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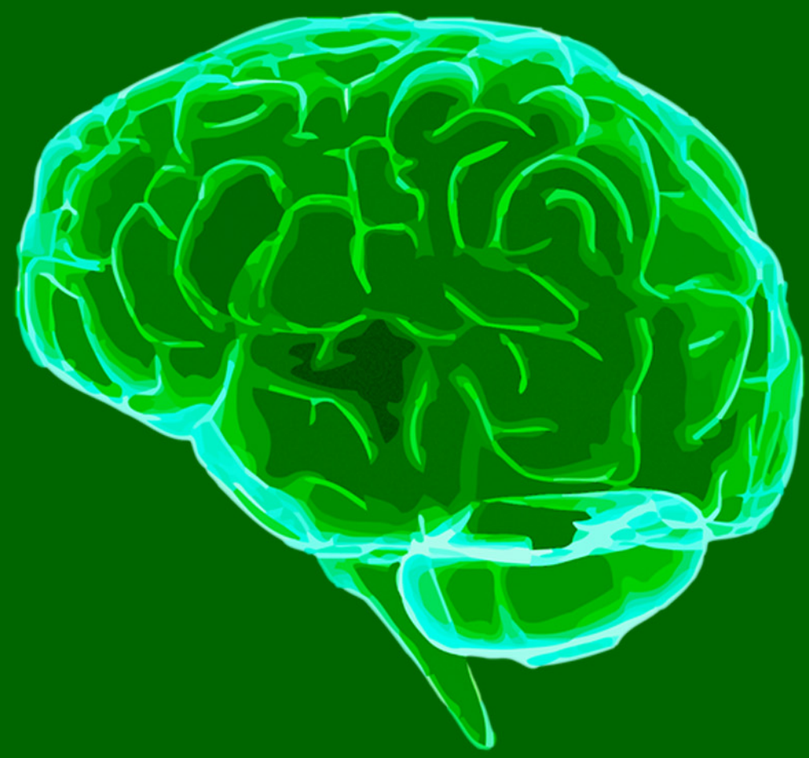

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Iranian Journal of Neurology

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Details

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

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

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Each section of the paper should begin on a new page

The manuscript must include:

Page 1: Title Page

Page 2: Abstract and Key Words

Page 3 and subsequent pages: manuscript body including Introduction, Materials and Methods, Results, Discussion, Conclusion, References, Tables, Figures

1. Title page:

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

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

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

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

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

Table of Contents

Iranian Journal of Neurology

Original Paper

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Identification of retention strategies for neurosurgeons in Iran: Results from expert panels

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Keywords
Retention; Strategy; Health Human Resource; Health Professional; Health Manpower; Neurosurgeon; Workplace

Abstract

Background: The key challenge is how to encourage and retain health professionals in their work location. There is a list of policy options for this purpose but applying an appropriate and effective set of strategies requires a country level research. Our study aimed to identify retention strategies for neurosurgeons and examine both the importance and feasibility of the identified strategies using expert panels' point of view.

Methods: First of all, a literature review was conducted to identify retention strategies for physicians. Then to gain consensus on the strategies and determine their importance and feasibility an expert panel was organized and a modified Delphi process was used.

Results: A total of 40 strategies were identified by the panel classified in seven categories of income and economic factors, professional/job factors, clinical infrastructure, personal/family factors, living condition and welfare, educational factors and career development, governmental regulations and management policies.

Conclusion: Based on the study results, three areas of economic incentives, personal and professional factors got the greatest priority in health professional planning for retention purposes.

Introduction

Shortage of health professionals whether due to poor distribution or insufficient admission quota in the profession has become a significant problem in many countries. To resolve such problems, planning for health professionals has got a great importance.[1] The aim is to ensure that health professionals are available and ready to provide services in "the right place at the right time with the right skills".[2,3]

In almost all countries health professional-mainly physicians–are likely to work in developed urban cities with proper economic condition, better living facilities and advanced clinical infrastructure.[4] This inclination would probably cause imbalanced concentration of health manpower in urban areas as well as continuing shortages in rural and remote communities.[5]

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Such inequitable distribution in health human resources not only decreases the accessibility to care and negatively affects quality of healthcare services, but also causes extra costs due to additional recruitment and replacements.[6] Malfunction in maintaining health professionals in places where they are most needed has been mentioned as the key reason for the occurrence.[7]

Almost all governments endeavored to provide an evidence based solution to attract physicians and improve their retention in different areas of the country.[8] Some focused on monetary incentives and some on nonfinancial motivations.[9] In this regard, World Health Organization has introduced 16 retention strategies such as regulatory policies, financial incentives, educational opportunities, and personal and professional inducement plans.[10,11]

Literature confirmed that successfulness of strategies was highly reliant on the country setting and type of health workers.[12] In Iran, about 2200 specialists are working in 270 underserved areas who generally are not satisfied with their income and work environment. Most of them do not ask for continuing to serve in remote areas and try to find an opportunity to leave as soon as possible.[13] To provide an appropriate feedback toward similar dilemmas, effective strategies for improving physicians' retention in such areas could be significantly helpful.[14,15]

On May 2014, a national program "Evolution in Health System of Iran" was established and obligated to be performed headed for overcoming obstacles to access health care services and increase the opportunity to obtain high quality and timely services among people. One of the main objectives of the program was to guarantee an equitable distribution of health professionals within a country and improve their retention in work places.

Moreover, need for neurosurgery services has dramatically increased due to an elderly population, inactive life styles among Iranian people and principal rise in road accident rates. Neurosurgeons play important role in diagnosis, treatment and rehabilitation of patients suffering from neurospinal disorders or injuries.[16,17] Thus planning for appropriate strategies to increase the probability of neurosurgeons' retention in underserved areas of the country has got a significant importance to properly respond population health needs.[18]

Literature emphasized that salary increase, improvement in quality of health facilities and opportunity for continued education and career development were some of the intervention policies to persuade health workforce maintain in their workplace. Research conducted in Ethiopia and Ghana also mentioned provision of superior living condition and welfare as one of the most imperative elements for health professionals to accept job retention.[19] Similarly, educational scholarships and career development opportunities were ranked as significant job profiles by most of the health workers.[20] Hanson and Jack declared that improved housing, adequate medical equipment and reduced time commitment were other key factors in physicians' decision to retain.[19] Findings of study conducted by Rafiei, et al.[21] revealed that neurosurgeons were ready to give up some amount of income in return to obtain subsidized housing and opportunity to have permission for dual practice. To work in large developed cities rather than rural areas, they also requested an increase in level of income. Authors added that mixtures of incentives could improve neurosurgeons' recruitment and retention in rural or remote areas.[21] Therefore, knowing important and applicable policy interventions could be beneficial for policy makers to better decide based on it.

To identify such applicable strategies, we conducted a study to determine retention strategies for neurosurgeons and examine both the importance and feasibility of the identified strategies using expert panels' point of view.

Materials and Methods

Study has been conducted in two phases: 1) literature review and 2) expert panel.

Identification of retention strategies: A literature review was done to identify retention strategies for neurosurgeons. Keywords used to find out relevant researches done in Medline, Ovid and Google Scholar (2000 to 2015) included: "health human resources or health professionals or health manpower", "neurosurgeons or neurosurgery specialists", "retention strategies", "workplace or place of activity". From the literature review, 85 strategies relevant to retention issues in various medical specialties were identified.

Strategies were assessed by two members of the study group for replication, transparency, applicability and compatibility with country circumstances. Some of them were omitted,

revised or reworded to comply with the conditions related to neurosurgery. This investigation resulted in 40 retention strategies categorized into seven themes: income and economic factors (n = 8), professional/job factors (n = 6), clinical infrastructure (n = 5), personal/family factors (n = 9), living condition and welfare (n = 5), educational factors and career development (n = 3), and governmental regulations and management policies (n = 4).

First stage of the expert panel: Rating the strategies: Members of the expert panel were selected among planners and policy makers in health human resource planning and establishers of retention policy package among physicians and specialists in form of health system reform. Panel composition based on individual's expertise and affiliated organization is shown in table 1. Finally, 14 panelists were chosen to participate in the study which was large enough to allow for variety of perspectives.

A Modified Delphi technique was used to implement the expert panel process.[22] In the first step, 40 strategies identified from the literature were sent to the panelists. Then they were asked to rank the strategies using a Likert type scaling system ranging from "minimum" (1) to "maximum" (9), based on two aspects of importance and feasibility. Importance was defined as how suitable and helpful the strategy could be for health human resource planning especially in the field of neurosurgery, while feasibility presented the rationality and applicability of the strategy. Results of the first round were consequently used as inputs for the second phase of the panel. Importance and feasibility rankings were entered in to a spreadsheet to conduct a descriptive analysis. Strategies that had been scored between 7-9 from both aspects of feasibility and importance by almost all panelists were considered high rating, those with a combination of 4-9 in any of the two facets were considered medium rating, while strategies rated between 1-3 were regarded as low rated ones.[23]

Second stage of the expert panel: A face to face meeting: After providing a list of rated strategies, a meeting with the presence of all panelists was held to reach an agreement and make final decisions. In the meeting, participants discussed on medium rated strategies since it was already agreed on high and low rated ones. In fact, strategies belonged to this group were rated for the second time. At this point, each expert had an opportunity to work on transparency, better understanding and applicability of the strategies.

Results

Results of scaling 40 retention strategies revealed that panelists had agreed on 25 strategies as high rating, 10 strategies as high/medium and 5 as medium rating. Among these, the most important and applicable strategy group was mentioned to be income and economic factors. Afterward job/professional, personal/family and educational factors got the greatest importance from the participants' point of view (Table 2).

In the second phase of the panel, participants were asked to review high/medium- and medium-rated strategies to re-rank them. Table 3 shows a modification in experts' opinion toward the rating of strategies in round II of the Delphi method. As data confirm, there was a 10% decrease in high/medium-rated strategies and 5% increase in those with medium and low rating.

Identification of each strategy's rating from both perspectives of importance and applicability provides valuable information for policy makers to plan for physicians' retention more effectively. Table 4 depicts a detailed description of average scores and total ranking of strategies.

As it is shown in table 2, timely fee for service payment to specialist has got the greatest priority while provision of an appropriate cooling or heating system had the least importance from the panelists' viewpoint.

Table 1. Panel composition based on expertise and affiliated organization

Expertise	Organization	Number of participants
Healthcare management	Curative Deputy of Ministry of Health Institute of health Sciences, Tehran University of Medical Sciences (TUMS)	6
Social medicine	Shahid Beheshti University of Medical Sciences	4
General practitioner	Curative Deputy of Ministry of Health	2
Neurosurgeons	Shariati Hospital, TUMS Trauma Research Center in Sina Hospital, TUMS	2

Table 2. Rated strategies in phase I

Strategy group	Number of strategies in each group	High-rated strategies [n (%)]	High/medium-rated strategies [n (%)]	Medium-rated strategies [n (%)]
Economic factors	8	6 (75.0)	1 (12.5)	1 (12.5)
Professional factors	6	4 (66.6)	2 (33.4)	0 (0)
Clinical infrastructure	5	3 (60.0)	1 (20.0)	1 (20)
Personal factors	9	6 (66.6)	2 (22.3)	1 (11.1)
Living condition	5	2 (40.0)	2 (40.0)	1 (20)
Educational factors	3	2 (66.6)	1 (33.4)	0 (0)
Governmental regulations	4	2 (50.0)	1 (25.0)	1 (25.0)
Total	40	25 (62.5)	10 (25.0)	5 (12.5)

Discussion

Study aimed to identify retention strategies to give an opinion to health human resource planners for specialists' retention working in Iran. Similar to the literature findings, our study revealed that combination of different monetary and nonmonetary incentives could improve neurosurgeons' retention in their workplace.[24] Results also emphasized on four main important issues in developing a competitive plan for physicians' retention including financial incentives, professional, personal and educational factors.

Economic factors/financial incentives: In many countries, the most influential factor for retaining health manpower in their workplace is financial incentives.[25] To achieve higher income levels, health workers especially physicians try to look for an opportunity to supplement their income through dual practice.[26] In fact to consider an attractive job profile, physicians are willing to have opportunity for dual practice and consequently gain higher levels of salary. Literature found out that the impact of income and monetary factors on physicians' retention ranged between 20% in USA[28] to 86% in Australia.[27]

Job/professional factors: Similar to our findings, literature confirmed that health workers looked beyond financial incentives and considered improvement in professional factors and quality of work environment as important retention strategies. Supportive management, team work, shared decision making about practice management, and open communication with supervisors are among strategies to improve working condition.[29] In a qualitative study among 16 nurses working in health centers of western Canada, study participants expressed their desire for improved teamwork and effective communication with members of clinical team.[30] Also important was adequate, trained and skilled auxiliary workforce such as nurses, physiotherapists and Anesthesiologists to give the feeling of working in a supportive environment to physicians.[31]

Numerous studies have regarded poor working atmosphere, lack of supportive management, poor job direction and inappropriate workload as key deterrents to attract or retain in a workplace.[32-34]

Maintaining safety was another strategy that could reduce violence and hostility in a work environment. Physicians support plan and provision of adequate number of guards in the workplace have been mentioned as related strategies to improve safety. Some studies have also emphasized on trigger role of administrative

Table 3. Rated strategies in phase II

Strategy group	Number of strategies in each group	High-rated strategies [n (%)]	High/medium-rated strategies [n (%)]	Medium-rated strategies [n (%)]	Low-rated strategies [n (%)]
Economic factors	8	6 (75.0)	1 (12.5)	1 (12.5)	0 (0)
Professional factors	6	4 (66.8)	1 (16.6)	1 (16.6)	0 (0)
Clinical infrastructure	5	3 (60.0)	1 (20.0)	1 (20.0)	0 (0)
Personal factors	9	6 (66.7)	1 (11.1)	1 (11.1)	1 (11.1)
Living condition	5	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)
Educational factors	3	2 (66.7)	0 (0)	1 (33.3)	0 (0)
Governmental regulations	4	2 (50.0)	1 (25.0)	1 (25.0)	0 (0)
Total	40	25 (62.5)	6 (15.0)	7 (17.5)	2 (5.0)

Table 4. Total ranking of retention strategies

Strategies	Overall priority		
	Applicability	Importance	Total
Timely fee for service payment	7.8	8.5	1
Distribution of physicians based on home prefectures	8.2	8.0	2
Supportive management	8.0	8.1	3
Permission for dual practice	7.8	8.2	4
Promotion of physical and clinical infrastructure	7.8	8.0	5
Promotion of educational facilities	7.8	8.0	6
Increase in full time payment	7.5	8.0	7
Employment opportunity for spouses	7.5	8.0	8
Opportunity for educational promotion	7.5	7.8	9
Reinforcement of family physician plan	7.0	8.0	10
Educational facilities for children	7.0	7.8	11
Improvement of neurosurgery equipment in hospitals	7.2	7.5	12
Additional quota for specialty acceptance	7.0	7.5	13
Competitive agreements with companies of high quality medical equipment	7.0	7.5	14
Clear regulation for physicians' distribution system	7.1	7.3	15
Long-term and low interest loan to open a clinic	7.0	7.4	16
Long-term and low interest loan to establish an image center	7.0	7.3	17
Subsidized housing	7.0	7.2	18
Improvement of para clinical infrastructure	7.0	7.2	19
Offer managerial position	7.0	7.2	20
Suitable transportation system	7.0	7.1	21
Increase fee for service payments	7.0	7.1	22
Transparent job contracts	7.0	7.0	23
Support team work	7.0	7.0	24
Respect for religion, culture and ethnicity	7.0	7.0	25
Supportive regulation	6.0	7.0	26
Improvement of rehabilitation system	6.0	7.0	27
Appreciation system	6.0	7.0	28
Proper workload	5.1	7.5	29
Safety provision	6.0	6.1	30
Recreational facilities	5.0	7.1	31
Allocation of monthly fixed payment	5.0	7.0	32
Effective communication with ministry of health	6.0	5.6	33
Organizing tele-education system	6.0	5.5	34
Provision of essential drugs	5	5.4	35
Practice within same proximity to the site where residency training took place	5.4	4.6	36
Human resource reinforcement	4.2	4.4	37
Long term and low interest loan to buy a house	4.0	4.1	38
Physician distribution based on educational place	3.0	3.0	39
Provision of proper cooling or heating system	3.0	2.9	40

or managerial positions offered to physicians.[35]

