasciculus) is a fiber tract stemming from the caudal part of the posterior and superior temporal cortex (mainly Wernicke's area) that arches around the insula and projects forward to end within the frontal lobe (mainly prefrontal and premotor gyri, especially Broca's area). Three segments of the perisylvian SLF have been identified: (1) anterior segment, connecting the supramarginal gyrus and superior temporal gyrus with the precentral gyrus, (2) posterior segment, connecting the posterior portion of the middle temporal gyrus with the angular gyrus, and (3) long segment of the arcuate fasciculus that connects the middle and inferior temporal gyri with the precentral gyrus and posterior portion of the inferior and middle frontal gyri.[46]

From the anatomy to the clinical features in TL+ epilepsy

According to Barba et al.[5] and other series of cases and case reports, we can describe the semiology of TL+ epilepsy as following:

Auras: The most frequently reported auras in these groups of patients are gustatory hallucinations and vestibular illusions. Although other different types of auras (emotional, psychic, visual, auditive, and vestibular) can be found. Gustatory auras are associated with an ictal onset zone in temporal insular subgroup, and vestibular auras in the TPO subgroup.[5,11] Typical auditory auras begin with a non-lateralized or lateralized auditory aura, described as a distortion of sounds ("things sound weird"), accompanied by a feeling of anxiety or as if his/her hearing was "muffled," associated with an indescribable feeling of an impending seizure. These could be triggered by music and specifically by a sudden change in musical rhythm but also can occur spontaneously. This type of aura can be associated with an ictal onset zone in inferior perisylvian cortex but can be also found in frontal opercular region.[5,12] TL + epilepsies less frequently presented an ability to warn at seizure onset, and to report abdominal aura.[5]

Motor manifestations in TL+ epilepsy: The patients suffering from TL+ epilepsies more frequently exhibit versive manifestations of the eyes and/or head, more especially contraversive motion of the head and/or eyes. Other signs found in TL+ epilepsies were piloerection and ipsilateral tonic motor signs. It is important to know that gestural automatisms are less associated with TL+ epilepsy. When secondary generalized seizures appear, a phase of tonic contraction of the hemiface with eye deviation occurred, with an initial extension of the arm on generalization. Furthermore, varied hyperkinetic motor movements and vocalization would follow the initial seizure onset.[10,11,19]

Consciousness: Consciousness was impaired in almost all cases in some point during seizures.[5]

Postictal phase: Postictal phase related to temporal epilepsy, postictal amnesia TL+ epilepsy is not frequently found in the postictal phase. Moreover, dysphoric signs are more frequently found in patients with TL+ epilepsy compared to those with TLE. Aphasia for 1-2 minutes or transient oromotor dysfunction (inability to speak) were reported and indicated opercular compromise.[5,12,40]

Role of other cortical structures in temporal plus epilepsy

Insula: Penfield and Flanigin[47] had already observed that seizures arising from the insula could mimic temporal lobe seizures. In a series of 21 patients with atypical TLE reported by Isnard[48] two patients showed stereoelectroencephalography (SEEG) evidence of spontaneous insular seizures, and both achieved a poor outcome (Engel class IV) following temporal lobectomy only.

The contribution of noninvasive investigations in the detection of insular epilepsy masquerading as or concomitant to TLE is limited.[23] The most useful technique is magnetic resonance imaging (MRI), as visualization of an insular lesion strongly supports the likelihood of insular involvement. Unfortunately, insular epilepsy is commonly non-lesional. Scalp EEG is of limited utility. Single-photon emission computed tomography and PET scans may reveal changes in the insular lobe, but their specificity is low. There is some promising evidence that magnetoencephalography (MEG) can be useful in localizing insular epileptogenic foci, but further studies are needed to assess its true clinical utility. In the absence of a visualized lesion on MRI, intracranial recording with insular sampling is necessary.[23,48] This is particularly true for those patients with TLE symptoms who also show "atypical" features such as occurrence at onset of somatosensory (e.g., laryngeal discomfort, throat constriction, limb paresthesias specifically distal hand paresthesia, any combination of perioral and hand paresthesia, trunk and distal hand paresthesia or bilateral sensorial symptoms) or motor symptoms (e.g., arm elevation, trashing, or pedaling).[18,23,48,49]

In an attempt to improve the outcome of TLE surgery, Penfield and Flanigin[47] were the first to perform insular resection, when residual epileptiform activity in the insula was recorded after removal of the temporal lobe.

However, this approach was abandoned after Silfvenius et al.[50] reported that this method did not benefit seizure control while significantly increased morbidity from 3 to 21% (mainly hemiparesis). It is of interest that patients in the same study by Silfvenius et al.[50] who underwent reoperation and had an insulectomy had a rate of unsatisfactory outcome of only 46% compared to 83% in patients who did not have insulectomy, suggesting that the insula could actually play a role in the surgical failure of some patients with TLE. Fortunately, several publications have recently shown that insular epilepsy surgery can be both safe and beneficial with modern neurosurgical techniques.[51-56]

OF cortex: OF seizures are characterized by integrated gestural motor behavior, distal stereotypes and fearful behavior.[56]

After reviewing case reports, some common features of OF-temporal epilepsy can be summarized as follows: lack of aura or nonspecific auras, autonomic changes, behavioral arrest and/or impaired awareness, complex motor and "hypermotor" activity, vocalization, oculocephalic deviation, olfactory or gustatory hallucinations and occasionally secondary generalization. Occurrence in clusters, nocturnal preponderance, relatively short duration and brief, if any, postictal confusion are also observed.[56-60] This semiology can be summarized as three "recognizable seizure patterns:"[57] (1) Olfactory auras accompanied or not by gustatory auras, autonomic changes, oroalimentary and/or gestural automatisms and "thymic alterations," (2) autonomic seizures,[57] (3) the so-called "hypermotor seizures." These hypermotor movements may appear violent, for example, thrashing, bicycling, kicking, frenetic striking or flailing of limbs and other rather peculiar motor behaviors. As it can be seen epileptogenic foci within the OF-temporal region can give rise to seizures, which are electro clinically indistinguishable from temporal lobe seizures given the widespread connections between the limbic system and the orbito-frontal region.[57-60]

Opercular cortex: Seizures arising from opercular cortex and temporal lobe (temporo-opercular seizures) are characterized by the association of opercular semiology (unilateral or bilateral clonic, tonic or myoclonic jerk in the chin or perioral muscles, paresthesia in the oral cavity or in the perioral region, drooling anartria or motor aphasia)[12,61-67] with some clinical, electrographic features of TLE in a patient with hippocampal sclerosis (unpublished data). Thompson et al.[12] reported auditories auras in two patients with seizures arising from the opercular region, but this symptom is very hard to explain by opercular activation.