Personal/family factors: Naturally, physicians like other humans have some personal needs which proper response to them could have a positive impact on work satisfaction. They expect to receive respect and recognition from the community. This sense of gratitude would satisfy their personal needs and encourage them to retain in a workplace.[36,37] Addressing emotional needs such as proximity to family and providing working condition in an area that is compatible with their religious beliefs had also positive impact on their retention.[38]

Educational factors: Study findings acknowledged that opportunity for continuous learning and career development was the fourth significant factor in physicians' retention. Mangham and Hanson confirmed that nurses would sacrifice some pay increases to obtain the opportunity for continuous education.[39] Continued education was also underpinned as key enthusiasm making rural jobs more attractive by Rockers, et al.[40] A similar study conducted by Vujicic, et al. announced that possibility for long-term education

and opportunity to exchange knowledge and experience with other colleagues could play an important role in increasing take up rate for rural jobs.[41] Evidence also indicated that further training opportunities acted as important motivation to attract and retain health manpower in Malawi, Zambia, Uganda, Namibia and South Africa.[34]

Conclusion

This is the first study conducted in Iran that provides a comprehensive list of retention strategies relevant to neurosurgeons arranged on the basis of importance and applicability. Study identified 40 strategies applicable for health human resource planners to retain physicians (neurosurgery specialists) in their workplace. Although the strategies with highest importance mainly focused on areas of income and economic enthusiasms, professional and work environment factors and personal incentives, other factors including living condition, clinical infrastructure, and governmental regulations also need to be considered in a planning process. Effective policy making in the field of health human resource retention requires inclusive and ongoing reviews of incentive methods to analyze their impact and select the most influential ones.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Acute management of stroke in Iran: Obstacles and solutions

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Keywords
Stroke; Thrombolytic Therapy; Tissue Plasminogen Activator; Hospital Rapid Response Team; Quality Improvement; Iran

Abstract

Background: Stroke is among the leading causes of mortality and permanent disability in the world. Iran is located in the stroke belt and has a high age-adjusted stroke incidence rate. In this multistep prospective qualitative study, we aimed at investigating the status and challenges of stroke management in Iran and explore possible solutions.

Methods: In the first and second phase, we attempted to define the status of stroke management in Iran by searching the relevant literature and conducting semi-structured interviews with health-care providers in thirteen hospitals located in seven large cities in Iran. In the third phase, we tried to recommend possible solutions based on international standards and experience, as well as interviews with stroke experts in Iran and the United States.

Results: Little public awareness of stroke symptoms and its urgency, low prioritization for stroke management, and an inadequate number of stroke-ready hospitals are some of the major obstacles toward timely treatment of stroke in Iran. Every hospital in our pool except two hospitals had guideline-based algorithms for the administration of intravenous thrombolysis. However, there was no single call activation system for stroke alert. Data from some of the centers showed that hospital arrival of stroke patients to final decision-making took 116-160 minutes. Although there were four endovascular programs in our target areas, there was no center with 24-hour coverage.

Conclusion: There are many challenges as well as potentials for improvement of stroke care in Iran. Improving public knowledge of stroke and establishing an organized and comprehensive stroke program in the hospitals will improve acute stroke management in Iran. The Iranian ministry of health should define and advocate the establishment of stroke centers, track the

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rate of death and disability from stroke, introduce pathways to improve the quality of stroke care through national data monitoring systems, and eliminate disparities in stroke care.

Introduction

Stroke is among the leading causes of death and permanent disability worldwide.[1] There is no national stroke registry in Iran. Therefore, a disparity exists between the reported regional incidences of stroke, ranging from 22 to 140 stroke patients per 100000 populations.[2,3] Compared with some of the developed countries, ischemic stroke occurs approximately one decade earlier among Iranian people and leads to a higher rate of mortality.[2,4]

Timely thrombolytic therapy with intravenous tissue plasminogen activator (IV-tPA) is an effective treatment for acute ischemic stroke.[5,6] Patients who are treated in a stroke center have a higher survival rate and better functional outcome.[7-9] The Brain Attack Coalition in the United States has accordingly proposed primary and comprehensive stroke centers, in addition to acute stroke-ready hospitals to increase the quality of care for stroke patients.[10-13]

Iranian healthcare system: Iran provides health-care services to its 79 million citizens through public and private sectors. The Iranian constitution entitles Iranians to basic healthcare, and the Ministry of Health and Medical Education has specific mandate to provide and monitor healthcare delivery.[14] Public medical schools as delegates of the Ministry of Health are responsible for providing healthcare services and medical education in each province. There is also a national healthcare network that provides basic healthcare services in rural and remote areas in Iran.[14] In Iran, public hospitals are usually affiliated with medical schools and are the primary provider of specialty and higher levels of care. These hospitals are generally the host of pilot studies for national decision making by Iranian Ministry of Health. Nongovernmental charitable organizations also operate a tiny number of specialty hospitals mainly in the major metropolitan areas in Iran. There is a considerable disparity in accessibility of advanced healthcare services between urban and rural areas in Iran.[15]

Stroke care in Iran: Although there has been a significant improvement in stroke care in Iran, reports indicate that the utilization of intravenous tissue plasminogen activator (IV-tPA) in Iran is lower than many other countries.[16] At the same time, there is no fine-tuned national standard for developing stroke centers in Iran. The Iranian Ministry of Health has recently declared that the prevention and treatment of stroke is a national health priority.[17]

The aim of this prospective qualitative study was to investigate the status and challenges of stroke management in Iran. We recommended adaptive solutions to improve the quality of stroke care in Iran.

Materials and Methods

We conducted this three-phase study from June to December 2015.

Phase one: In the first step, we retrieved published studies on stroke in Iran through PubMed and Iranmedex (Table 1) with no date/time, language, document type, and publication status limitations on July 31, 2015. We selected the keywords through controlled vocabulary Medical Subject Headings (MeSH), literature review and experts' opinion. We also examined reference sources of relevant studies. In addition, we browsed portals of Iranian Medical Council, Iranian Ministry of Health, medical universities and news agencies with open source electronic archives for stroke-related news, statistics, and strategies.

We included all the studies containing any data on stroke in Iran. The primary focus was centered around providing stroke care, stroke team, public awareness and education, therapies and management, rehabilitation, prevention, protocols, monitoring, epidemiology, burden, morbidity, and mortality. Studies focusing on the pathophysiological aspects of stroke such as reports of cellular, molecular and immunologic events, genetic variations, neuroimaging findings and classifications, animal studies and studies lacking any information regarding Iran were excluded from this review.

Phase two: For the second phase of this study, we conducted semi-structured, targeted, one-to-one interviews with different practitioners and care providers in thirteen tertiary public hospitals in seven large Iranian cities. Our survey included a series of questions related to the requirements of acute stroke management (Table 2). To design the questionnaire, we reviewed the United States practice standards[18-22] and the concept of stroke unit in Europe.[7,23,24] We also reviewed the details of two city-wide stroke protocols in Memphis, Tennessee, and Birmingham, Alabama, United States.

Table 1. Search strategies

A. http://www.ncbi.nlm.nih.gov/

1- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) OR ("acute"[All Fields] AND "stroke"[All Fields]) OR ("acute stroke"[All Fields]) AND ("organization and administration"[MeSH Terms]) OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields] OR "Brain Ischemia"[MeSH] OR "Cerebral Infarction"[MeSH] OR "Hypoxia-Ischemia, Brain"[MeSH] OR "Ischemic Attack, Transient"[MeSH] OR "Infarction, Posterior Cerebral Artery"[MeSH] OR "Brain Stem Infarctions"[MeSH] OR "Infarction, Middle Cerebral Artery"[MeSH] OR ("Infarction, Anterior Cerebral Artery"[MeSH])

2- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND unit[All Fields])

3- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND team[All Fields])

4- (public[All Fields]) AND ("awareness"[MeSH Terms] OR "awareness"[All Fields])

5- (public[All Fields]) AND ("education"[Subheading] OR "education"[All Fields] OR "educational status"[MeSH Terms] OR ("educational"[All Fields] AND "status"[All Fields]) OR ("educational status"[All Fields] OR "education"[All Fields] OR "education"[MeSH Terms])

6- ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])

7- ("tissue plasminogen activator"[MeSH Terms] OR tissue plasminogen activator [Text Word] OR thrombolysis[All Fields]) OR ("Thrombectomy/adverse effects"[MeSH] OR "Thrombectomy/contraindications"[MeSH] OR "Thrombectomy/education"[MeSH] OR "Thrombectomy/epidemiology"[MeSH] OR "Thrombectomy/instrumentation"[MeSH] OR "Thrombectomy/legislation and jurisprudence"[MeSH] OR "Thrombectomy/methods"[MeSH] OR "Thrombectomy/mortality"[MeSH] OR "Thrombectomy/nursing"[MeSH] OR "Thrombectomy/organization and administration"[MeSH] OR "Thrombectomy/pharmacology"[MeSH] OR "Thrombectomy/psychology"[MeSH] OR "Thrombectomy/standards"[MeSH] OR "Thrombectomy/statistics and numerical data"[MeSH] OR "Thrombectomy/therapeutic use"[MeSH] OR "Thrombectomy/therapy"[MeSH] OR "Thrombectomy/trends"[MeSH] OR "Thrombectomy/utilization"[MeSH])

8- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("rehabilitation"[Subheading] OR "rehabilitation"[All Fields] OR "rehabilitation"[MeSH Terms])

9- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("prevention and control"[Subheading]) OR ("prevention"[All Fields] AND "control"[All Fields]) OR ("prevention and control"[All Fields] OR "prevention"[All Fields])

10- (public[All Fields]) AND ("education"[Subheading] OR "education"[All Fields] OR "educational status"[MeSH Terms]) OR ("educational"[All Fields] AND "status"[All Fields]) OR ("educational status"[All Fields] OR "education"[All Fields] OR "education"[MeSH Terms])

11- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("nurses"[MeSH Terms] OR "nurses"[All Fields] OR "nurse"[All Fields])

12- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND (protocol[All Fields])

13- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND (monitoring[All Fields])

14- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms])

15- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms])

16- ("stroke"[MeSH Terms] OR ("stroke"[All Fields]) AND burden[All Fields])

17- ("stroke"[MeSH Terms] OR ("stroke"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])

18- ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms])

19- ("Iran"[MeSH Terms] OR "Iran"[All Fields]) OR ("Iranian"[All Fields] OR "Persian"[All Fields]) OR ("Tehran"[All Fields] OR "Shiraz"[All Fields] OR "Mashhad"[All Fields] OR "Tabriz"[All Fields] OR "Isfahan"[All Fields] OR "Ahwaz"[All Fields] OR "Zahedan"[All Fields]) OR ("Middle East"[MeSH Terms] OR "Middle"[All Fields] AND "East"[All Fields]) OR "Middle East"[All Fields])

20- (#1) AND (#2 OR #3 OR 3# OR #5OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) AND (#19)

B. http://iranmedex.ir/

1- stroke OR infarction OR cerebrovascular event OR CVA OR brain ischemia

2- stroke unit OR stroke team OR stroke awareness OR therapy OR thrombolysis OR thrombectomy OR rtPA OR tissue plasminogen activator OR rehabilitation OR prevention OR public education OR nurse OR protocol OR monitoring OR epidemiology OR mortality OR morbidity

3- #1 AND #2

4- Corresponding terms in Persian

Table 2. The questions for semi-structured interviews and collective results: evaluating the current state of acute stroke management

Requirements of acute stroke management	Hospital met the requirement (%)
EMS stroke screening protocol, early management, and sending pre-notification to receiving hospital	0
Fast and efficient triage system in the ED for patients with stroke-like symptoms	0
Single call activation system for stroke alerts	0
On-call neurologist available for urgent consultation	100 (Neurology house staff)
Active 24-hour stroke program (trained nurses, available pharmacist) to deliver emergency intravenous therapies to eligible stroke patients	0
24-hour access to CT scans for an urgent scan within 30 minutes of a patient's arrival to emergency room	100 (No stroke protocol exist)
24-hour access to urgent and basic laboratory studies in emergency room	100 (No stroke protocol exist-results delayed in all centers)
Active 24-hour program to deliver emergency endovascular treatment to eligible stroke patients or a referral system in place to transfer the patient to an appropriate center	31 (Not available 24-h)
Guideline-based algorithms, order sets, tPA dosing charts in emergency rooms	85
Periodic educational programs in stroke care for ED staff	38
Inpatient facility to admit patients with stroke. In the absence of intensive care unit, a referral system should be available to transfer the patients to appropriate units	100
Patient care and daily visit by a neurologist and a multidisciplinary team	100 (By neurology team-no multidisciplinary team available)
Access to advance imaging for further stroke diagnosis	85
Cardiologist and cardiac imaging facilities	100
Active 24-hour program to deliver emergency neurosurgical treatment to eligible stroke patients or a system in place to transfer the patient to an appropriate center	100
Trained stroke nursing staff in stroke service	0
Periodic educational programs in stroke care for stroke service nursing staff	8
Established and organized palliative care/end of life pathway	0
Stroke nurse-coordinator	0
Ongoing commitment reflected in the quality assurance measures for better stroke care	0
Stroke data bank to collect measures applicable to quality assurance and better patient care	0
Stroke Rehabilitation program in the hospital	0
Rehabilitation hospital or outpatient rehabilitation unit with specialized stroke program	0
Special training course for patient, family, and caregiver to focus on secondary prevention and rehabilitation	0
Organized approach to follow-up visit by a neurologist or stroke rehab specialist	100 (The first neurologic visit following discharge)
Organized support group for patient and family	0

EMS: Emergency medical services; CT scan: Computed tomography; tPA: Tissue plasminogen activator; ED: Emergency department; Total number of hospitals evaluated in this study: 13

To choose the hospitals, we stratified the Iranian population into seven strata according to the geographical and population density distribution. Then, we chose the most populated city in each stratum (two-stage clustered sampling method). The selected cities are among the twelve most populated metropolitans in Iran-altogether they include about 50% of the Iranian population.[25]

Only a small number of the major cities in Iran have private hospitals, and the Iranian national referral network does not include these private hospitals. In addition, many healthcare insurance providers do not cover for services offered in

private centers. Consequently, negligible percent of stroke patients visit private hospitals. Therefore, we only selected thirteen tertiary public hospitals-seven hospitals in Tehran and one hospital in each of the following cities: Isfahan, Shiraz, Tabriz, Mashhad, Ahwaz and Zahedan (Iran).

We used judgment selection method followed by snowball sampling to select and interview providers and other healthcare personnel in each hospital.

The interviews were performed either in-person or by phone. Each interview lasted between 30 to 40 minutes. The interviews were done in a neutral and collaborative setting. The identity of interviewees remained confidential.

Phase three: We examined our results and tried to recommend some targeted and adaptive solutions for stroke care in Iran. To achieve that, we consulted with several local experts and policy makers, in addition to a few stroke experts in the United States.

We analyzed the data using the first coding process through initial coding. This type of coding was chosen to examine, compare, and search for similarities and differences throughout the data. The second level coding was pattern coding to explain major themes underneath the segments of the data and to understand the relationships.

Results

Review of literature: We reviewed more than 1500 news reports and research articles. Fifty-eight articles were selected and adequately studied (Figure 1). The most prominent obstacle toward timely treatment of stroke was a lack of priority for acute stroke management and low public awareness of stroke symptoms and its urgency. Almost 95% of the stroke patients who had visited a tertiary stroke care in Tehran lacked any awareness and prior education about stroke symptoms.[26] Studies from Iran showed that more than 17 percent of Bushehr's residents[27] and 48.7% of the stroke patients admitted to a referral center in Tehran[28] could not name even one stroke risk factor. The gap between the knowledge of stroke risk factors and behavior[4] and wrong attitude toward availability, efficiency, and affordability of the stroke management[4] were also reported.

Reports from Tabriz, Mashhad, and Isfahan demonstrated that less than 30% of the stroke patients arrived at the hospital within three hours of symptoms onset. Up to 40% of ischemic stroke patients did not present to the emergency department (ED) on the day of symptom onset.[16,29-31] It was also reported that 45% to 86% of the patients who arrived within 3-hour window of symptom onset missed thrombolytic therapy due to the lengthy diagnostic process.[26,30,32-34]

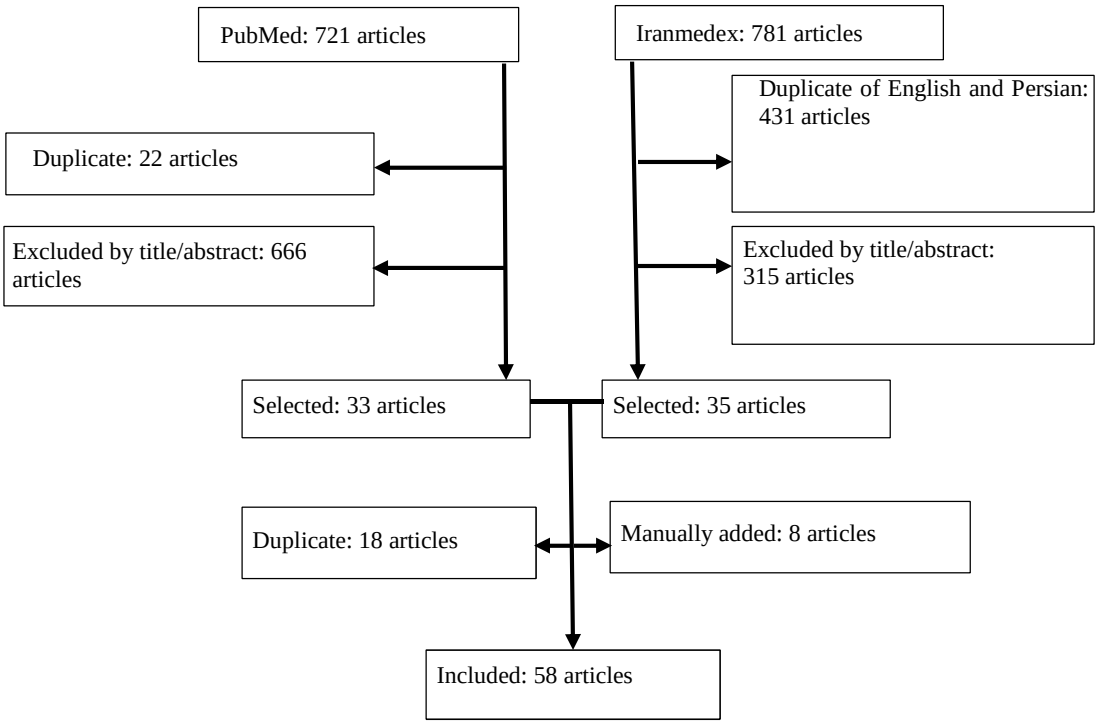

Figure 1. Literature search and selection of studies (phase one)

Semi-structured interviews: For the second phase of the study, we interviewed a total of 76 practitioners and care providers (Table 3) in thirteen public tertiary centers in seven large metropolises in Iran. All thirteen hospitals in our cohort had a 24-hour neurology service and a neurology resident available for urgent consults. Every hospital had access to 24-hour computed tomography (CT) scan; however, immediate access to advanced imaging including CT angiogram, perfusion imaging or magnetic resonance imaging (MRI) was limited in all selected hospitals. Every hospital in our pool except two hospitals had guideline-based algorithms for the administration of intravenous thrombolysis. There was no single call activation system for stroke alert. Although there were four endovascular programs in our target areas, there was no center with 24-hour coverage.

Table 3. The study participants (second phase) in thirteen hospitals

Participants	n	Participants	n
Neurologists	24	Pharmaceutical representatives	2
Neurosurgeons	7	ED physicians	6
EMS staff	11	Hospital receptionists	3
Cardiologists	2	Imaging and laboratory staff	3
Radiologists	3	Administrators	9
Intensivists	3	Triage staff	5
Nurses	16	Case managers	4

ED: Emergency department; EMS: Emergency medical services; Some participants owned more than one responsibility.

There was no stroke registered or trained nurses in the ED, stroke nurse-coordinator, stroke navigator, systematic data monitoring or feedback system in any of our surveyed hospitals. Only one hospital offered annual stroke training courses for nursing staff. Table 2 includes the percentage of hospitals who met each of our defined requirements for acute stroke management.

Almost every ED in our cohort was suffering from the delayed assessment of stroke patients and prolonged "door to needle" time for IV-tPA. Data from some of the centers showed that hospital arrival of stroke patients to final decision-making took 116-160 minutes.

There was not a regular and formal training as well as protocol regarding stroke screening and pre-hospital stroke management at least in our surveyed centers. Every hospital suffered from a lack of stroke rehabilitation programs and organized palliative care service.

Discussion

Our study, similar to the other studies[35-39] suggests that delayed hospital presentation in addition to the lack of an organized and comprehensive stroke program in the hospitals are the biggest obstacles to receiving proper acute stroke treatment.

Several studies published since 2000, reporting a median delay of symptom onset to ED arrival, indicated that the 50th percentile for delay occurred between 3 and 4 hours[35] with 14%-48% arrival within two hours and 15%-60% arrival of the patients within three hours after symptom onset.[39]

The rate of early presentation to the ED after stroke is significantly lower in Iran. Although lack of health insurance can be associated with delays in seeking emergency care,[40] it does not seem to be a significant factor in Iran especially after extending universal health insurance (so-called "RouhaniCare") to all Iranians. Limited public knowledge of stroke warning symptoms[26] and false attitude toward availability and affordability of the stroke management[4] had been reported as possible causes. In addition, similar to other health services, a disparity exists in stroke care in Iran, and except large and industrialized cities, other small towns do not have adequate infrastructures or trained personnel for management of patients with stroke.[15]

Emergency medical services (EMS): The pre-hospital workplace

EMS are the integral component of stroke centers by their vital role in rapid transport of the stroke patients to designated facilities.[12] Based on stroke statements and guidelines, the average time between notification and ambulance arrival should be less than eight minutes, with the application of alternatives such as air ambulance when it takes more than one hour to access the medical center.[41] In Iran, rapid transport of the patients is challenging.[42,43] Moreover, our study showed that EMS staff in our studied pool did not receive enough training about stroke, and they might be confused about their role in stroke assessment and care.

In-hospital stroke management: from acute treatment to rehabilitation

Improper triage is another time sparing factor in stroke management.[44-46] Although all the centers had a 24-hour neurology service, several physicians in our study reported that a considerable number of patients were improperly

triaged in the ED.

Other reasons for delay were late imaging or laboratory evaluations, prioritizing acute stroke patients or overwhelmed EDs with critically ill patients and high demands for diagnostic modalities. The ED was also suffering from a lack of resources. Despite these limitations, it is expected that adaptation of stroke alert and sending pre-notification to the destination hospital accelerate the treatment.

Performance monitoring and feedback system: an essential step for quality improvement

Data collection and care performance surveillance system for the stroke care pathway is essential. Introducing pathways to improve the quality of stroke care through national data monitoring systems is imperative. Unfortunately, there is no national data surveillance system in Iran. There was also no comprehensive data monitoring or feedback system in our participating centers.

What are the solutions?

The most important step to improve the management of stroke in Iran could be to put stroke as a top healthcare priority. Studies in other countries[47,48] and also experience in the management of myocardial infarction in Iran[49,50] showed that by making stroke care a top priority and using mass media to increase awareness, many of the cited impediments could be solved. During the last phase of our study, we tried to recommend some targeted and adaptive solutions for stroke care in Iran based on several local and international experts' opinions. Table 4 summarizes some of the recommendations to improve stroke management in Iran.

Table 4. The obstacles and possible solutions for stroke care in Iran

Obstacles	Possible solution
Public awareness	Campaigns to increase community awareness
Lack of public awareness about stroke symptoms and its urgency	Public education in health houses and health centers: face-to-face education with considering language and cultural considerations
	Mass media: television, radio, outdoor banners, newsletters, the Internet
	Group educations for relatives of stroke victims in the hospital
	Special programs for the elderly population in parks, senior recreation centers, religious centers, etc.
	Education for school children and their family, Banners, and flyers in health centers, physician office, etc.
Pre-hospital assessment and care	Increase EMS resources
Traffic congestion and delayed EMS arrival	Provide regular education for emergency call attendances to identify
Lack of or inefficient screening protocol and early stroke assessment and management by EMS personnel	possible cases of stroke through the phone conversation and rapidly dispatch the EMS team
	Prioritize stroke response in EMS system
Lack of public awareness to yield the right of way to an emergency vehicle	Improve public awareness to yield the right of way when approached by an emergency vehicle
	More training for EMS staff about early stroke recognition, recognizing possible cases of large vessel occlusion, and their role in early stroke assessment and care
	Evaluate the feasibility and effectiveness of Stroke Emergency Mobile in largely populated cities like Tehran. Stroke mobile includes a CT scanner and point-of-care laboratory installed in a fully equipped ambulance
In-hospital acute stroke management	Install several easy-to-read wall posters in the ED waiting room to draw
Incorrect or delayed assessment of stroke patients in triage	patients' attention to the signs of stroke requiring them to alert the triage nurse immediately
Long "Door To Needle" time secondary to lack of fast and efficient triage system, lack of single activation call system, delayed imaging	Establish standard operating procedures and protocols to triage stroke patients rapidly
	Provide general education for triage nurses
	Enable triage nurses to activate stroke alert
Lack of emergency guideline-based algorithms, trained stroke nurses, urgent access to advanced imaging, 24-hour endovascular program	Establish a team-based approach in the ED and train professional stroke registered nurses
	Provide organized and professional stroke team at the hospital with a focused goal
Lack of regular educational program for ED personnel	Single Call Activation System: a single call should activate the entire stroke team at the hospital
Lack of organized data and performance monitoring and feedback system for quality improvement	Provide rapid triage protocol for inpatient and early stroke team notification at the hospital
	Every hospital medical staff should be able to activate stroke alert

	Mobilize the imaging and laboratory facilities by the aid of activated stroke alert or pre-notification system
	Performing CT scan (or MRI) within 25 minutes of arrival and complete interpretation of the CT scan within 45 minutes of arrival
	Rapidly recognize patients with large vessel occlusion and alert the interventional team
	Provide regular educational programs for ED staff
	Have a protocol in place for the rapid transfer of patients to a tertiary care center, if needed
	Establish an organized data monitoring and feedback system for quality improvement evaluation
Inpatient stroke management	Admit stroke patients directly to a stroke unit or stroke service under the care of a stroke specialist and a multidisciplinary team. Access to a neurological ICU
Lack of trained stroke nursing staff, routine training for nursing staff, and timely physical, occupational and speech therapist evaluation and a multidisciplinary team round.	Easy access to advance imaging for further investigation of stroke patients
	Provide routine training for nursing staff to provide high-quality nursing care
Access to advanced neurological and cardiovascular imaging/testing can be a challenge	Daily monitoring and documentation of NIH stroke scale
	Perform swallowing screening assessment on admission by appropriately trained and competent staff
Lack of coordinated palliative care/end of life pathway	Nutritional screening assessment performed within 24 hours of admission
Lack of organized data and performance monitoring and feedback system for quality improvement	Protocol for the promotion of bladder and bowel continence including a policy to avoid urinary catheters
	Provide established protocols for the prevention and treatment of common complications
	Establish an organized palliative care/end of life pathway
Rehabilitation program	Establish a designated stroke rehabilitation inpatient unit
Lack of a comprehensive in-patient, out-patient stroke program in all studied centers	All medically stable patients with stroke should be transferred from the stroke service without delay
	Screen for cognitive deficits, visual neglect, attention deficits and emotional problems and have access to a specialist in clinical psychology
	Involve families and caregivers in day-to-day care and rehabilitation
	Encourage patient and family in secondary stroke prevention and change of lifestyle (nutrition, weight loss, medicine compliance, physical activity)
	Establish a protocol for patients' follow-up visit
	Organize stroke support groups for patients and families
	Organize the rehab protocol based on patient, family, and community
Other challenges	Develop telehealth capabilities for remote stroke diagnosis and treatment
Disparity in stroke care in Iran	Develop programs for underrepresented minority populations and women
Lack of national guideline for primary and comprehensive stroke center designation	Public-private partnerships and shared resources
Lack of a pathway to improve the quality of stroke care through national data monitoring systems	Develop and certify primary stroke center policy through the national legislative system: examples include primary stroke center designation through a national program, EMS protocols, or hospital bypass policies
	Monitor, and improve the quality of and access to care for stroke patients from the onset of stroke symptoms through the rehabilitation
	Track the rate of death and disability from acute stroke
	Monitor and eliminate disparities in stroke care
	Increase the epidemiological knowledge of stroke in Iran
	Introduce pathways to improve the quality of stroke care through national data monitoring systems

EMS: Emergency medical service; CT scan: Computed tomography scan; ED: Emergency department; MRI: magnetic resonance imaging; ICU: Intensive care unit; NIH: National Institutes of Health

The Iranian primary healthcare system is a unique system that was established to improve access to healthcare for the disadvantaged and reduce the gap between the urban and rural areas.

The smallest unit of Iranian healthcare system is called "health house." Health houses are designed to cover a target population of about 1500 in rural areas with careful attention to their cultural and social characteristics. We believe that health houses can have a crucial role in stroke education and support in remote regions.

It is evident that stroke centers can further improve stroke patients' outcome. Patients treated in stroke centers are 11% less likely to die, 11% less likely to be in institutional care, and 16% more likely to live at home one year after their stroke than patients treated in other hospitals.[51] Therefore, defining national criteria for stroke center is an essential step in Iran. We believe that many of the medical centers in Iran have the potential to become a stroke center.