Scalp-EEG findings in TL+ epilepsy

Interictal and ictal recordings show some commons characteristic EEG patterns**:**

a. Interictal, TL+ patients more frequently

exhibit bilateral spikes and/or slow waves, as well as precentral (F4-C4; F3-C3) spike-and-waves complexes

b. Ictally, the first EEG changes were more frequently localized over the anterior frontal (FP2-F4; FP1-F3) region, the temporoparietal (T5-P3; T6-P4) region and the precentral (F4-C4; F3-C3) region. These changes are found to be more frequently associated with the TF, TPO and TI subgroups, respectively.[5] These findings are supported by some reports utilizing MEG.[16]

PET studies[14,15]

In a study of 54 consecutive patients with pharmacoresistant TLE that were retrospectively enrolled after a comprehensive presurgical evaluation (at least brain MRI, 18FDG-PET, surface video-EEG electroclinical exploration, and SEEG recordings), 18FDG-PET was especially used with MRI and surface video-EEG electroclinical exploration to guide SEEG recordings. The authors found that patients with TL+ epilepsy showed temporal hypometabolism ipsilateral to the atrophic hippocampus, involving the middle and superior temporal gyrus, the uncus and the PHG, but also one of the following structures: the lingual gyrus, the inferior parietal lobule and the supramarginal gyrus, the pre- and post-central gyrus, the inferior and middle frontal gyrus, the rectal gyrus or the insula. On the whole, the extratemporal cortical involvement was a typical finding for TL+ epilepsy.[14]

Evoked related potentials in TL+ epilepsy

The memory-related modulations of the N400 and P600 are usually referred to as evoke related potential "old/new" effects. These studies have demonstrated large amplitude gradients and local polarity reversals within and adjacent to the hippocampal formation and amygdala, suggesting a local generation of these potentials. Hippocampal recordings have revealed that both N400 and P600 effects were less pronounced or even absent in patients with TL+ epilepsy compared with patients with TLE.[68,69]

Functional MRI (fMRI) in TL+ epilepsy

Preliminary studies showed that magnetic source imaging (MSI) may be used to help identify the epileptogenic zone and epileptic networks including the temporal plus regions related with those networks. MSI may detect interictal spikes from mesial temporal structures, and therefore, may provide important localizing information in patients with mesial temporal sclerosis, especially when MRI and/or ictal scalp EEG are not localizing.[30] An MSI study was performed on 22 patients with mesial temporal sclerosis candidates for surgical treatment. 60% of patients with non-localizing ictal scalp EEG had well-localized spikes on MSI ipsilateral to the side of surgery and 66.7% of patients with non-localizing MRI had well-localized spikes on MSI ipsilateral to the side of surgery.[31]

Continuous EEG-fMRI is a simple neuroimaging tool that has already improved initial presurgical planning by helping to identify irritative foci that necessitate further study with more invasive techniques to identify the epileptogenic region. Notwithstanding these advantages, an early study reported that continuous EEG-fMRI yields low sensitivity in definitively identifying an irritative focus in the mesial temporal lobe.[32] Although this study made no distinction between patients whose EEG showed slow and high firing, a recent study suggests that firing rates could have a major role in detecting brain hemodynamic activation related to interictal epileptiform discharges.[33]

The study of Avesani et al.[30] provided information related with the possible EEG-fMRI patterns in temporal epilepsy, however, the authors did not explore the differences between patients with temporal and temporal plus epilepsies. This study sought more information on blood oxygen level dependent activation, especially contralateral temporal and extratemporal spread, during continuous EEG-fMRI recordings in four patients with mesial temporal sclerosis. fMRI analysis confirmed a single activation in the mesial temporal region in two patients whose EEG showed unilateral focal activity, while it demonstrated a bilateral activation in the mesial temporal regions in the other two patients. In the third patient (with the most drug-resistant form and also extratemporal clinical signs), fMRI demonstrated an activation in the supplementary motor area, ipsilateral to the irritative focus. This study confirms the most significant activation with a high firing rate of the irritative focus, but also suggests the importance of using new techniques (such as EEG-fMRI to examine cerebral blood flow) to identify the contralateral limbic activation, and any other extratemporal activations, possible causes of drug resistance in temporal plus epilepsies that may require a more precise presurgical evaluation

with invasive techniques.

Invasive coverage of temporal and "plus" cortices-The planning

As the diagnosis of TL+ epilepsy relies on invasive recordings, it is very important to get an adequate spatial intracerebral sampling of temporal and extratemporal structures.[13] Structures that should be sampling include:

- Temporal lobe: amygdala, hippocampus, parahippocampus, EC, superior, medium and inferior temporal gyrus and temporopolar region
- Extratemporal structures: it is important to take into account the possible hypothesis (temporo-insular epilepsy, TPO epilepsy, temporo-perisylvian epilepsy, temporo-frontal epilepsy (temporo-opercular-frontal or temporo-fronto-basal).

Electrodes for the insular cortex should be inserted using lateral orthogonal trajectory through the fronto-parietal and temporal operculum cortex or using an oblique trajectory through frontal or parietal cortices.

When orbito-temporal epilepsy is suspected investigation of gyrus rectus, orbital cortex, frontopolar cortex and anterior cingulated cortex and temporal lobe are needed.

In the cases of TPO epilepsy the targets should include the lingual lobule, fusiform gyrus, the precuneus and posterior cingulate cortex, the angular and supramarginal gyri, the temporal lobe and an electrode to register the parahippocampus electrical activity. These implantation patterns, obviously, depend on the knowledge we have, at the time of implantation, of the anatomo-functional systems that underlie the electroclinical features of TL+ seizures, so they can change with time.

In temporo-perisylvian epilepsies almost eight electrodes should be inserted in the temporal lobe including amygdala, hippocampus (three electrodes: anterior, middle and posterior), EC, temporopolar cortex, medium, and inferior temporal gyrus. It is also important to cover the perisylvian cortex: angular, supramarginal gyri, all upper blank of the operculum (anterior, medium and posterior operculum), and three electrodes should be placed in the superior temporal gyrus (anterior, medium and posterior).[13].

Conclusion

The TL+ epilepsy is a diagnosis that can be done only after the invasive recordings have been analyzed verifying that the epileptogenic network encompasses the temporal lobe and some of the neighboring cortical areas. However, an adequate suspicion may arise based on clinical, EEG and imaging data.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Review Paper

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Population attributable fraction of modifiable risk factors for Alzheimer disease: A systematic review of systematic reviews

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Keywords
Alzheimer Disease; Risk Factors; PAF

Abstract

Background: Alzheimer's disease (AD) is the most common type of dementia. Demonstrating the modifiable risk factors of AD can help to plan for prevention of this disease. The aim of the current review was to characterize modifiable cardiovascular risk factors of AD using existing data and determine their contribution in AD development in Iran and the world.

Methods: The systematic search was done in Medline, Scopus, and Cochrane databases from inception to May 2014 to find systematic reviews or meta-analyses about association between AD and cardiovascular modifiable risk factors included diabetes, hypertension (HTN), physical inactivity, smoking, hypercholesterolemia, and overweight and obesity. The population attributable fraction (PAF) was calculated for these risk factors in Iran and the world.

Results: Of 2651 articles, 11 were eligible for data extraction after assessing relevancy and quality. Diabetes mellitus (DM) type 2, smoking, physical inactivity, overweight and obesity were significantly associated with increased risk of AD. Physical inactivity with 22.0% and smoking with 15.7% had the highest PAF for AD in Iran and the world, respectively.

Conclusion: Our findings demonstrated that modifiable cardiovascular risk factors could increase the risk of AD. Moreover, about one-third of AD cases were attributed to five modifiable risk factors.

Introduction

Dementia is one of the most common and debilitating disorders in late life. The number of people affected by dementia in 2010 was estimated to be 35.6 million worldwide and 4.6 million new cases occur annually. The number doubles every 20 years.[1]

Alzheimer's disease (AD) is the most common type of dementia that includes 60-80% of this problem. The prevalence of AD is growing mainly due to demographic changes and increasing life expectancy. Nowadays, approved drugs have little effect on dementia, particularly on AD, and

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are unable to stop progression of disease. Therefore, identification and implementation of preventive strategies seem to be more practical and essential to fight with this disease.[2]

Finding new ways to postpone the incidence of the disease is considered a valuable therapy too. It is generally accepted that postponing symptoms even for 5 years can cut down the disease incidence to half.[3] In other words, if this delay extends to 1 year, it will save 9 million lives in the next 40 years.[2]

Studies that focus on risk factors are valuable among investigations of neurological diseases because they are directly associated with primary prevention.[4]

Numerous studies have demonstrated that various modifiable risk factors are associated with AD such as obesity,[5] smoking, diabetes, hypertension (HTN) in midlife,[6,7] and hypercholesterolemia.[1,8-10] It is also verified that physical activity would be a protective factor against AD.[2,4,9]

Barnes and Yaffe[2] have focused on studying about the contribution of some modifiable risk factors on AD incidence and have found that nearly half of AD could be attributed to these factors. It has been shown with 10-25% reduction of the prevalence of all these risk factors, almost 1.1-3 million new cases would be averted, respectively.