Our study had some limitations. In this study, we only included thirteen tertiary centers in seven large cities. Some other hospitals in smaller cities might have more limitations in terms of infrastructure and personnel required for proper stroke management. We performed some of our interviews by phone. It might be more difficult to connect and build rapport in a meaningful way over the phone. Although on many occasions we interviewed more than one individual from the same department, we did not have any other ways to confirm the accuracy of individual responses.

Conclusion

There are many challenges as well as potentials for improvement of stroke care in Iran. Improving public knowledge of stroke and establishing an organized and comprehensive stroke program in the hospitals will improve acute stroke management in Iran. The Iranian ministry of health should define and advocate the establishment of stroke centers, track the rate of death and disability from stroke, introduce pathways to improve the quality of stroke care through national data monitoring systems and eliminate disparities in stroke care.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Modified Atkins diet in adult with refractory epilepsy: A controlled randomized clinical trial

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Keywords
Epilepsy; Drug Refractory; Modified Atkins Diet; Adult

Abstract

Background: The usefulness of the modified Atkins diet (mAD) in refractory epilepsy in adults has been rarely investigated. We aimed to evaluate the efficacy of mAD in adult with refractory epilepsy.

Methods: In a controlled randomized clinical trial, we enrolled 66 refractory adult epileptic cases from February 2010 to December 2012. The patients were randomly divided into two groups, case groups (22 patients) used antiepileptic drugs and mAD and control group (32 patients) only use antiepileptic drugs. The primary outcome was at least 50% decrement in seizure frequency after 2 months of therapy.

Results: No significant difference was shown in our data between groups regarding baseline characteristic. The differences of mean seizure attack after 2 months ($P < 0.001$). (17.6%) had > 50% seizure decrease at 1 and after 2 months and 12 (35.3%) had 50% decrease in seizure frequency. Furthermore, in mAD group, the mean urinary ketone positivity was 1.75 ± 0.28 and increasing liver enzyme was shown 5 cases (14.7%) in mAD group and 5 cases (15.6%) in control group ($P < 0.050$).

Conclusion: The mAD may be effective as a cotherapy treatment for adults with refractory epilepsy and decrease 2.19 times seizure frequency in comparison with control groups. Trials with the more tolerant dietary regime, with larger sample size and longer duration, should be performed in future.

Introduction

Despite the appropriate consummation of several anticonvulsants, 10-30% of patients with epilepsy have refractory seizures. The ketogenic diet is a separately considered and severely controlled high-fat (80%), low protein (15%), and low carbohydrate (5%) diet used for the management of refractory seizures.[1]

The Atkins diet (AD) also limits carbohydrates, but unlike the ketogenic diet, it does not restrict usage of calories or proteins. The modified AD (mAD) provokes ketosis, but without neither fluid, calorie and protein limitation nor the requirement for fasting, food evaluating and hospitalization.[2,3]

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In the past few years, there have been studies that Atkins and the mAD can be potentially applied as cotherapy for patients with refractory epilepsy.[2-7]

The use of dietary therapy treatment for epilepsy is technologically simple, and there are many studies about children that have showed the usefulness of mAD in refractory epilepsy.[4-6] However, the mAD is rarely offered to adults.[7] We aimed to assess the efficacy of mAD in adults with refractory epilepsy in a controlled randomized clinical trial.

Materials and Methods

In a controlled randomized clinical trial, we compared the efficacy and tolerability of mAD in adults with refractory epilepsy. This study was registered in the Iranian Registry of Clinical Trials under ID number IRCT138803051949N1. We enrolled 66 refractory adult epileptic cases, aged from 18 to 57 years, who referred to the Adult Neurology Clinic of Kashani Hospital from February 2010 to December 2012. The inclusion criteria were the age of ≥ 18 years and refractory epilepsy (two or more seizures attacks every month in spite of treatment with at least two appropriate antiepileptic drugs). No changes were made in the study participants' medications or treatment plans until informed consent was obtained. Exclusion criteria were previous use of the AD or mAD for > 1 week, previous use of the ketogenic diet within the past year, patients with kidney, heart, renal disease or hypercholesterolemia, patients with history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, atherosclerosis, previous myocardial infarctions, or renal dysfunction, pregnant individuals, body mass index (BMI) below 18.5, status epilepticus within the past 6 months, 2 week seizure-free period within the past 6 months. This study was accepted by the Ethics Committee of Isfahan University of Medical Sciences, Iran.

The patients were randomly separated into two groups according to random number table, case groups used antiepileptic drugs and mAD and control group only used antiepileptic drugs. After enrollment, case groups referred to nutritionist for education of mAD by using simple comprehensible terms and followed them for 2 months. The mAD was customized to the cultural and financial status of the families (Figure 1).

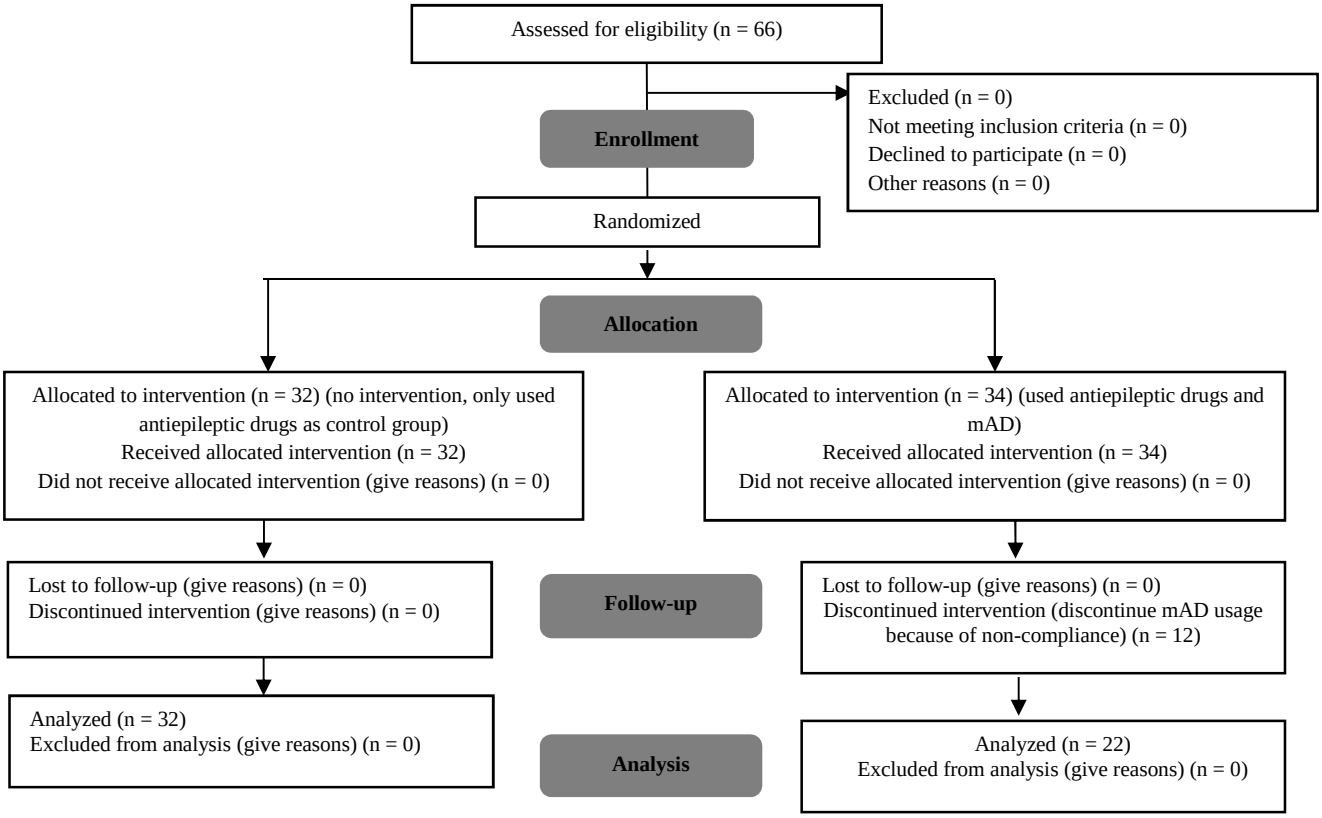

Figure 1. Flowchart consort
mAD: Modified Atkins diet

The diet in case group was initiated with carbohydrates limited to 15 g/day, without any changes or limitations in calories and liquid in dietary pattern, it means 4-6% carbohydrate, 20-30% protein, and 60-70% fat. Before launching the diet, the patients were asked to record the frequency of their seizures (number/day) for 1 month. A monthly calendar with instructions to document seizures daily was provided. During 1 month every week by phone and after 1 month, calendars by clinic visit were reviewed. We measured the weight, height, lipid profile, serum electrolyte and liver function tests at onset and monthly during 2 months. Urinary ketones and weight were measured weekly for 2 months. However, the patients in case group were recommended to use high-fat food. Antiepileptic drug therapy continued unchanged for at least the 2 months, but when necessary, the drugs were changed in both groups. Low carbohydrate, multivitamins, and calcium supplementation were given to all patients. The least follow-up was 2 months and after that, if the diet was useful, the regimen was continued. The primary outcome was at least 50% decrease in seizure frequency after 2 months of therapy; the secondary outcome was the effects of diet on weight loss and ketone body.

Data on seizure frequency, age of the patients at the onset of epilepsy, classification of seizures, medications profile, demographic data, and results of serial biochemical assessment were collected and entered into SPSS software (version 18, SPSS Inc., Chicago, IL, USA). We employed an intent-to-treat (ITT) analysis for outcomes which were analyzed using independent sample t-test, paired sample t-test and chi-square except fisher test. Here, A two-tailed $P < 0.050$ was considered statistically significant. We compared the two groups concerning the study outcomes based on the per-protocol and ITT principles (Figure 2).

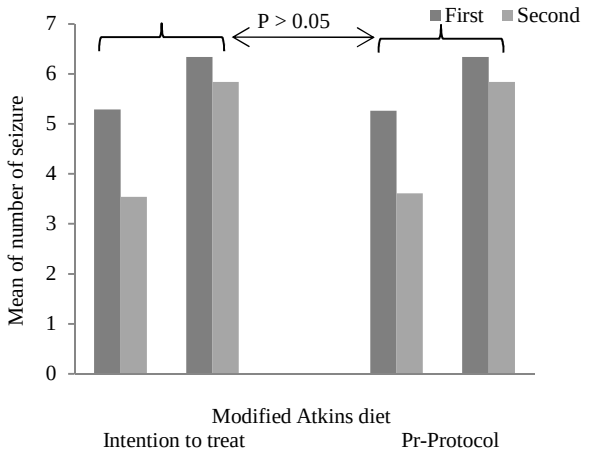

Figure 2. Comparison of change in mean number of seizure per month between intention to treat and pre-protocol analysis

Results

In this study, the control group includes 21 males (65.6%) and 11 females (34.4%) with the average age of 27.2 ± 7.3 years and mAD group composed of 34 males (70.6%) and 10 females (29.4%) with the average age of 29.4 ± 8.8 years, while both groups are the same in terms of age and sex without any significant differences statically ($P > 0.050$). Furthermore, between both groups there is no significant differences in terms of other factors such as duration of epilepsy, number of attack in month prior of study, family history of epilepsy, and so on ($P > 0.050$) (Table 1).

Table 1. Baseline and clinical characteristics of patients in two groups

Variables	mAD group (n = 34)	Control group (n = 32)	P
Age (year) (mean ± SD)	29.4 ± 8.8	27.2 ± 7.3	0.280
Sex [n (%)]			
Male	24 (70.6)	21 (65.6)	0.430
Female	10 (29.4)	11 (34.4)	
Duration of epilepsy (year) (mean ± SD)	17.80 ± 10.6	14.09 ± 7.50	0.100
Number of drugs (mean ± SD)	2.80 ± 0.98	3.03 ± 1.06	0.550
Number of attack in month prior of study (mean ± SD)	8.50 ± 7.00	6.50 ± 3.20	0.140
BMI prior of study (mean ± SD)	23.07 ± 3.60	22.95 ± 1.80	0.860
Past history of febrile convulsion [n (%)]	4 (11.8)	6 (18.8)	0.320
Family history of epilepsy [n (%)]	6 (17.6)	8 (25.0)	0.330
Type of seizure [n (%)]			
Complex partial	18 (52.9)	18 (56.3)	0.490
Generalized tonic clonic	16 (47.1)	14 (43.7)	

BMI: Body mass index; mAD: Modified Atkins diet; SD: Standard deviation

Table 2. Clinical characteristics of patients in which use of intention to treat was reported in two groups

Variables	Month	mAD group (n = 34)	Control group (n = 32)	P*
Number of seizure attacks per months (mean ± SD)	First	5.26 ± 2.81	6.34 ± 3.06	0.141
	Second	3.61 ± 1.88	5.84 ± 2.92	< 0.001
P**		0.006	0.001	
50% reduction in seizure frequency [n (%)]	First	6 (17.60)	0 (0)	0.037
	Second	12 (35.30)	0 (0)	0.001
P**		0.084	-	
Seizure free [n (%)]	First	0 (0)	0 (0)	-
	Second	0 (0)	0 (0)	-
P**		-	-	
BMI (kg/m^2) (mean ± SD)	First	23.07 ± 3.60	22.95 ± 1.80	0.860
	Second	22.32 ± 3.52	23.02 ± 1.94	0.365
P**		0.038	0.237	
Increasing cholesterol level during 2 months [n (%)]		7 (20.59)	0 (0)	0.004
Increasing liver enzyme during 2 months [n (%)]		5 (14.71)	5 (15.62)	0.007
The mean urinary ketone positivity during 2 months (mean ± SD)		1.75 ± 0.28	-	-

*Significant level for comparing two groups in each months, **Significant level for comparing two month in each groups. SD: Standard deviation; mAD: Modified Atkins diet

Of participants, who started the mAD, due to discontinuing mAD usage or non-participation to final follow-up, 12 of them were excluded and 22 (64.7%) participants continued in the study. 6 (17.6%) had > 50% seizure reduction at 1 month using ITT analysis. After 2 months, 12 (35.3%) had > 50% reduction in seizure frequency using ITT analysis, and anybody was seizure-free. Furthermore, the mean of patients' BMI in the 1st month has no significant differences (P = 0.860) and in mAD group; in the 2nd month, BMI had a significant reduction from 23.07 ± 3.60 to 22.32 ± 3.52 kg/m^2 (P = 0.038). While in the control group, the mean of BMI had an increase from 22.95 ± 1.80 to 23.02 ± 1.94 kg/m^2 but this increase was not significant statistically (P = 0.237). Furthermore, in mAD group within 2 months increasing cholesterol level has been seen in seven cases (20.0%) compared to control group suggests no increase in cholesterol level. Moreover, in mAD group, increasing liver enzyme has been seen in five cases (14.71%) compared to five cases (15.62%) in control group that shows a significant deference between two groups (P < 0.050). The mean urinary ketone positivity was reported only in mAD group 1.75 ± 0.28 (Table 2).

Finally, as figure 2 shows, both groups suggest no significant differences in terms of change in mean number of seizure per month and by taking into account two methods of intention to treat and pre-protocol analysis (P > 0.050).

Discussion

This open label, prospective randomized clinical trial has revealed that the mAD appears to be an effective and well-tolerated management for adults with refractory seizures. At the end of the 2nd month, 45.5% of patients had > 50% seizure decrease. It appears that mAD co-therapy can decrease 2.19 times more seizure reduction in comparison with control groups.

The results of this small, open label, prospective and randomized clinical trial study agree with previous findings,[7-9] which suggest that some benefits exist for the use of the mAD as a form of cotherapy in the managing of intractable epilepsy in an adult population. Therefore, data on mAD treatment in adults are limited. Only three open-label reports have shown the use of the mAD exclusively for adults.[7-9] A literature review of studies which include data specifically on individuals aged > 18 on the mAD is shown in table 3. Data from three studies showed, on average, 9 of 32 (28.1%) adults achieved > 50% seizure reduction; among these 32 none of them became seizure-free. No specific data were provided for the adults included in some studies; but for those with seizure reduction, the mean time to improvement was 2 weeks (range: 1-8 weeks).[7] However, to our literatures, this is the first randomized clinical trial, showed that mAD cotherapy can decrease 2.19 times more seizure reduction in comparison with control groups for adults with refractory seizures.

Table 3. Summary of studies involving adults treated with the modified Atkins diet (mAD) in refractory seizure patients

References	Study type	Number	Ages (year)	Diet type	> 50% decrease (%)	Seizure free (%)	End point (month)	% dropout before end of study	Adverse side effects
Kossoff, et al.[7]	Prospective	30	18-53	mAD (carbohydrate restriction 15/day)	47% had a > 50% seizure reduction after 1 and 3 months on the diet; 33% after 6 months.	0	6 months	53	Lethargy, weight loss, elevated total cholesterol, leg swelling
Carrette, et al.[8]	Prospective	8	31-55	mAD (carbohydrate restriction 20/day)	33% after 6 months	0	6 months	62.5	Vomiting, headache, nausea, diarrhea, constipation, weakness, weight loss, elevated total and LDL cholesterol
Smith, et al.[9]	Prospective	18	18-55	mAD (carbohydrate restriction 20/day)	12% had a > 50% seizure reduction after 3 months; 28% after 6 months, and 21% after 12 months	0	12 months	22	Weight loss (desired), left arm jerks

mAD: Modified Atkins diet

A positive correlation was observed between the mean urinary ketone level and > 50% seizure reduction in case group. However, the previous study showed that ketone levels had no correlation with improved efficacy in adults.[7,9]

In this study, may be due to high consumption of lipid and fatty liver consequently, cholesterol and liver enzyme level were higher in case group. Gastrointestinal complaints and unfavorable lipid profiles (low density lipoprotein and total cholesterol increment) were side effects of mAD in another study.[7,10,11] We showed no significant weight loss in mAD group, however, weight loss was more common in adults who initially requested to lose weight.[7] One study showed a correlation of BMI reduction and diet effectiveness,[7] but another study did not find this.[9]

Nevertheless, it appears that tolerability of the mAD in adults is similar to that of the ketogenic diet and long-term side effects of the mAD are unknown in adults and should be evaluated in future study with larger sample size and longer duration.

In this study, we showed 35.2% of patients discontinued the mAD treatment. Data from other three studies showed that, on average, 46.6% of patients discontinued the treatment.[7-9] The main cause for treatment discontinuation appears to be the lack of efficiency.[7-9] The percentage dropout with the ketogenic diet ranged from 10% to 88% (mean = 53%),[7-9] despite limited sample sizes; retention appeared higher on the mAD than on the ketogenic diet, and so more tolerant regimens may be proposed as feasible alternatives for older people. Nevertheless, more than 50% of patients in various studies were motivated to maintain it as long as seizures were reduced.[7-9]

However, this study has some limitation, first of all the small sample size, the second the two groups were not similar according to antiepileptic drug therapy.

Conclusion

The mAD may be effective as a cotherapy treatment for almost the half of adults with refractory epilepsy that decrease 2.19 times seizure frequency in comparison with control groups. The retention levels are poor (near to 40%). However, studies are limited about adults and trials with more tolerant dietary regime, with larger sample size and longer duration should be performed in the future.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Original Paper

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Atherogenic indices in stroke patients: A retrospective study

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Keywords
Stroke; Lipid Profile; Atherogenic Indices

Abstract

Background: Stroke makes a significant cause of morbidity and mortality worldwide. Although derangements in the lipid profile have been suggested as a risk factor for the development of stroke, various studies show inconsistent results on the association between lipid profile and stroke. A very few studies have commented on the status of lipid indices in stroke patients.

Methods: After obtaining ethical medical records of the study populations were analyzed, and data collected from patients admitted to the hospital with clinically diagnosed stroke and control group consisted of apparently healthy volunteers selected from the master health checkup department. Baseline characteristics and lipid profile parameters and the number of days of hospital stay for stroke patients were collected. Lipid indices were calculated using following formulae. Atherogenic index of plasma (AIP) = log triglyceride/high-density lipoprotein cholesterol (HDLc), Castelli's Risk Index (CRI-I) = Total cholesterol/HDLc, CRI-II = Low density lipoprotein cholesterol/HDLc, atherogenic coefficient (AC) = (Total cholesterol–HDLc)/HDLc, and non-HDLc (NHC) = Total cholesterol–HDL.

Results: The study included 620 participants of which 290 were stroke patients and 330 healthy volunteers. 61% of stroke patients were hypertensives and 38% were diabetics 28% were both diabetic and hypertensives. In this study, the lipid parameters and the indices were significantly higher in stroke patients than the control group. Three indices, namely, CRI-I, AC, and NHC were found to be contributing to the risk of stroke significantly. There was no statistically significant correlation between the duration of hospital stay and lipid indices or individual parameters of lipid profile.

Conclusion: In this study, the atherogenic lipid indices were significantly higher in stroke patients compared to controls.

Introduction

Stroke is defined as "an acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain."[1] It is one of the leading causes of mortality and disability globally.

The prevalence of stroke in India varies in different regions of country, and the estimated prevalence rates increase from 0.3/1000 in < 45 years age group to 12-20/1000 in the 75-84 years age group.[2]

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There are several studies in India determining risk factors of stroke. Goldstein, et al.[3] described the various non-modifiable and modifiable risk factors of stroke. The non-modifiable risk factors include age, gender, ethnicity, and previous family history of stroke. The modifiable risk factors include hypertension, smoking, diabetes, asymptomatic carotid stenosis, atrial fibrillation, pre-existing cardiac disease, and hyperlipidemia.

Abnormalities of serum lipids have traditionally been regarded as a risk factor for coronary artery disease but not for stroke. However, the relationship between lipids and stroke was elucidated and it has been made clear that the risk of stroke and amount of carotid atheroma can be reduced with cholesterol-lowering medications.[3] Thus, lipid profile abnormalities are found to have profound influences in the development and outcome of stroke.

It has been emphasized that in an attempt to optimize the predictive capacity of the lipid profile, several lipoprotein ratios or "atherogenic indices" have been defined. The various atherogenic indices are atherogenic index of plasma (AIP), Castelli Risk Index I and II (CRI), atherogenic coefficient (AC), and non-high density lipoprotein cholesterol (HDLc) (NHC).

AIP is based on two important parameters, serum triglyceride, and serum HDLc. The concurrent use of triglycerides and HDLc in this ratio reflects the multiple interactions among the metabolism of different lipoproteins and can be useful for predicting plasma atherogenicity.

Based on the study by Dobiasova,[4] we suggest that AIP values of -0.3 to 0.1 are associated with low, 0.10-0.24 with medium and above 0.24 with high cardiovascular risk.

It is calculated according to the following formula:

AIP = Log (serum triglyceride/serum HDLc).[4]

CRI-I and II are two important indicators of vascular risk, the predictive value of which is greater than the isolated lipid parameters. They are calculated as per the given formulae:

CRI-I = Serum total cholesterol/Serum HDLc,

CR-I II = Serum low-density lipoprotein (LDL)-cholesterol/Serum HDLc,[5]

AC is calculated as:

(Serum total cholesterol−Serum HDLc)/HDLc.[6]

NHC represents the cholesterol content present in all the atherogenic lipoproteins. It is calculated as the difference between total cholesterol and high-density cholesterol (serum total cholesterol–serum HDLc).

Studies have shown that lipid indices calculated from parameters of lipid profile were found to have better predictive capacity in cardiovascular disease.[7] However, there were no conclusive studies to show the association of atherogenic indices in stroke patients. This study was conducted to assess the various lipid indices in stroke patients and also compare the same with healthy controls.

Stroke is associated with serious morbidity and disability which contributes to the burden caused by stroke. Longer the duration of hospital stay in stroke patients, more is the severity of stroke and vice versa. This study also aimed to correlate these lipid indices with the duration of hospital stay in stroke patients which can be considered as an index of the severity of stroke.

Materials and Methods

Ethical clearance was obtained from the Institutional Human Ethics Committee. The study group consists of patients admitted to the hospital with clinically diagnosed stroke during the period January 2015-2016. The control group consisted of apparently healthy volunteers selected from the master health checkup department.

The medical records of the study participants were analyzed, and data collected include age, gender, lipid profile parameters (total cholesterol, HDL, LDL and triglyceride levels), and the number of days of hospital stay for stroke patients.

All parameters were estimated using dedicated kits and reagents in autoanalyzer. Lipid indices were calculated using following formulae:

AIP = Log (serum triglyceride/serum HDLc),

CRI-I = Serum total cholesterol/serum HDLc,

CRI-II = Serum LDL cholesterol/serum HDLc,

AC = (Serum total cholesterol−serum HDLc)/serum HDLc,

NHC = Serum total cholesterol-serum HDLc.

All statistical analysis was performed with SPSS version 19. Data were expressed as mean ± standard deviation (SD). For comparison of variables, statistical test was done using Mann-Whitney U-test for skewed distribution and chi-square test for categorical variables. Odds ratio and 95% confidence interval was calculated. Factors found to be significant in the univariate analysis were subjected to logistic regression analysis. $P < 0.050$ was considered as statistically significant.

Table 1. Characteristics of the study population

Characteristics	Cases	Controls	P
Number of participants	290	330	
Age (year) (mean ± SD)	60.48 ± 13.61	58.78 ± 10.24	0.080
Gender [n (%)]			
Males	200 (69.0)	214 (64.8)	0.305
Females	90 (31.0)	116 (35.2)	
Hypertension [n (%)]	178 (61.4)	-	-
Diabetes mellitus [n (%)]	111 (38.3)	-	

Results

A total of 620 participants were included in the study, out of which 290 were cases and 330 were controls. Age and gender matched controls were included in the study. The most commonly associated comorbid conditions related to stroke was found to be hypertension and diabetes mellitus. The characteristics of the study population are described in table 1.

The results of lipid profile and lipid ratios in the study population are given in table 2.

Among the 290 stroke patients, 251 (86.5%) had associated comorbid conditions such as hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, thyroid dysfunction, hyperhomocysteinemia and anemia.

Cutoff levels of the atherogenic indices to assess cardiovascular risk were taken from previous studies.[4,8] AIP value of < 0.1 was considered as low risk and ≥ 0.1 was considered high risk.[4] CRI-I values of < 4 and CRI-II values of < 3 were taken as low risk.[8] AC value of < 2 and NHC value of < 130 were considered to be low risk.

Using these cutoff values, study participants were categorized as low- and high-risk individuals.

96.6% of stroke cases had AIP levels > 0.1 and only 81.5% of controls had AIP above the cutoff levels. 70.0% of cases had CRI-I levels > 4 and only 15.5% of controls had higher CRI-I levels. 59.7% of cases had CRI-II levels > 3 and only 13.6% of controls had higher CRI-II levels. 92.4% of cases had AC levels > 2 and only 44.2% of controls had AC above the cutoff levels. 53.4% of cases had NHC levels > 130 mg/dl and 11.8% controls had higher NHC levels.

Chi-square test was performed to assess the significance between the two groups and the results are tabulated. Odds ratio was also calculated and the results are included in table 3.

Further logistic regression analysis (Table 4) was performed and three indices, namely, CRI-I, AC, and NHC were found to be contributing to the risk of stroke significantly.

There was no significant correlation between the duration of hospital stay and any of the lipid profile parameters or lipid indices among the stroke patients.

Discussion

Stroke makes a significant cause of morbidity and mortality worldwide. There are several etiologies and risk factors which are associated with the development of stroke. Although derangements in the lipid profile have been suggested as a risk factor for the development of stroke, various studies show inconsistent results on the association between lipid profile and stroke.[9]

Table 2. Lipid profile parameters and lipid indices in study participants

Parameter	Cases (mean ± SD)	Controls (mean ± SD)	P
Serum cholesterol (mg/dl)	170.80 ± 44.00	144.10 ± 28.92	< 0.001*
Serum triglycerides (mg/dl)	140.50 ± 82.00	95.98 ± 37.25	< 0.001*
Serum HDL (mg/dl)	36.11 ± 10.40	47.37 ± 10.87	< 0.001*
Serum LDL (mg/dl)	116.23 ± 38.68	90.63 ± 29.06	< 0.001*
AIP	0.56 ± 0.27	0.26 ± 0.22	< 0.001*
CRI-I	4.99 ± 1.52	3.21 ± 1.16	< 0.001*
CRI-II	3.39 ± 1.26	2.06 ± 1.06	< 0.001*
AC	3.99 ± 1.50	2.21 ± 1.16	< 0.001*
NHC	134.78 ± 41.25	96.74 ± 30.32	< 0.001*

*P < 0.050 was considered as statistically significant.

AIP: Atherogenic index of plasma; CRI: Castelli Risk Index; AC: Atherogenic coefficient; NHC: Non-high density lipoprotein cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation

Table 3. Association of atherogenic indices and stroke

Parameter	Cases (%)	Controls (%)	P	OR	CI
AIP	96.6	81.5	< 0.001*	6.34	3.18-12.65
CRI-I	70.0	15.5	< 0.001*	12.76	8.64-18.85
CRI-II	59.7	13.6	< 0.001*	9.36	6.32-13.86
AC	92.4	44.2	< 0.001*	15.35	9.44-24.95
NHC	53.4	11.8	< 0.001*	8.56	5.70-12.85

*P < 0.050 was considered as statistically significant.
AIP: Atherogenic index of plasma; CRI: Castelli Risk Index; AC: Atherogenic coefficient; NHC: Non-high density lipoprotein cholesterol; OR: Odds ratio; CI: Confidence interval

Table 4. Adjusted odds ratio using logistic regression

Parameter	Adjusted odds ratio	CI
CRI-I	6.470	12.52-16.58
AC	5.191	2.87-9.37
NHC	1.912	1.11-3.28

CRI: Castelli Risk Index; AC: Atherogenic coefficient; NHC: Non-high density lipoprotein cholesterol; CI: Confidence interval

Calculations of various lipid ratios and indices may show the existence of association if any. These indices include AIP, CRI, AC, and NHC.

In this study, stroke was found to be more prevalent among men (69%) compared to women, which is consistent with many previous studies in which males have 25-30% higher risk of developing stroke.[10] 61% of stroke patients had hypertension and 38% were diabetics 28% were both diabetic and hypertensives.

Based on ATP III guidelines, 91% of stroke patients (n = 265) had alterations in one or more lipid parameters. All the parameters of lipid profile were significantly higher in cases when compared to controls. Our findings were inconsistent with studies by Shahar, et al.[11] and Bowman, et al.[12] which reported the lack of association between lipids and stroke.

Lipid indices have been associated with increased cardiovascular risk in many previous studies.[4-6] A very few studies have commented on the status of lipid indices in stroke patients.[13,14] In the present study, the lipid indices were significantly higher in stroke patients than the control group. With inconsistent lipid profile parameters between stroke patients and control subjects, the lipid indices show a significant increase in stroke patients compared to controls. Even if lipid profile fails to show any risk, calculation of lipid indices will help to show the true risk existing between lipid abnormality and stroke development.