Since Iranian population are undergoing the aging phenomena, which can be accompanied by increasing the incidence of AD,4 we decided to characterize cardiovascular modifiable risk factors of AD and determine their contribution in disease development in this country compared to the world.

Materials and Methods

Search strategy and eligibility criteria

Medline, Scopus, and Cochrane databases were systematically searched from inception to May 2014 to retrieve systematic reviews and/or meta-analyses focused on the association between AD and seven modifiable risk factors included diabetes, HTN, physical inactivity, smoking, hypercholesterolemia, and overweight and obesity. MeSH terms of ("Alzheimer" OR "dementia) in combination with ["diabetes mellitus (DM)" OR "hyperglycemia" OR "smoking" OR "HTN" OR "physical activity" OR "physical inactivity" OR "exercise" OR "overweight", OR "obesity"] were searched in mentioned databases. The types of studies were restricted to "systematic reviews" in Medline (PubMed) and to "reviews" in Scopus. Moreover, references of selected studies were evaluated for additional relevant studies. Only papers in English were included in the study. Two authors (NH and LS) reviewed titles and abstracts of articles independently to select more potentially relevant studies and third person (ZR) were consulted if any disagreement took place.

Inclusion and exclusion criteria

Inclusion criteria: (a) systematic review and/or meta-analysis; (b) addressing the association between diabetes, HTN, physical inactivity, smoking, hypercholesterolemia, and overweight or obesity with AD.

Exclusion criteria: (a) other types of studies; (b) assessment of cognitive decline, other types of dementia or dementia as a whole instead of AD.

Quality assessment

The quality of relevant studies according to their titles, abstracts, and inclusion and exclusion criteria was evaluated by two authors (NH and LS) independently using "A Measurement Tool to Assess Systematic Reviews" (AMSTAR) as a critical appraisal checklist for quality assessment of systematic reviews and meta-analysis.[11] There were 11 questions with four types of answer (yes, no, cannot answer, not applicable) in AMSTAR and only questions with "yes" answer had 1+ score. In this manner, papers rated as low (0-4), medium (5-8), and high (9-11) quality according to their scores.[12] Finally, medium and high-quality studies were selected for data extraction.

Data extraction

Two authors (LS and ZR) independently reviewed selected studies to extract the following information: first author's name, publication year, searched databases, types of studies, risk factor (exposure), doing meta-analysis and effect size (if provided) and finally conflict of interest. Any conflict between two authors resolved with consult of third person (NH).

Population attributable fraction (PAF)

The PAF is defined as the proportion of patients with specific disease attributed to a risk factor, and subsequently, this proportion could be avoided in terms of risk factor elimination.[13] With respect to the Levin's formula,[13] calculation of PAF would be done with risk factor prevalence (P_{RF}) and relative risk (RR) for AD for each risk factor as it is shown in the following formula:

$$PAF = \frac{P_{RF} \times (RR-1)}{1+P_{RF} \times (RR-1)}$$

We applied adjusted estimates of risk factors to this formula. RRs or estimates of them [odds ratio (OR)] were obtained from meta-analyses. If there were more than one study on a specific risk factor, the study with higher quality was selected. In the case of assessing smoking, because tobacco industries usually support the studies focused on tobacco (which could affect the outcomes), we selected the meta-analyses considering tobacco industry affiliation. We acquired most recent reported prevalence for each risk factor among Iranian and the world population through simple search in the literature. If reported risk was restricted to a specific age group, we restricted estimates of prevalence to that age group.[14-17] We reported 95% confidence interval (CI) for RR and also we calculated 95% CI for PAF using lower and upper limit of selected RR of each risk factor. Finally, combined PAF was calculated using the following formula:

$$PAF = 1- [(1-PAF_1) * (1-PAF_2) * ...]$$

All data organization and processing were performed using Endnote and Excel 2010 software.

Results

Study selection

After conducting systematic search, 2651 articles were identified. We selected 79 potentially relevant articles according to titles and abstracts. Among these, 29 studies were selected based on the inclusion/exclusion criteria (Figure 1). 11 studies with a score of five or more were eligible for data extraction.[12] Characteristics of the eligible studies are displayed in table 1.

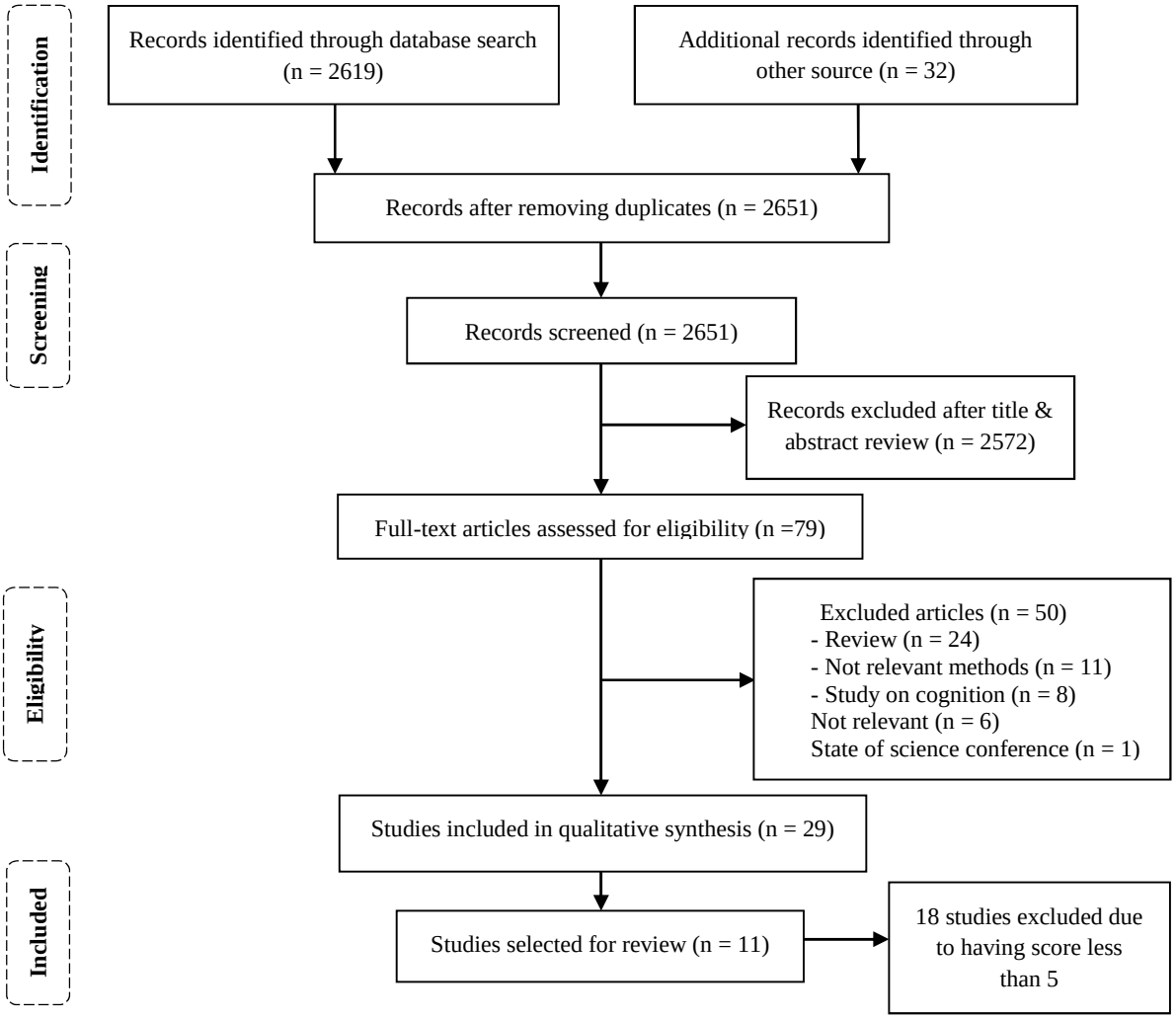

Figure 1. Flow chart of selected studies to review

Table 1. Characteristics of systematic reviews describing the relationship between seven modifiable risk factors and Alzheimer

ID	Review name	Searched databases	Type of studies included	Number of studies included	Total number of participants	Sex	Age (year)	Exposure (risk factor)	Time of follow-up	Quality of study	Effect size (CI) for AD	Conflict of interest	Meta-analysis (+/−)
1	Stern and Konno[24]	Medline, CINAHL, Embase, Cochrane (Central), PsycINFO, PubMed, EBM Reviews, ISI, ERIC, Austhealth Health Scopus	Case-control Cohort	2 15	18,024-55,136 for case-control 29435-461534 for cohort		≥ 60	Physical leisure activities	6 study for 5-10 year, 1 study for 5 years 5 study for < 5 years, for midlife study 21-36 years	5	-	None	−
2	Lu et al.[18]	PubMed, PsycINFO	Prospective cohort	21 (8 on AD)	23,257 (for AD, vascular and all cause dementia)		69-83	DM	2.1 years to more than 10 years	5	1.39 (1.16-1.66)	None	+
3	Hamer and Chida[23]	Medline, Cochrane ISI	Prospective cohort	16 (6 on AD)	13771 (in meta for AD)	F/M	In one study 39-64 years with 21 years follow-up and others ≥ 65	Physical inactivity	5-21 years (in meta)	5	0.55 (0.36-0.84)	None	+
4	Lee et al.[21]	PubMed, Embase, and PsycINFO	Prospective cohort	37	_	_	≥ 65	Physical inactivity, Smoking, BMI, Alchohol, Diet	1.8-20.9 years 2-25 years 18-36 years 4-24 years 3.9-32 years	5	-	None	−
5	Cataldo et al.[20]	PubMed, PsycINFO, Cochrane CENTRAL Google Scholar	Case-control	26	_	_	_	Smoking	1.5-27 years for cohort studies	5	RR: 1.72 (1.33-2.12) (for cohort studies of average quality in 2007), Controlling for study design, quality, secular Trend and tobacco industry affiliation	No role for sponsor in design, conduct or writing manuscript	+
6	Anstey et al.[22]	PubMed, PsycINFO, Cochrane	Cohort Prospective cohort	17 16 (11 on AD)	Low versus nl BMI in midlife: 8259 Overweight versus nl BMI in midlife : 13506 Obese versus nl BMI in midlife: 9401 Obese versus not obese BMI in late: 4067	F/M	42-74	BMI	29.7 years (BMI in midlife), 6.82 years (BMI in late-life)	6	Low/nl BMI in midlife: RR: 1.96 (1.32-2.92) Overweight versus nl BMI in midlife: RR: 1.35 (1.19-1.54) Obese versus normal BMI in midlife: RR: 2.04 (1.59-2.62) Obese versus not obese BMI in late-life: RR: 1.46 (0.97-2.21)	None	+

ID	Review name	Searched databases	Type of studies included	Number of studies included	Total number of participants	Sex	Age (year)	Exposure (risk factor)	Time of follow-up	Quality of study	Effect size (CI) for AD	Conflict of interest	Meta-analysis (+/−)
7	Almeida et al.[19]	Medline, PsycINFO	Case-control Cohort	21 8	5323 in case control 43885 in cohort		-	Smoking	2-27 years for cohorts	6	Case control* OR: 0.82 (0.70-0.97) Four case control** OR: 0.82 (0.53-1.27) Cohort studies RR: 1.10 (0.94-1.29) Two cohort***: RR 1.99 (1.33-2.98)	….	+
8	Anstey et al.[27]	PubMed, PsycINFO, Cochrane CENTRAL	Prospective cohort	18 (8 for TC and AD)	14,331	F/M	40-78	Total cholesterol	4.8-29 (mean: 13.34) years	5	RR: 0.85 (0.67-1.10)† RR: 1.03 (0.79-1.35)†† RR: 0.85 (0.65-1.12)†††	….	+
9	Power et al.[26]	Medline, Embase, Web of Science, Google Scholar, CINAHL, Review of citations from relevant articles, consultation with experts hand searches of publication archives from cohorts	Prospective cohort, Nested case-control	18			> 50	HTN	3.2-27 years	5	RR: 0.98 (0.80-1.19)# RR: 0.95 (0.91-1.00)## RR: 0.94 (85-1.04)###	….	+
10	Guan et al.[25]	Embase, Medline	Cohort	12	7270 with HTN 8022 without HTN	F/M	> 40	HTN	1-32 years	6	RR: 1.01 (0.87-1.18) in random-effects RR: 1.02 (0.91-1.14) in fixed-effects models	None	+
11	Cheng et al.[1]	Embase, Medline	Cohort	19 (16 on AD)	5700 with and 36 191 without diabetes	F/M	> 50	DM	1-12.7 years	7	RR: 1.46 (1.20-1.77) in random effect and RR: 1.54 (1.40-1.70) in fixed effect model	….	+

*Analysis incorporating ORs adjusted for confounding variables (such as age, sex, schooling and alcohol use), **Analysis that included only the four case-control studies that used matched design, ***Restricting the analysis to the two cohort studies that described the number of subjects who were smokers at baseline and later developed AD. †Association between total cholesterol measured in late life and AD between first quartile and second, ††Association between total cholesterol measured in late life and AD between first quartile and third, †††Association between total cholesterol measured in late life and AD between first quartile and fourth, #10 studies reporting on association between a "history of HTN" and AD, ##4 studies considering the association between a 10 mm Hg increment in systolic BP and AD, ###4 studies considering the association between a 10 mm Hg increment in diastolic BP and AD.

AD: Alzheimer's disease; BP: Blood pressure; OR: Odds ratio; RR: Relative risk; HTN: Hypertension; BMI: Body mass index; DM: Diabetes mellitus; EBM: Evidence based medicine; ERIC: Education Resources Information Center; CI: Confidence intervals

Alzheimer risk factors

DM Type 2: From selected articles, two had systematically reviewed the association between DM and AD.[1,18] Lu et al.[18] had found 21 prospective cohorts on AD, vascular and all causes of dementia in which eight had addressed the DM and AD association. After data pooling with meta-analysis, they concluded that patients with DM have a higher risk for AD in comparison with non-diabetics [RR = 1.39 (95% CI: 1.17-1.66). Another study with higher quality[1] that was a meta-analysis on 16 prospective cohorts with 41891 participants, had revealed that diabetic patients were 1.46 times more risky than patients without diabetes for AD [RR = 1.46 (95% CI: 1.20-1.77)]. We used RR of 1.46 for estimation of relevant PAF.