Study participants were categorized using cutoff levels for the various atherogenic indices. It was found that stroke cases had statistically significant individuals in the high-risk group as shown in table 3.

Logistic regression analysis (Table 4) was performed and three indices, namely, CRI-I, AC, and NHC were found to be contributing to the risk of stroke significantly.

CRI-I was also a significant risk factor for stroke development which is similar to the study by Zhang, et al.[15] which showed a positive association of CRI-I with the risks of total and ischemic stroke in both men and women. AC is a measure of cholesterol in LDL and very LDL fractions with respect to HDL. As AC value increases, the risk for developing cardiovascular diseases increase and vice versa. This study shows that higher levels of AC are a significant risk factor for stroke development. NHC was found to be a significant risk factor for the development of stroke (odds ratio-1.912). This finding was consistent with the study by Wu, et al.[16] which stated that higher serum NHC is associated with increased risk for stroke independent of other potential confounding factors.

Further this study also assessed the severity of stroke patients by analyzing the duration of hospital stay. Pearson's correlational analysis revealed that there was no statistically significant correlation between the duration of hospital stay and lipid indices or individual parameters of lipid profile. Patil and Raghuwanshi[17] concluded that since all lipid parameters showed a considerable decrease on 7th day, as the stroke severity decreased, it could be proportionally linked with the severity of stroke. However, there are no previous studies which show an association between the lipid indices and severity of stroke.

Hence, this study shows that lipid indices may help in assessing the risk of stroke if not the severity of the same. This study may also help guide future trials attempting to relate lipid alterations with the occurrence of stroke events.

Conclusion

In the present study, the atherogenic lipid indices

were significantly higher in stroke patients compared to controls. Three indices, namely, CRI-I, AC, and NHC were found to be contributing to the risk of stroke significantly. These can be easily estimated from routinely done parameters and is therefore a cheaper alternative to other costly diagnostic tests and modalities. The inclusion of these indices in routine clinical setup may help to identify at risk individuals and guide effective treatment modalities in stroke patients.

Limitations and Recommendation

The study did not include the other comorbid conditions that are associated with stroke. Prospective studies can be undertaken to assess the various complications associated with stroke and its association with the various lipid indices.

Conflict of Interests

The authors declare no conflict of interest in this study.

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None.

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Review Article

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S100 B: A new concept in neurocritical care

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Biologic Marker; Surrogate Marker; Serum Marker; S100B Protein; Progressive Patient Care

Abstract
After brain injuries, concentrations of some brain markers such as S100B protein in serum and cerebrospinal fluid (CSF) are correlated with the severity and outcome of brain damage. To perform an updated review of S100B roles in human neurocritical care domain, an electronic literature search was carried among articles published in English prior to March 2017. They were retrieved from PubMed, Scopus, EMBSCO, CINAHL, ISC and the Cochrane Library using keywords including "brain", "neurobiochemical marker", "neurocritical care", and "S100B protein". The integrative review included 48 studies until March 2017. S100B protein can be considered as a marker for blood brain barrier damage. The marker has an important role in the development and recovery of normal central nervous system (CNS) after injury. In addition to extra cerebral sources of S100B, the marker is principally built in the astroglial and Schwann cells. The neurobiochemical marker, S100B, has a pathognomonic role in the diagnosis of a broad spectrum of brain damage including traumatic brain injury (TBI), brain tumor, and stroke. Moreover, a potential predicting role for the neurobiochemical marker has been presumed in the efficiency of brain damage treatment and prognosis. However further animal and human studies are required before widespread routine clinical introduction of S100 protein.

Introduction

In the recent past decades, various elements have been recommended as practical biochemical indicators of brain injury, including myelin basic protein, adenylate kinase, lactate, creatinine phosphokinase isoenzyme BB, S100B, neuron specific enolase, and glial fibrillary acidic protein (GFAP).[1] Biochemical markers have been incrementally identified as potential accurate diagnostic tools. In theory, a biomarker should be accurate and accessible and have specific properties such as suitable predicting variables including high sensitivity, specificity, positive predicting value, positive likelihood ratio, area under the care, and low negative predictive value

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and negative likelihood ratio.[2,3] Moreover, reproducibility and cost-effectiveness of analytical methods are other important properties.[3] Recently, clinical use of bioneurocritical markers like S100 proteins has been evaluated and extensively increased. Researchers believed that astrocytes cultivate the calcium-binding peptide, which conducts an autocrine and paracrine effect on glial cells and neurons. The increased levels of S100B peptide can be detected in a variety of clinical or pathological injuries to the central nervous system (CNS).[4,5] Due to the non-availability of various imaging techniques as gold-standard diagnostic tools and the need for immediate medical intervention to prevent permanent brain damage and disability, it seems plausible to seek alternative available methods. For this purpose, biomarkers can play a prominent role in a neurocritical care setting. The succinct review is an updated explanation of the role of S100B in human neurocritical care domain.

Search Strategy

To perform an updated review on role of S100B in human neurocritical care domain, we carried an electronic literature search among articles published in English prior to March 2017. Articles were retrieved from PubMed, Scopus, EMBSCO, CINAHL, ISC and the Cochrane Library using keywords including "brain", "neurobiochemical marker", "neurocritical care", and "s100b protein". The integrative review included 48 studies until March 2017 that are presented and discussed as follow.

Structure and functions of S100B protein: The Biologic marker, S100 protein, belongs to the family of Ca^{2+} binding proteins from chromosome 21.[6] The protein can help to regulate intracellular levels of calcium.[7] Moore and colleagues were the first to name S100 as a protein in 1965, based on the characteristic of protein which is 100% solubility in a saturated solution with ammonium sulphate.[4] Subsequently, two related homodimeric proteins S100A1 and S100B were identified.[7] The former (consists of two α subunits) is mainly detected in kidney, neurons to muscle, and other organs. The second (consists of two β subunits), is rare and is found in neural glial cells and Schwann cells.

Nowadays, S100B protein has broad spectrum as minimally 25 biomarker proteins have been recognized that had similar structure to this protein.[4] Together with other proteins of S100 family, S100B is located in the cytoplasm and nucleus of the astrocytes and conducts regulatory function of cytoskeletal structure and cell proliferation. Although it is significantly built in Schwann cells and astrocytes, the protein has been detected in other tissues such as bone marrow cells, chondrocytes, lymphocytes, adipocytes, and melanocytes. The protein is eliminated via renal excretion.[8]

S100B has been suggested to play a part in a variety of cellular processes, primarily via binding to key synaptic proteins and inhibiting their phosphorylation.[9] The extracellular form of S100B is physiologically involved in the development and maintenance of CNS homeostasis.[3] This form is synthesized and secreted by astrocytes.[10,11] The mechanisms of regulating S100B secretion are not completely understood and appear to be related to different factors[12,13] including interleukin β, the proinflammatory cytokines, metabolic stress,[14] and tumor necrosis factor alpha α1.[15] Furthermore, a previous research suggested that S100B secretion involves the MAPK pathway and seemingly could involve NF-kB signaling.[13] Within cells, it has several roles such as Ca_2^+ homeostasis, protein phosphorylation, and regulation of cell proliferation, transcription, differentiation, enzyme activity, and metabolism. When secreted into the extracellular medium, S100B exerts regulatory effects on neighboring cells i.e., astrocytes, neurons, and microglia.[10]

S100B effects are closely dependent on its levels. At nanomolar concentrations and in vitro, it can enhance survival of neurons in various systems during development, and stimulate neurite outgrowth in cerebral cortex neurons.[16] In vitro neurotrophic activity of S100B has been ascertained for neuronal cells in two points including the neuronal maturation and glial cell proliferation.[17] Decreasing the loss of mitochondrial function and cell death are other effects of S100B.[16,18]

The roles of the protein in CNS development and recovery after injury are related to the neurotrophic and gliotrophic actions. Extracellular micromolar levels of S100B may have toxic effects.[19] The protein at micromolar levels in vitro induces apoptosis and stimulates the expression of proinflammatory cytokines. The neurotoxic effects of S100B in vitro is mediated by induction of apoptosis in neurons.[19] Astrocytes release nitric oxide that cause neuronal death in high levels of S100B.[16] To the best of the

knowledge, the mechanism of the effects may begin in two ways: by inducing raised levels of intracellular calcium and activating caspase-3 and by activation of inducible nitric oxide syntheses.[20-24] Besides the mentioned mechanisms, the receptor for advanced glycation end products (RAGE) pathways mechanism is also submitted.[22-26] RAGE, a member of the immunoglobulin super family, can be bound by several ligands such as S100B. It is assumed that RAGE-mediated nuclear factor β activation can be responsible for the toxic (at high levels) and the pro-survival (at low levels) effect of S100B.[26,27] S100B can also up regulate neuronal RAGE expression.[28,29] S100B has short biological half-life (approximately 30-minute). However sustained high levels of S100B can be due to uninterrupted release from influenced and injured tissues.[30,31] S100B has highest level in milk, cerebrospinal fluid (CSF), and serum. In addition, the protein can be detected and found in other fluids including amniotic fluid, urine, and in cord blood.[32] Serum and CSF levels of S100B can be considered as a marker in postmortem and clinical investigations in brain damage field.[33]

S100B: A suitable CNS diseases marker

Traumatic brain injury (TBI): Recently, S100B measurement in suffering patients from TBI has been interested among researchers because high levels of S100B in CSF and serum has been considered as marker of cell damage in human CNS after TBI.[34] A review of the literature showed that there is a positive correlation between S100 parameters and intracranial pressure and cranial computed tomography (CT) findings.[35] For example, diagnosis of head trauma related lesions on CT scan with knowing the level of S100B with a cut-off of 0.1 µg/l is possible and the S100B level can be helpful in this clinical scenario (99% sensitivity and 30% specificity). Furthermore, knowing the level of S100B in clinical diagnostic protocol in minor head injury in accordance with cranial CT scan can decrease scanning by up to 30%.[36]

In severe TBI, S100B levels more than 1.13 ng/ml were correlated with high mortality (100% sensitivity and 41% specificity).[37] In this regard, it was concluded that serum S100B demonstrates the severity of injury and improves the prediction of outcome after severe TBI.[9] It is expressed that S100B level few hours post mild TBI is a suitable predictor for post-concussion syndrome in later times. A study showed that early S100B levels in 3 and 6 hours post mild TBI can possibly be informative in predicting some events about the outcome,[34] because there was a positive correlation between the pathological findings of CT and high levels of S100B.[38]

In predicting the treatment efficacy post severe TBI, the evidence suggested that S100B protein is a sensitive biomarker.[39] The biomarker plays a significant role in early predicting the development of intracranial pressure and mortality after acute brain injury. Furthermore, it is possible to identify secondary intracranial pressure increase with monitoring the S100B levels in risky patients and ultimately, to prevent from succeeding fatal outcome. The main goal of monitoring can optimize treatment protocol.[19]

Although according to the literature S100B level is not an FDA approved tool for clinical use, in mild TBI patients without significant extra-cranial injuries, S100B level less than 0.1 µg/l in four hours post injury may replace CT.[40] In Scandinavia, serum S100B levels of 0.1 µg/l within six hours post injury in accordance with Glasgow Coma Scale score of 14-15 in patients without known risk factors were applied in the initial management of minimal, mild, and moderate head injuries. The patients can be discharged from the hospital without performing CT scan, although the level of evidence for management protocol is strong recommendation with moderate quality.[41]

Brain tumors

Elevated levels of S100B in neoplastic conditions such as astrocytomas have been spotted.[42] It is assumed that S100B can monitor progression of cancer through inhibiting the function of tumor suppressor gene p53 with calcium dependent pathway.[43] For meningeal tumors, the involvement of S100B has been explored in two reports. The first report investigated serum S100B levels of 50 meningioma patients preoperatively and post-craniotomy for 7 serial days.[44] Results showed that augmented S100B had high correlation with larger tumors, intraoperative difficulties, post-craniotomy acute degradation and long-term poor outcome. In addition, higher levels of S100B in postoperative period were associated with higher deterioration risk concurrent with poorer outcome. Moreover, the hypothesis that S100B levels can be used as an early biomarker in post-craniotomy brain damage

in meningioma patients was verified.[45]

Stranjalis, et al. evaluated the connection between serial serum S100B protein measurements and post-craniotomy clinical worsening in patients with meningioma surgery.[44] S100B serum condensation in patients diagnosed with glioma have been surveyed in some studies.[46,47] Gartner, et al.[48] showed elevated plasma levels of S100B in the peripheral blood of two of three patients, at 11 and 13 months prior to the detection of a malignant glioma. Vos, et al.[49] indicated notably shorter survival in patients with high serum S100B levels, and proposed that serum S100B protein may be predictive in variable cerebral gliomas. In addition, serum S100B levels are utilized for the early detection of recurrence of tumor or metastases.[30]

Stroke

Serum S100B levels have been extensively studied as a biomarker in acute ischemic stroke. In fact, the score of admission National Institute of Health Stroke Scale[50] and total infarct volume[51] had a positive correlation with S100B levels. Although the S100B levels in CSF are forty folds higher than serum, serum S100B level has been ascertained to significantly rise following ischemic stroke from 10 hours to 2-3 days from onset of stroke.[52] In addition to the increasing S100B profile, serum S100B levels are helpful in distinguishing between nonvascular vertigo and posterior circulation strokes. The declaration was approved by two prospective observational studies that showed serum S100B levels in posterior circulation stroke were remarkably high.[53,54] Detecting stroke in vertigo patients by serum S100B had excellent sensitivity (94.4%) and partially poor specificity (31.8%).[54] One study reported that patients with transient ischemic attack or normal CT brain imaging at onset had notably lower serum S100B levels, with little alteration over time, compared to patients with an appreciable neurological deficit and abnormal brain imaging at the onset.[51] Usually, the peak levels of serum S100B are during the first 3-4 day succeeding acute ischemic stroke[55] but single serum S100B level in 48 and 72 hours following stroke attack can provide suitable prediction of infarct volume and functional outcome in non-lacunar middle cerebral artery infarction.[56]

The importance of considering serum S100B over time is reflected in the published results with different validities. A 12-hours serum S100B level more than 0.35 ug/l could predict the malignant infarction with good sensitivity and specificity (75% and 80%, respectively) while a 24-hours serum S100B level more than 1.03 ug/l could predict the event with higher sensitivity and specificity (94% and 83%, respectively).[57] Several studies have shown that serum S100B levels measured in samples taken more than 24 h after stroke onset had a strong correlation with the degree of neurological deficit and the final infarct volume. Some clinical pearls can be concluded from raised levels of serum S100B after acute spontaneous intracranial hemorrhage that are "worse early", "later evolution", and "strict correlation with initial hematoma volume".[58] After ischemic and hemorrhagic strokes, S100B protein is released into the blood. There is good association between the release pattern of S100B and volume of vascular lesion. S100B protein is a sensitive biomarker of brain injury following stroke. It is probable to employ serum S100B level in monitoring treatment for stroke.[59] In stroke patients, there was a regular increase in S100B 1-3 days after the onset of symptoms followed by slowly decreasing values as already depicted by others.[60]

In subarachnoid hemorrhage (SAH), the serum S100B levels are helpful and can help clinicians to examine the hemorrhage severity because there is a strong positive correlation between serum S100B values and initial SAH severity.[61,62] The initial SAH severity has been studied by Fisher score in para clinical settings[63] and Federation of Neurological Surgeons grading scale in clinical settings.[64] It can be expressed that S100B levels in CSF and blood are excellent predictors of SAH outcomes in affected patients.[65,66] For example, daily mean value of S100B more than 0.4 µg/l have a remarkably poor prognosis.[67] S100B and GFAP following spontaneous SAH have strong positive correlation with neuroimaging and clinical severity of the disease. The clinicians can use the correlation in better initial and late assessments,[45] and even to determine the outcome.[65] Higher levels of S100B in SAH patients is concurrent with indeterminate prognosis and inadequate outcome.[11]

S100B has a broad spectrum of clinical and paraclinical use in SAH, cerebral infarction, and intracranial hypertension. However, vasospasm as SAH secondary complications can be diagnosed or predicted by neither serum nor CSF

S100B level.[68]

Conclusion

New biomarkers of CSF and serum have been evaluated to improve diagnosis and predict outcome more accurately. Among them the S100B protein is a suitable CNS neurobiochemical candidate for diagnostic, prognostic, and even therapeutic purposes. However, there are risk of false positive and false negative laboratory errors and should be used with caution. Further animal and human studies are required before widespread routine clinical introduction of S100 protein.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Review Article

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Prevalence of familial multiple sclerosis in Iran: A systematic review and meta-analysis

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Keywords
Familial; Multiple Sclerosis; Meta-Analysis; Prevalence; Iran

Abstract

Background: Familial history of multiple sclerosis (MS) has been considered as one of the etiologic factors of MS by several studies. It is valuable to combine the results of these studies. The aim of this study is to estimate the pooled prevalence of familial MS in Iran using meta-analysis.