Smoking: There were three systematic reviews that evaluated the association between smoking and AD.[19-21] One of them[21] discussed multiple modifiable risk factors' effects on various types of cognitive impairment. They did not do meta-analysis because of heterogeneity of data. Other two studies had conducted meta-analysis. Cataldo et al.,[20] had identified 26 case control and 17 cohort studies and had included them in meta-analysis according to their designs and existence of tobacco industry affiliation. At the end, they had reported multiple pooled RRs. The best one was RR: 1.72 (1.33-2.12) that was based on cohort studies without tobacco industry affiliation, published in 2007. This study had a medium quality in which possible confounders such as tobacco industry affiliations were controlled. Another meta-analysis was conducted on 21 case control and 8 cohorts studies by Almeida et al.[19] After controlling various confounders, two ORs for case controls and two RRs for cohorts were measured that had a conflict with each other. For two cohorts, in which participants were current smokers at the beginning of the follow-up, RR was 1.99 (1.33-2.98). We used RR of 1.72 (1.33-2.12) to calculate PAF for AD.

Overweight and Obesity: Two studies addressed the relationship between body mass index (BMI) and AD.[21,22] There was no meta-analysis in the study of Lee et al.[21] However, other had run meta-analysis on 11 prospective cohorts to illustrate any association between BMI and AD.[22] There were significant associations between both overweight and obesity in middle age and incidence of AD later in life [RR: 1.35 (1.19-1.54) and RR: 2.04 (1.59-2.62), respectively].

Physical inactivity: Three out of 11 selected studies had addressed association between physical activity and AD.[21,23,24] Of these, two studies could not perform meta-analysis due to the existence of heterogeneity and their final results were explained just in narrative form.[21,24] There was just one meta-analysis on 6 longitudinal studies that had tried to investigate the association between physical activity and AD.[23] The pooled RR was 0.55 (0.36-0.84), meaning that physical activity behaves as a protective factor and has the ability to decline incidence of AD in the late life. As in available studies, physical activity instead of inactivity was in the center of scientists' attention and it played a protective role in AD, we reversed these values to display risk of physical inactivity (RR: 1.81, 1.19-2.77).

HTN: In 2011, two groups of medical scientists separately conducted comprehensive systematic reviews and meta-analysis on the association between HTN and AD.[25,26] One of them pooled data using both fixed and random effect models. Another one considered the impact of an increase in systolic blood pressure (BP), diastolic BP (DBP), history of HTN, and presence of HTN on AD at the beginning of the study. None of them could find any significant association as mentioned in table 1.

Hypercholesterolemia: Our search could find just one meta-analysis assessing the impact of high blood cholesterol level on AD.[27] The authors concluded that high level of cholesterol had a significant effect on AD neither in midlife, nor in late life.

Risk factors prevalence

We searched the prevalence of the each risk factor among Iranian and world population in the literature. Ultimately, we decided to use two reports from the World Health Organization (WHO) to extract the prevalence of smoking, diabetes, and physical inactivity in Iran[15] and the world.[14] Because overweight and obesity had a positive relationship with AD just in middle age, we could calculate midlife overweight and obesity using the size of population and prevalence of overweight and obesity in 40-60 years old population.[22] Hence, we used one population-based study that had provided prevalence in favored age groups for Iran[16] and another one for the world.[17] Unfortunately, because there was no population-based study for Iran that could

Table 2. Population attributable fraction (PAF) for Iran and the world

Risk factor	Prevalence (%)	RR	PAF
Iran			
DM	8.3	1.46 (1.20-1.77)	0.036 (0.016-0.060)
Smoking	8.1	1.72 (1.33-2.12)	0.055 (0.026-0.083)
Physical inactivity	35.7	1.81 (1.19-2.77)	0.220 (0.060-0.380)
Midlife overweight	3.3	1.35 (1.19-1.54)	0.011 (0.006-0.017)
Midlife obesity	1.6	2.04 (1.59-2.62)	0.016 (0.009-0.025)
World			
DM	11.0	1.46 (1.20-1.77)	0.048 (0.021-0.078)
Smoking	26.0	1.72 (1.33-2.12)	0.157 (0.079-0.225)
Physical inactivity	17.0	1.81 (1.19-2.77)	0.120 (0.030-0.230)
Midlife overweight	5.8	1.35 (1.19-1.54)	0.020 (0.010-0.030)
Midlife obesity	2.5	2.04 (1.59-2.62)	0.025 (0.014-0.039)

PAF: Population attributable fraction; DM: Diabetes mellitus; RR: Relative risk

provide overweight and obesity in 40-60 years old population, we used 45-65 years old group as midlife.[28] The sizes of desired age groups of the population for both Iran and the world were derived from the website of the United Nations, Department of Economic and Social Affairs.[29]

PAF

PAFs calculated for the targeted risk factors for Iran and the world are presented in table 2. In Iran, physical inactivity and smoking had the first degree in PAF for AD with 22 and 5%, respectively. The calculated PAF for the world was different. Smoking and physical inactivity had the largest PAF (15.7 and 12%, respectively) for the world. It means that more than one-quarter of AD in Iran and the world was attributed to two modifiable risk factors. Combined PAF for all risk factors were 0.308 and 0.352 for Iran and the world, respectively..

Discussion

The aim of this study was to determine any association between seven potentially modifiable risk factors and AD. Finally, we estimated PAF for five risk factors except HTN and hypercholesterolemia.

Based on two high-quality meta-analyses,[19,20] there was an association between smoking and increased the risk of AD. Smoking had the highest PAF in world and was in the second order for Iran among five assessed risk factors. It has been shown that metabolites derived from increasing arachidonic acid peroxidation in smokers' plasma cause oxidative stress.[30] Furthermore, a high level of damage could be observed in the cerebral cortex of smokers due to the presence of free radicals.[31] As a fact, free radicals can kill neurons or alter their function, leading to AD.[32] Moreover, smoking could induce atherothrombosis through several mechanisms like inflammation, proliferation of smooth muscles and platelet and leukocyte activation,[33] which can play a role in AD.[34]

Besides, the results of two systematic reviews and meta-analyses have mentioned that diabetic patients are at higher risk for AD than non-diabetics.[1,18] Both diabetes and AD are common and debilitating diseases particularly in the elderly.[3] Diabetes contributes to AD development not only as an interactive factor with the other cardiovascular and neurodestructive risk factors such as HTN and dyslipidemia but also as an independent risk factor.[35]

Two main mechanisms explain the effect of diabetes on AD development. The first is vascular mechanisms such as microinfarctions, increased blood brain barrier permeability, increased beta-amyloid production, and it's deposition in the white matter.[4] In addition, resistance to insulin and hyperinsulinemia as two important components of diabetes can contribute in vascular mechanisms. The second mechanism is the non-vascular one; hyperglycemia that leads to anaerobic metabolism and lactic acidosis, decreases cholinergic transmission through blood brain barrier and causes glutamate receptors dysfunction.[36-40]

Overweight and obesity in midlife can increase the risk of AD in later life.[22] One possible explanation of this relationship is that obesity is a risk factor for DM[41] which is also a risk factor for AD by itself.[1,18] Another explanation is that there is a relationship between obesity and resistance to insulin[42] and insulin resistance could play a role in

AD.[43] With respect to PAF, and despite the importance of these two risk factors, reduction of them has lesser effects on AD prevention comparing to the others, both in Iran and the world.

Among five evaluated risk factors in the current study, physical inactivity had the highest PAF in Iran. Physical inactivity acts both directly and indirectly through obesity and diabetes which are proven risk factors for AD.[41] On the other hand, there is some trustworthy evidence that physical activity has preventive effects on AD.[23] Furthermore, it has been shown that exercise could lead to activation of growth factor cascade that is essential for neurogenesis and vascular function. Besides, exercise could lessen some risk factors of metabolic syndrome which contributes to brain dysfunction and degenerative process.[44] Exercise could assist brain function through boosting antioxidant activity and oxidant destruction renewing system.[45]

The rationale for selection of these risk factors was that these risk factors were potentially modifiable and the existence of any association between them and AD could help policy makers to plan for prevention of this problem. Because of high PAF for physical inactivity in Iran, health policy makers should focus on building and strengthening infrastructure in collaboration with other sectors to promote physical activity as a protective behavior. For this purpose, studies on cost-effectiveness of this intervention should be encouraged. Besides, food market policies should be revised to reduce the risk of DM, obesity, and overweight problems. In addition, screening of people for diabetes and obesity could be offered. Finally, encouraging tobacco cessation especially in young people can have an enormous effect on AD reduction.