Methods: Using relevant keywords, national and international databanks were searched. Considering the significant heterogeneity between the results, random effect model was utilized to estimate the pooled prevalence of familial MS using Stata software.

Results: After screening the selected articles, 15 studies with total sample size of 6248 (from 60 to 1718) were identified eligible for final meta-analysis. Overall prevalence of familial MS in Iran was estimated as of 11.4% [95% confidence interval (CI): 8.7-14.1]. Point prevalence varied between 3.3% and 26.7%.

Conclusion: Our study showed that the familial prevalence of MS among Iranian people is relatively high. More studies are warranted to investigate the effect of familial history as a risk factor for MS.

Introduction

Multiple sclerosis (MS) is an inflammatory disease which is characterized by multifocal inflammation, demyelination, gliosis, and neuronal loss of the brain and spinal cord.

In the United States, 400000 people are affected by MS and this inflammatory disease affects 2.5 million individuals worldwide, the prevalence of MS varying greatly with geography.[1] It is hypothesized that MS is a complex and multifactorial disease and is believed several environmental factors and genetic risk factors, as well as their interaction, are the causes of disease.[2,3] Some of nongentical risk factors of MS are included lack of sunlight exposure (mediating vitamin D synthesis), exposure to infectious agents, smoking, immunization, hormonal factors, nutritional habits, and psychological stress.[3] Inheritance of MS does not follow Mendelian

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model. Multiple independent or interacting polymorphism genes with small or moderate effect have role in etiology of MS.[4]

Regardless of sporadic occurrence of MS, a considerable proportion of patients (almost 20%) are related by family.[5] The greater recurrence risk of MS in twins, sibling, conjugal MS individuals, and lower recurrence risk in adoptees has clearly demonstrated an important role of genetic factors in etiology of disease and familial aggregation of disease.[6-8] It also strongly supports that MS susceptibility is polygenic.[9]

It is well known that MS accumulate within families. The degree of the familial risk[5] and its difference in various geographic remain uncertain.[10]

Although in 15 years ago Iran was considered to be located in a low-frequency zone of MS (prevalence rate fewer than 5 per 100000),[11] recent epidemiological studies reported the different prevalence of MS in different provinces in Iran. Its prevalence ranged from 7.4 to 89 per 100000 with an average prevalence and incidence of 54.51 and 5.87 per 100000 people, respectively (Isfahan[12] and Mazandaran).[12-14] Despite the partially high prevalence of MS in Iran to our knowledge, there is no systematic review regarding the prevalence of familial MS in Iran. The aim of this study was identifying the prevalence of familial MS using a systematic approach.

Materials and Methods

We searched electronic papers published from 2000 to 30 August 2015. The search was conducted using international databanks including Web of Sciences, PubMed, Google Scholar, and Scopus. National databanks such as SID, Iranmedex, Magiran, and Irandoc were investigated with appropriate keywords. The following keywords and their Farsi equivalents were applied for electronic search: "Multiple sclerosis or MS AND familial (OR family) AND prevalence, prevalence, frequency, familial, Iran, epidemiology."

Two independent researchers conducted the search during 1-15 September 2015. They also investigated all references of the articles to increase the search sensitivity. A third researcher randomly evaluated the results to identify any probable ignored article. Moreover, none electronic papers were investigated by the research team. To find relevant gray literatures, the experts of some research centers were interviewed.

We extracted full texts or abstracts of all articles identified during the primary search. Then, duplicates were excluded from the study. Finally, none relevant studies (by reviewing the titles, abstracts, and full texts, respectively) were removed. To minimize re-print bias, we had to investigate the results of each study and omit repeated articles.

Selected papers were quality assessed using a previously applied checklist.[13] The quality of studies was assessed using checklist designed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) contents[14] which included 22 questions about regarding different aspects such as sample size and sampling methods, study design and study population, methods and instruments for data collection, variable definition, statistical methods, study objectives and illustration of the results. Each study was assigned a score from 0 to 44 then all studies were categorized into low quality, moderate quality, and high quality. We excluded studies with low quality from the final analysis.[14]

Title, first author name, date of study conduction, type of the study, sample size and sampling methodology, language of the article and prevalence of familial MS were extracted from each study. The information was entered into the Excel spreadsheet.

All Persian and English-written papers reporting sample size and prevalence of familial MS and achieved enough quality scores were included in the meta-analysis.

Studies did not report the familial MS prevalence, those with unknown sample size, abstracts presented in congresses without full text, case reports, and case–control studies as well as clinical trials and finally, studies with low-quality scores were excluded from the meta-analysis.

Stata SE (version 11, Stata Corporation, College Station, TX, USA) software was utilized for statistical analysis. The standard error of the MS prevalence was estimated based on binomial distribution formula. According to the amounts of the heterogeneity indices [Cochrane (Q) test and I-square index)] fixed or random effect models were applied to combine the prevalence. In addition, studies with the most influence on the heterogeneity were determined using sensitivity analysis. Factors associated with the heterogeneity were investigated using meta-regression models. We also illustrated the point and pooled prevalence of MS by forest plots. The weight of each study was shown by the sizes of the boxes and bilateral lines indicating the 95% confidence interval (CI) of the prevalence.

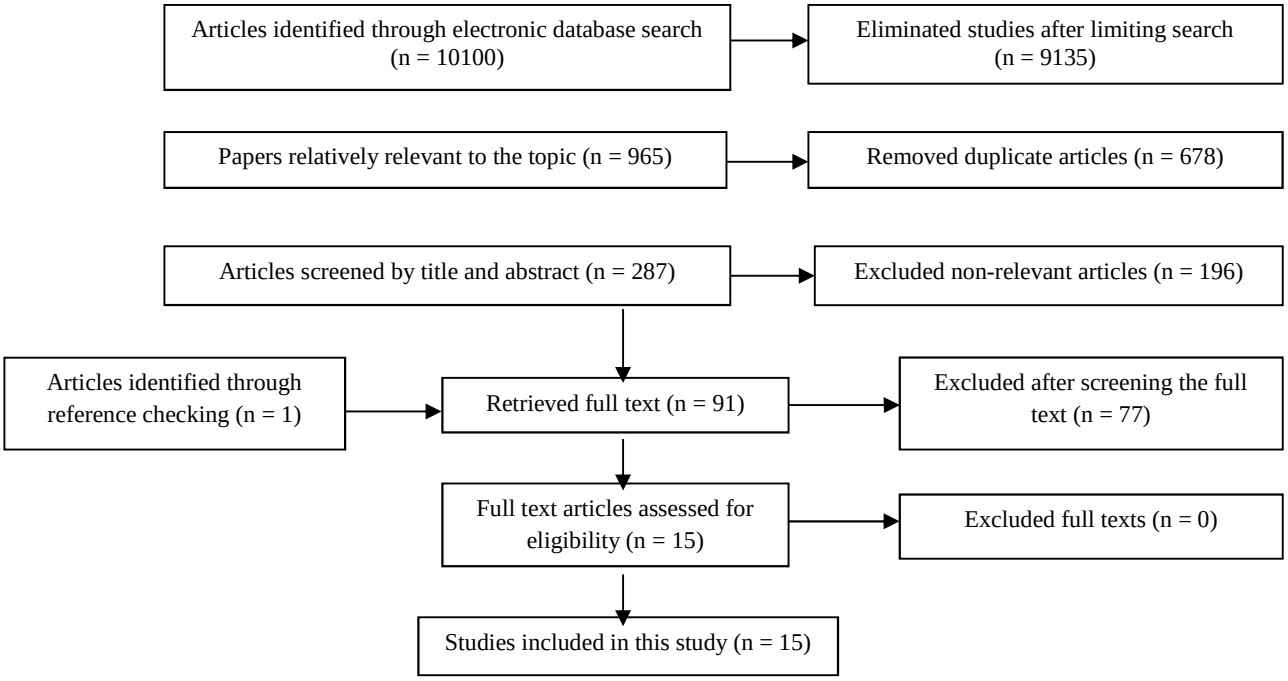

Figure 1. Literature search and review flowchart for selection of primary studies

Results

The primary search identified 10100 articles which were reduced to 287 studies after restricting the search strategy as well as duplicates exclusion. Reviewing titles and abstracts revealed 196 irrelevant papers. Investigating the full texts showed 77 none eligible studies and reference review added one relevant study to the results. Finally, 15 articles were entered into the meta-analysis (Figure 1).

Studies had been published from 2003 to 2015 and written in Persian (six studies) and English (eight studies). Results of an unpublished study were received from the authors. These studies were conducted in different provinces such as Isfahan (two papers), Tehran (four papers), Razavi Khorasan (one paper), East Azerbaijan (one paper), Kermanshah (one paper), Hamadan (two papers), Zanjan (one paper), Qom (one paper), Mazandaran (one paper), and multiple provinces (one paper). In total, these studies had been conducted among 6248 individuals differed from 60 to 1718 (Table 1).

Table 1. Characteristics of the primary studies included to this meta-analysis

References	Local study	Publication language	Publication year	Sample size	Prevalence
Ashtari, et al.[15]	Isfahan	Persian	2011	593	20.1
Baghizadeh, et al.[16]	Tehran	English	2013	338	13.6
Danesh-Sani, et al.[17]	Khorasan-Razavi	English	2013	500	15.4
Ghabaae, et al.[18]	Tehran	English	2007	70	8.6
Hashemilar, et al.[11]	East Azarbaijan	English	2011	1000	7.1
Mazaheri, et al.[19]	Hamadan	Persian	2007	155	12.9
Payamani and Miri[20]	Tehran	Persian	2011	200	13.0
Pourmemari, et al.[21]	Zanjan	Persian	2011	96	7.3
Rezaali, et al.[22]	Qom	English	2013	592	11.2
Rezaie and Panahi[23]	Hamadan	Persian	2005	60	26.7
Saadatnia, et al.[24]	Isfahan	English	2007	1718	12.2
Taraghi, et al.[25]	Mazandaran	Persian	2007	101	7.0
Kalanie, et al.[26]	Tehran	English	2003	200	5.0
Nasehi, et al.[27]	Some province	English	2015	177	16.4
Saman-Nezhad, et al.[28]	Kermanshah	English	2013	448	3.3

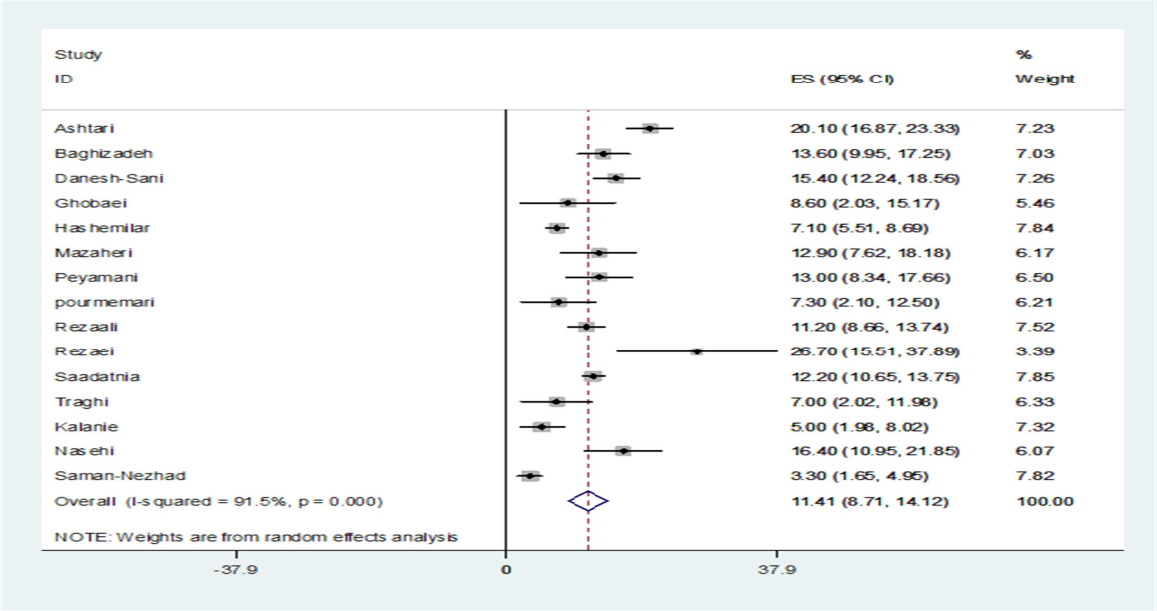

Figure 2. The prevalence of familial multiple sclerosis (MS) in among primary studies and prevalence of pooled estimate in Iran

The prevalence of familial MS was reported as 3.3% in Saman-Nezhad, et al. study, among 448 persons in Kermanshah[28] to 26.7% in Rezaie and Panahi study, among 60 citizens in Qom[23] (Table 1). Significant heterogeneity was observed between the results of the primary studies (Q = 165.02, I^2: 91.5%, P < 0.001). Therefore, random effect model was used to combine the results. The total prevalence of familial MS among Iranian people was estimated as of 11.4% (95% CI: 8.7-14.1) (Figure 2).

According to the meta-regression models, geographical area was not associated with MS prevalence (β = 0.02; P = 0.900). We did not conduct subgroup analysis based on the geographical areas due to the low number of the studies.

During the primary and secondary steps of the sensitivity analysis, Saman-Nezhad, et al.[28] and Hashemilar, et al.[11] studies were found as studies with extreme results. Although excluding these studies from the meta-analysis changed the I^2 (86.7% and 82.2% respectively), the heterogeneity was still remained.

Discussion

Results of our study showed the prevalence of familial MS was in the range of 3.3-26.7%, and the pooled prevalence was estimated about 11.0% for Iran.