The strength of our study is doing a wide and systematic review for finding risk factors of AD and estimating PAF for the first time in Iran.

However, our study has some limitations. The first one was restriction of our search to just English papers. Second, midlife has several definitions in terms of age span, so for obesity and overweight, we consider age group of 40-60 as midlife. However, because of unavailable data for this age group, calculation was done on 45-65 years old adults. Finally, as a third limitation, although physical activity has different types in terms of intensity and frequency that may have various effects, we considered it as a general protective factor.

Conclusion

Our findings showed that about one-third of cases of AD were attributed to five modifiable risk factors which are almost similar in both Iran and the world in terms of combined PAF. If we could eliminate physical inactivity and smoking among population, about 27% of AD would be avoided. Therefore, a large number of AD cases could be avoided with lifestyle modification.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Letter to Editor

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Carpal compression, Phalen's and Tinel's test: Which one is more suitable for carpal tunnel syndrome?

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Keywords
Carpal Tunnel Syndrome; Phalen's Test; Tinel's Test; Carpal Compression Test

One of the main causes of hand dysfunction is carpal tunnel syndrome (CTS) and because of its high occurrence, early diagnosis is very important and may reduce disability caused by this condition.[1] In addition to paraclinical procedures including electrodiagnostic (EDX) studies and median nerve sonography,[2] a variety of clinical tests have been suggested for assessment of CTS among them, Tinel's test (TT) and Phalen's test (PT) are the most popular ones.[3]

Previous studies revealed differences in sensitivity and specificity with values of 61-91 percent and 33-93 percent for the PT, and 41-74 percent and 80-91 percent for the TT, respectively.[3] Carpal compression test (CCT) was introduced recently and had greater sensitivity and specificity than TT and PT in some studies.[4,5] In this study, we aimed to compare the efficacy of CCT with TT and PT in diagnosis of CTS.

In our study, all the patients suspected to suffer from CTS referred to the electrodiagnostic ward of Ghaem Hospital (Mashhad, Iran) from 2011 to 2012 were included. After taking detailed medical history and performing physical examination including the PT, TT and CCT, all the data were gathered in a checklist for each patient. EDX studies were conducted and definitive diagnosis of CTS was based on the results (by EDX criteria). Patients were divided into two groups of CTS and non-CTS.

Statistical analysis was performed using independent-sample t and chi-square tests via SPSS software (version 15, SPSS Inc., Chicago, IL, USA). P-value of less than 0.05 was accepted as statistically significant. The sensitivities and specificities of the PT, TT and CCT were gained via comparison with the electrodiagnostic tests, as gold standard.

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Of 89 patients, CTS was diagnosed in 80.9%. In terms of gender, age and employment, there was no statistical significant difference between the CTS and non-CTS groups (P > 0.050 for all).

The frequency of CCT-positive patients was statistically greater in CTS group (80.6%) than non-CTS one (47.1%) (P = 0.008). The frequency of the PT-positive patients was greater in non-CTS group (59.7 vs. 64.7%) with no statistically significant difference (P = 0.464).

The calculated sensitivity and specificity were 80.6 and 52.9% for CCT, 59.7 and 35.3% for PT, and 65.3 and 47.1% for TT, respectively.

In receiver operating characteristics (ROC) curve analysis, the area under the curve (AUC) was 0.67 (95% CI: 0.51-0.82, P = 0.032) for CCT, 0.56 for TT and 0.48 for PT (P > 0.050 for both) (Figure 1).

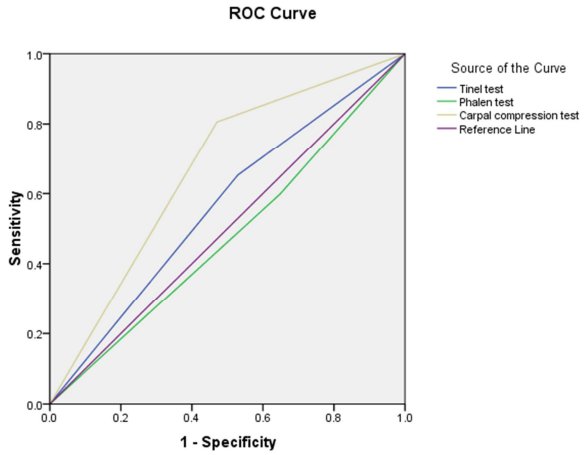

Figure 1. Receiver operating characteristics (ROC) curve analysis of carpal compression test (CCT), Tinel's test (TT) and Phalen's test (PT) for diagnosis of carpal tunnel syndrome (CTS)

In non-CTS group, there was a moderate negative agreement between the TT and CCT (k = -0.524; P = 0.030). There was a moderate positive agreement between the PT and TT in CTS group (k = 0.409; P < 0.001).

In our study, TT and CCT were more positive in CTS group and PT was more positive in non-CTS group but just positive CCT was statistically different between CTS and non-CTS groups. ROC cure analysis showed the accuracy of CCT for diagnosis of CTS is higher than TT and PT. AUC for TT and PT were around 0.5 which means that these tests cannot help us in depicting patients with CTS. Previous studies reported contradictory results about the sensitivity and specificity of CCT, but in most of them, they were greater than the sensitivities and specificities of the TT and PT.[4,5] Our results confirm the importance of CCT in diagnosis of CTS.

One another point is that the moderate negative agreement between the TT and CCT in non-CTS group means that both the tests would rarely be positive among them. In other words, if both CCT and TT were positive, the diagnosis is more likely to be CTS. In addition, the positive agreement between the PT and TT in CTS group means that performing one of these tests is sufficient for patients suspected to suffer from CTS; because if one of them is positive, it is very probable that the other one is also positive and vice versa.

In conclusion, as the sensitivity and specificity of the CCT are greater than those of the TT and PT, we recommend routine use of CCT for screening the patients suspected to CTS.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Letter to Editor

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Bacterial meningitis in a patient with multiple sclerosis receiving Tysabri

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Keywords
Bacterial Meningitis; Multiple Sclerosis; Tysabri

The most important adverse effect of natalizumab is progressive multifocal leukoencephalopathy (PML).[1] Apart from PML, there are reports of other cerebral infections including herpes simplex encephalitis (HSE)[2,3] and cryptococcal meningitis[4] in the literature.

The patient was a 29-year-old woman, a known case of multiple sclerosis (MS) for at least 5 years. She was treated using natalizumab since 6 month before. She was under treatment with prednisolone 1 g daily for 5 days for optic neuritis, which was 2 weeks before the onset of symptoms of meningitis. Approximately three days before visiting the neurologist, a continuous headache in the left temporal lobe was developed. The patient was febrile at that time as well. Besides, two days before this, she had started ciprofloxacin for treatment of a urinary tract infection.

An investigation for the John Cunningham (JC) virus was negative. The brain magnetic resonance imaging (MRI) showed periventricular lesions (Figure 1-A) with no evidence of PML or HSE encephalitis. Meningeal enhancement was seen after the injection of the contrast medium (Figure 1-B).

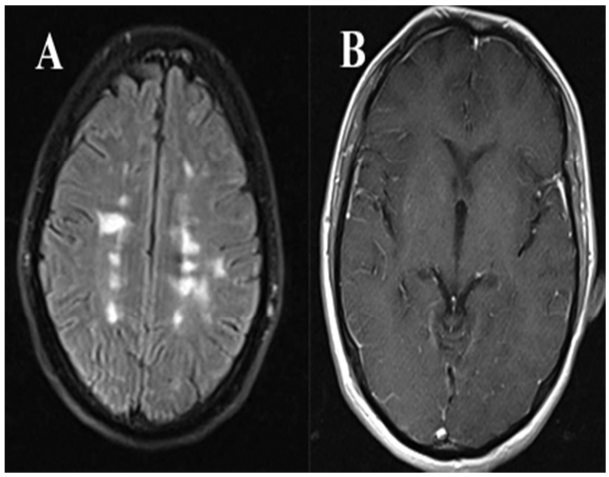

Figure 1. Periventricular lesions confirming the diagnosis of multiple sclerosis (MS) in the FLAIR MRI view (A). Meningeal enhancement was seen after gadolinium injection (B)

The patient underwent a lumbar puncture. Simple analysis of the cerebrospinal fluid (CSF) showed the following: white blood cell

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(WBC) = 350 (55% lymphocytes and 45% polymorphonuclear cells); red blood cell (RBC) = 20; protein = 150 mg/dl; glucose = 37 mg/dl; and concomitant blood sugar = 155 mg/dl. Other routine tests including blood biochemistry and complete blood cells (CBC) were all normal.

Considering the patient's condition and her CSF profile, treatment with ceftriaxone, vancomycin, and acyclovir was started. Since polymerase chain reaction (PCR) assay for HSE-1 and 2 was negative, acyclovir was stopped and other antibiotics were continued with a diagnosis of partially treated bacterial meningitis. The patient's headache and fever also subsided.

Other investigations including PCR of the CSF for tuberculosis, cryptococcus, and human immunodeficiency virus (HIV) were all negative.

CSF culture and smear were negative, which could be due to the previous administration of ciprofloxacin. The most probable diagnosis was partially treated bacterial meningitis in consideration of CSF analysis and other investigations as well as the patient's response to treatment.

Through targeting the α-4 integrin, natalizumab prevents activated T lymphocytes from entering the brain.[5] However, despite its marked clinical benefits in patients with MS, there is an occasional cause of fetal adverse effects like PML and HSE.[5] These mechanisms might have facilitated the development of meningitis in our patients as well.

This case report introduces a different probable complication of natalizumab in a patient with MS. As mentioned above, natalizumab can cause infection in brain and it is not limited to HSE and PML. It should be considered that in every patient receiving any drugs with the potential to alter the immunity of the brain, high suspicion of opportunistic infections is one of the most important points in the patient's follow-up.[6]

Conflict of Interests

The authors declare no conflict of interest in this study.

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Clinical Note

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Multiple cerebral infarctions in a patient with idiopathic thrombocytopenic purpura

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Keywords
Cerebral Infarction; Idiopathic Thrombocytopenic Purpura; Neuroimaging

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune condition with detectable antibodies against several platelet surface antigens. The diagnostic criteria of ITP include isolated thrombocytopenia, normal bone marrow, and absence of other causes of thrombocytopenia. This condition is characterized by minor and serious bleeding complications, but it is rarely accompanied by thrombosis.[1] We describe a patient with ITP that was not previously diagnosed, who developed cerebral infarction a few days after undergoing platelet transfusion and initiating steroid therapy.

Our patient was a 31-year-old woman, with no prior medical history, who presented at the gynecology department of our hospital with heavy menstrual bleeding as her chief complaint. She was referred to hematology department and admitted as the initial laboratory evaluation showed microcytic anemia [red blood cell (RBC) count: 302 × 10^4/μl, hemoglobin: 7.8 g/dl, hematocrit: 23.3%] and a platelet count of 0.6 × 10^4/μl. Extensive blood tests were performed including platelet-associated IgG, lupus anticoagulant, antinuclear factor, anti-cardiolipin antibody (ACA), and anti-Helicobacter pylori (H. pylori) immunoglobulin G, and all the results were either normal or negative.

She underwent platelet transfusion (20 IU in a single administration) and steroid therapy (methylprednisolone 1000 mg/day for 5 days and 50 mg of prednisolone thereafter). After treatment, the platelet count on the second day of hospitalization increased to 13.2 × 10^4/μl and remained within normal levels thereafter. The patient, however, gradually became disoriented. A brain computed tomography scan 3 days after admission showed multiple low-density areas in both frontal lobes (Figure 1, A and B). Thus, the patient was referred to neurosurgery department.

The bifrontal lesion was found to be acute cerebral infarction using diffusion-weighted magnetic resonance (MR) imaging (Figure 1, C and D). The MR angiography revealed stenosis in bilateral distal internal carotid arteries and middle cerebral arteries (Figure 1, E); therefore, a cerebral angiography was performed. In the cerebral angiography, mild stenosis of the bilateral distal internal carotid artery (ICA) and stenosis of the middle cerebral artery (MCA) were confirmed.

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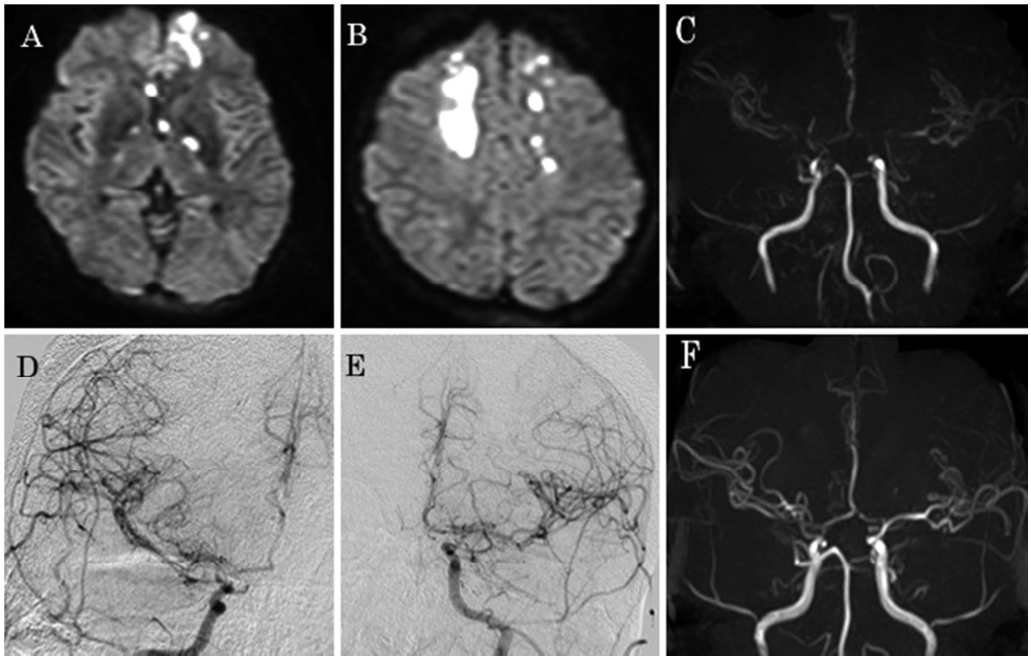

Figure 1. Magnetic resonance (MR) assessments for the patient
Diffusion-weighted MR images show acute ischemic lesions (A, B). MR angiography at the time of presentation to neurosurgery revealed distal and bilateral stenosis of the internal carotid artery (ICA) and middle cerebral artery (MCA) (C). On the left (D) and right (E) cerebral angiography, moderate stenosis was identified in bilateral distal ICA and MCA. In MR angiography 7 weeks after admission, stenosis of bilateral ICA and MCA considerably improved (F).

Antiplatelet therapy for the newly acquired stroke was initiated considering the patient's platelet count remained within the normal range with steroid therapy. Symptoms gradually improved, and she was discharged from the hospital 3 weeks after admission. In a follow-up MR angiography taken 7 weeks after admission, the bilateral ICA stenosis had improved considerably (Figure 1, F).

Generally, ITP is not a life-threatening disease; therefore, treatment may not be needed in mild cases. Treatment is usually initiated when the patient's platelet count is less than $2.0 \times 10^4/\mu l$. A causal link between H. pylori infection and ITP has been suggested in previous clinical studies, showing a platelet count response in approximately 50% of patients following H. pylori eradication.[2] A new treatment guideline, therefore, has been proposed in which the presence of H. pylori infection is confirmed first and the eradication therapy is administered in positive cases.[2] As H. pylori infection was not observed in our patient, steroid treatment was used as the backbone of therapy. Additionally, platelet transfusion was administered during the critical stage to rapidly increase the platelet count, which was less than $1.0 \times 10^4/\mu l$ and was associated with heavy menstrual bleeding.

In the literature, ischemic complications are reported after the treatment for ITP. Moreover, a previous report described cases of myocardial ischemia after a platelet count increase, resulting from intravenous immunoglobulin therapy or splenectomy.[3] When the platelet count and viscosity of the blood increase as a result of treatment, the risk of thrombotic complications may also increase. The risk of ischemic complications should be considered when treating these patients with thrombocytopenia.

In contrast, some cases have been reported in which ischemic complications occurred in patients with ITP even when platelet count was extremely low.[1] Antiplatelet antibodies induce complement-mediated platelet fragmentation and induce platelet microparticles (PMPs). These PMPs play an important role in the hemostasis of patients with thrombocytopenia. A high level of hemostatically active PMPs can be thrombogenic in certain clinical settings.[4] Patients with ITP often present with higher PMP levels, which may lead to an increase in thrombotic events.[4]

We used antiplatelet therapy because the patient's platelet count remained within normal levels with steroid therapy, and a successful

outcome was achieved. However, the management of ischemic stroke in patients with ITP remains controversial. Therapy for the ischemic stroke should be individualized according to the presumed pathophysiologic mechanism of stroke, comorbidity, and estimated risk of hemorrhagic complications.

As far as we have been able to ascertain from the literature, this case is the first to report improved arterial stenosis after antiplatelet therapy. Because of this change in MR arteriography findings, reversible cerebral vasoconstriction syndrome, which is reported in cases of thrombotic thrombocytopenic purpura,[5] should be included in the differential diagnosis. Reversible cerebral vasoconstriction syndrome is a cerebrovascular disorder associated with multifocal arterial constriction and dilation. Its primary clinical presentation is characterized by recurrent and severe thunderclap headaches over 1-3 weeks, often accompanied by nausea, vomiting, photophobia, confusion, and blurred vision.[5] As these symptoms were not present in our case, we speculate that the change in the MR arteriography finding of our case illustrates the thrombolysis occurring gradually in major intracranial arteries after antiplatelet therapy.

This case showed a mutually exclusive relationship between ITP and ischemic stroke. In patients with ITP, the risk of thrombotic complications should be considered, especially when treatment is given to rapidly increase the platelet count.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Clinical Note

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Follow-up of hypertension in patients with multiple sclerosis

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Multiple Sclerosis; Hypertension; Follow-up

The prevalence of hypertension is estimated over 10% in the multiple sclerosis (MS) population and increases with age.[1] In some studies comparing the prevalence of hypertension in the MS population with a comparator, hypertension was reported more commonly among these patients.[2-6] Only one cohort study reported the incidence of hypertension over a maximum follow-up of 30 years as 3.73% in patients with MS.[7]

Sometimes, new-onset hypertension could be a presenting sign of an adverse event. Transient hypertension may be an adverse event of intravenous methylprednisolone. Hypotension, a known adverse effect of interferon (INF), is a known risk factor of ischemic colitis and ischemic colitis is one of the serious adverse events of treatment with IFNs type I. Ischemic colitis should be considered in INF and acetylcholine inhibitors (AChI) and calcium channel blockers (CCB) co-administration.[8,9]

Treatment with IFN type I could predispose the patient to develop an autoimmune disease.[10]

Some reports define INF-induced de novo Raynaud's phenomenon, sometimes with progression to systemic sclerosis. A new-onset accelerated arterial hypertension could be a part of systemic sclerosis triad.[11] Similarly, new-onset hypertension could be a sign of INF-induced systemic lupus erythematosus (SLE).[12]

Thrombotic microangiopathy is a known rare adverse event of INF-therapy and new-onset hypertension is one of its important presentations advised to be evaluated carefully and controlled regularly in patients with MS receiving IFN-β.[13]

Hypertension is reported in approximately 10% of patients with MS exposed to glatiramer acetate in premarketing studies. During post marketing period, there are reports of hypertensive crisis with glatiramer acetate complicated with acute pulmonary edema and myocardial ischemic injury.[14]

Fingolimod could cause vasodilation and associated hypotension via activation of the endothelial nitric oxide synthase/nitric oxide (eNOS/NO) pathway.[15-18] As a result, in some patients experiencing a slight transient hypotension after the initiation of fingolimod therapy, it is not strange. Sometimes, this is followed by a small hypertension (~3 mmHg systolic and ~1 mm Hg diastolic blood pressure); but after 6 months of treatment, hypertension is placed in a stable plateau level.[19]

After the infusion of natalizumab and typically following two days, there are some reports of hypertension but much less frequent; this side

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effect is defined as probable and very likely.[20]

In teriflunomide trials, hypertension is reported in 3.1 and 4.3% of the patients treated with 7 or 14 mg of teriflunomide compared with 1.8% for the placebo.[21] In a phase-II teriflunomide clinical trial, high blood pressure was a cause of withdraw.[22] European medical agency recommends careful hypertension history taking and appropriate management during the treatment with teriflunomide.[23] Hypertension could be a common side effect of alemtuzumab.[24]

Up to now, there is not any information on arterial hypertension induced by dimethyl fumarate.

Essential hypertension is common in patients with MS similar to general population and probably could affect mortality, morbidity and final disability. New-onset hypertension could be a presenting sign of a treatment adverse event. MS healthcare professionals should measure and observe patients' blood pressure in follow-up visits and manage it appropriately.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Bodybuilding championships and myotonia congenita

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Keywords
Myotonia Congenita; Bodybuilding; Muscle Hypertrophy

A 25-year-old man presented with a 10-year history of difficulty in relaxing his muscles. He was bodybuilding champion in his city without doing any exercise.

Neurologic examination revealed well-formed skeletal muscles (first part of the video: http://ijnl.tums.ac.ir/public/891-725-1-Part1.mov) and myotonia most prominent in the eyes (a lag in opening the eyes after forceful closure) and hands (delayed hand opening after gripping) (second part of the video: http://ijnl.tums.ac.ir/public/891-726-1-Part2.mov).

There was percussion myotonia in thenar muscles without prominent muscle weakness. Electromyogram showed myotonic discharges.

Myotonia congenita is a rare hereditary neuromuscular channelopathy characterized by delayed relaxation of skeletal muscles following voluntary contraction, beginning in the first or second decade of the life. It can be associated with muscle hypertrophy, stiffness, transient weakness, or cramping.[1,2] Only patients with symptomatic myotonia require treatment with medications such as phenytoin, carbamazepine, or procainamide to reduce the excitability of the muscle membrane.

Legends to the video

First part of the video shows hypertrophic muscles of the arms and shoulder girdles; the second part shows delayed opening and relaxing the hands after gripping; and the third part shows myotonic discharges on electromyography.

Conflict of Interests

The authors declare no conflict of interest in this study.

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