Nielsen, et al.[5] utilized a nationwide registry data and reported that risk of MS in families with a positive history of MS was 7 times more than normal population (relative risk = 7.1, 95% CI: 5.8-8.8). They also reported that first-degree relatives had 2.5% (95% CI: 2.0-3.2) excess risk irrespective of their gender and the relative. Carton, et al.[8] also reported 10-fold to 12 increased risk of MS for first degree, 3-fold for the second degree relatives increase risk for the risk for the first degree in their population (674 probands with MS in Flanders).

In a study in Jordan, the prevalence of family history of MS reported in 9.4% of the patients.[29]

In study that was carried out by Fricska-Nagy, et al. in Hungry, the familial prevalence of MS are estimated between 5% and 10%.[30]

In favor of our study results, the finding of population-base cohort study showed that prevalence of MS among first-degree and non-biological relatives of patients with MS was not more than general population but it was significantly less than biological relatives. These findings indicate the role of genetics factors in familial aggregation of MS. They did not detect any effect of shared environment was detectable.[9] These findings demonstrate the familial clustering of the disease. Studies have shown factors influencing onset age also increase recurrence risk in patients' siblings. This can support the opinion that individuals with a greater genetically influenced susceptibility to MS tend to have an earlier onset, which means genes influencing

susceptibility also contribute to determining precocious disease.[6]

Most etiologic studies focused mainly on the environmental factors and rarely investigated the genetic causes. Some researchers believe that environmental factors provide background of the disease, while genetic factors exacerbate the environmental effects. Risk of developing MS is increased more than 2-4% among first-degree relatives. The corresponding risk for other family members was 0.1%. Another study conducted in 2007 rejected the monogenic cause of MS and reported that two genes are responsible for developing the disease.[7,31]

The above results show the stronger association of the genetic factors with MS. Our meta-analysis provided descriptive evidence regarding MS prevalence. However, analytic studies are required to prove the causal inference.

Unfortunately, we could not estimate the pooled prevalence based on different genders and geographical areas because of inadequate relevant studies. Considerable heterogeneities between the results of the primary studies was another limitation of the current study. Geographical area might be one of the related factors for this heterogeneity which was not investigated due to lack of enough information.

Conclusion

Our findings showed that familial prevalence of MS among Iranian people is relatively high. Further studies are suggested to investigate the effect of familial history as a risk factor for MS. This finding support the involvement of genetic factors in the etiology of MS and consulting with geneticist for individuals with a positive history of MS must take into account.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Letter to Editor

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The unexpected finding of a hemangioblastoma on the cerebellum of a patient undergoing treatment with natalizumab for multiple sclerosis

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Keywords
Multiple Sclerosis; Natalizumab; Brain Neoplasms

Natalizumab, a humanized recombinant monoclonal antibody used for the treatment of multiple sclerosis (MS), affects the flow of lymphocytes into the central nervous system (CNS). The drug binds to the alpha-4 chain of the alpha-4-beta-1 integrin (very late activation antigen 4 or VLA-4) and alpha-4-beta-7 integrin. Natalizumab decreases the numbers of CD4+ and CD8+ T lymphocytes, CD19+ B cells and CD138+ plasma cells in the cerebrospinal fluid of patients with MS receiving this therapy.[1] Thus, at least in theory, this mechanism of action could compromise the immune surveillance within the CNS[2] and favor the growth of tumors. There have been reports on primary central nervous system lymphoma in patients undergoing treatment with natalizumab,[3-5] but the association between these two findings has been deemed unlikely by some.[6]

We want to report a case of hemangioblastoma of the cerebellum in a patient undergoing treatment with natalizumab. The present report was approved by the Ethics Committee at Universidade Metropolitana de Santos and the patient gave consent to its publication, provided confidentiality was guaranteed. Disability is described using the expanded disability scale score (EDSS).[7]

The patient was a woman who is now aged 38 years, with MS diagnosed when she was 28 years old. She was initially prescribed glatiramer acetate, which provided adequate disease control for two years (EDSS: zero). Feeling much better, the patient interrupted her treatment and follow-up for one year, but returned at the age of 31 years presenting acute disease relapse. She was treated with pulses of corticosteroids, but disease control with glatiramer acetate or interferon beta was not achieved. She progressed with relapses and accumulation of disability, presenting tetraparesis, ataxia, severe gait

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limitations, dysphonia and dysarthria, nystagmus, cognitive dysfunction, and fatigue. Her magnetic resonance imaging (MRI) showed high lesion burden and acute demyelination. The patient started treatment with natalizumab at the age of 34 years and complete control of relapses and lesions, as seen on MRI, was achieved without further accumulation of disability (EDSS: 5.5) over the course of 44 monthly infusions of the drug, and did not show any new neurological signs or symptoms. A cystic formation was then detected in the cerebellum on her yearly routine MRI (Figure 1). Total surgical resection 90 days ago (April 2016) confirmed the diagnosis of hemangioblastoma (Figure 1).

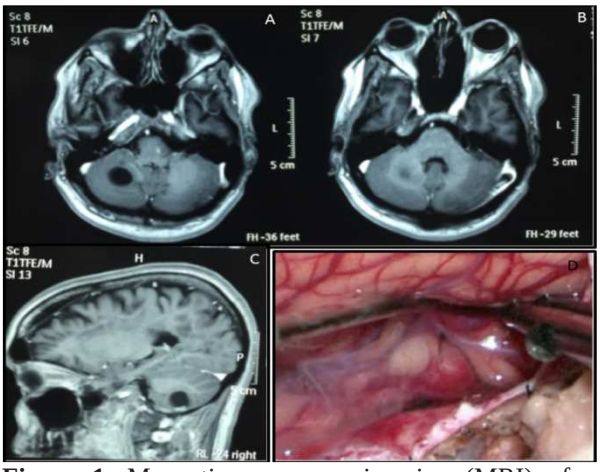

Figure 1. Magnetic resonance imaging (MRI) of a cystic formation on the cerebellum (A, B and C); detail of surgical resection of the tumor (D), later confirmed to be an hemangioblastoma

The patient has been stable since surgery, without further disability, and natalizumab has been withdrawn. There is a previous report of a patient with MS presenting von Hippel-Lindau syndrome.[8] This condition leading to cystic tumors was investigated and excluded in the patient reported here.[9]

Although no causal relationship can be established between use of natalizumab and this finding of hemangioblastoma, these are rare tumors. The finding may have been purely coincidental, but the purpose of the present report was to contribute further on the discussion of a potential association between insufficient immune surveillance and brain tumors.

Disclosure: The authors have no conflicts of interest to declare. Pharmacovigilance at Biogen Idec has been informed of the adverse event.

Conflict of Interests

The authors declare no conflict of interest in this study.

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None.

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Letter to Editor

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Oculopharyngeal muscular dystrophy misdiagnosed as myasthenia gravis: Case report and review of literature

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Keywords
Ptosis; Oculopharyngeal Muscular Dystrophy; Myasthenia Gravis; Diagnosis

Oculopharyngeal muscular dystrophy (OPMD) is an adult-onset disease with eyelid ptosis, progressive dysphagia, and proximal limb weakness. Despite recent advances in understanding of its molecular basis, it seems that OPMD remains under diagnosed or delayed in diagnosis.[1] This could be due to slow progression of this disease, low prevalence of 1:100000[2] or low attention of neurologists that may diagnose and treat the disease as other neuromuscular disorders. Herein, we present a case of genetically approved OPMD in which the patient underwent unnecessary therapeutic intervention due to misdiagnosis of myasthenia gravis (MG) and then in regard to this case, explain some clinical clues to make the appropriate diagnosis.

A 55-years-old man known case of MG from eight years ago was referred to us for plasmapheresis due to progressive difficulty in swallowing. He had history of ptosis for the last eight years with no complain of diplopia. His dysphagia had been begun since three years ago. Thymectomy was performed for him three years ago via thoracotomy with normal thymus pathology. He denied any positive family history of similar disease. His medications contained mestinon, azathioprine 150 mg and prednisolone 15 mg/day for the last 6 years. His neurologic exam revealed bilateral moderate to severe ptosis, bifacial paralyses, and ophthalmoplegia on both eyes. Neck flexion and extension were 4/5. Motor strength had decreased in proximal of lower limbs (4/5). Previous laboratory evaluations consisted of a negative serum acetylcholine receptor antibody (< 0.1 nmol/l) and low frequency repetitive nerve stimulation (RNS) with 10% decrement on trapezius muscle. Creatine phosphokinase (CPK) was normal. Electrophysiological studies were repeated that showed chronic myopathic process and 3-Hz RNS revealed no reproducible decremental response. Regarding the patient's clinical history and disease course, we discouraged him for plasmapheresis and set an appointment where his

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sister and parents were present. We observed bilateral ptosis and bulbar speech in his 45-year-old sister and their mother. Molecular genetic analysis was performed. The poly-(A) binding protein nuclear-1 (PABPN1) DNA fragment flanking the (GCG)n(GCA)n repeat was amplified and a mutated allele (GCG)6(GCA)(GCG)4(GCA)3GCG was identified as compared to (GCG)6(GCA)3GCG in healthy subjects of PABPN1 gene.

OPMD is a degenerative, predominantly autosomal dominant disorder. The disease is characterized by a mutation in PABPN1 gene, resulting in a short GCG expansion in the polyalanine tract of PABPN1 protein.[1] Its clinical features may have many similarities with MG. Both of them characterize with ptosis, extraocular muscle weakness, dysphagia, and limb weakness. The distribution of the affected muscles in OPMD largely overlaps with the muscles involved in MG and muscle biopsy may be non-specific.[3] Moreover, fluctuating course in OPMD simulating MG is also reported.[3] We described a genetically confirmed case of OPMD who was managed as a seronegative MG for ten years. He had been underwent a major thoracic surgery (thymectomy) and received immunosuppressive agents for long years. Regarding these unnecessary interventions, several points should be considered in clinical practice when dealing with the patients complaining of ptosis, ophthalmoparesis, and dysphagia. First, attention to the patient's clinical history is the main key of correct diagnosis. Fatigability and diurnal fluctuations is hall mark of MG versus insidious and slow progression in OPMD. Second, positive family history of patients with OPMD may be overlooked due to slowly progressive nature of the disease as in our patient. In a study of 14 patients with OPMD only six patients could report a family history of ptosis.[1] Thus, visiting patient's family members or their photos could be helpful.

The next important point is the limitations of laboratory studies and possible technical errors. Autoantibodies against the postsynaptic nicotinic acetylcholine receptor can be detected in the serum of 50% of patients with ocular MG. The low-frequency RNS test is of great value in the diagnosis of MG, but its sensitivity is low in ocular MG. In a study of patients with ptosis or ophthalmoparesis due to MG, RNS had sensitivity of 61%, specificity of 83%, positive predictive value of 79%, and negative predictive value of 68%.[4] Furthermore, the diagnostic yield of RNS in different muscles could be varied. Therefore, the results of these tests, especially in borderline circumstances should be interpreted with caution. The course of our patient suggests that when a suspected patient of MG is unresponsive to different therapeutic interventions, reevaluation of patient and considering other neuromuscular differential diagnosis are logical before considering patient as a refractory case. In addition, the possibility of addition of a secondary disorder should also be considered as occurrence of OPMD in a seropositive patient with MG was reported.[5]

In conclusion, OPMD may be a great mimicker of MG, but often neglected. Awareness would improve diagnosis and preclude unnecessary and sometimes harmful therapeutic interventions.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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Clinical Note

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Acute beriberi neuropathy mimicking Guillain-Barré syndrome after a strict vegetarian diet

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Keywords
Thiamin; Deficiency; Beriberi; Polyneuropathies; Guillain-Barré Syndrome; Diet; Vegetarian

Vitamin B1 (thiamin) is required in the metabolism of carbohydrates, lipids, proteins, and energetic metabolism within Krebs cycle. It has also an essential role in acetylcholine synthesis and neurotransmission.[1] Thiamin deficiency can lead to various manifestations such as Gayet-Wernicke syndrome, wet beriberi with congestive heart failure, or dry beriberi with peripheral neuropathy. We report herein a case of Guillain-Barré-like neuropathy caused by acute vitamin B1 deficiency in a young girl consecutive to a strict vegetarian diet.

A 14-year-old girl with unremarkable medical history has presented with numbness and weakness of lower limbs developing insidiously for a month. Two weeks before admission, weakness progressed to upper limbs and cramping pain in legs has appeared. The patient had difficulties at swallowing and she has become unable to walk 1 day before admission. In the preceding 3 months, the patient has undergone a strict diet made only of vegetables and yogurt to get thinner. Her weight has dropped from 66 to 42 kg. At examination, the girl was thin and pale and her voice was dysphonic. Her body mass index (BMI) was 15.24 kg/m². She was not able to walk without double help. Her muscular testing revealed distal-dominant weakness in her four limbs. Deep tendon reflexes were absent. She had also hypoesthesia in her legs. Cranial nerves examination noted a facial diparesis. Psychological interrogatory did not reveal any behavioral or alimentary disorder. Nerve conduction studies showed a severe sensory and motor neuropathy with axonal and demyelinating mechanism predominantly in lower limbs. It has revealed decreased motor potentials amplitude with conduction blocks, abnormal temporal dispersion of the motor responses, and the sensory potentials were not recordable (Table 1).

Cerebrospinal fluid analysis made on the day of admission revealed normal protein content (0.29 g/l) and no leukocytes. Thiamin plasma level was low: 13 ng/ml (normal range: 20-50 ng/ml). Concentration of vitamin B12 (cobalamin) and B9 (folic acid) were normal. Routine hematological and biochemical tests showed no abnormalities. Electrocardiogram was also normal. Intravenous

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Table 1. Nerve conduction study

Stimulation site	Median nerve					Tibial nerve			Sural nerve	
	Motor			Sensory		Motor			Sensory	
	MCV (m/s)	DL (ms)	CMAP (mV)	SCV (m/s)	SNAP (µV)	MCV (m/s)	DL (ms)	CMAP (mV)	SCV (m/s)	SNAP (µV)
Right										
Distal	61.7	8.0	4.0	NR	NR	70.0	8.5	1.5	NR	NR
Proximal			1.3					1.0		
Left										
Distal	51.4	9.3	3.0	NR	NR	63.8	7.8	2.8	NR	NR
Proximal			1.9					1.1		

CMAP: Compound muscle action potential; DL: Distal latency; MCV: Motor nerve conduction velocity; NR: Not recordable; SCV: Sensory nerve conduction velocity; SNAP: Sensory nerve action potential

(IV) thiamin supplementation was administered at 300 mg 2 times a day for 1 week, associated to multivitamin perfusion.

Daily physiotherapy, psychologist, and nutritionist consulting were also practiced. Subsequent follow-up showed slow but significant improvement. The girl was discharged after 2 weeks on intramuscular thiamin injections (300 mg bd) for four additional weeks; then, she was placed on oral thiamin tablets. One month later, she was able to walk by herself with dropping feet and she had no more dysphonia. Six months later on physiotherapy and balanced alimentation, her examination showed almost normal gait, normal deep tendon reflexes, and her BMI was 22.49 kg/m².

Thiamin deficiency results habitually from chronic alcoholism, hyperemesis gravidarum (HG), and gastric bypass or cancer surgeries.[1] Its prevalence is underestimated since symptoms are often latent and some conditions such as high carbohydrates intake or excessive physic activity can make it manifest.[1] Historical cases of dry beriberi were known since the 19th century in sailors after long sea voyages and poor diet. Nowadays, alimentary thiamin shortage is rare in the developed and in most of developing country. It may happen in cases of anorexia nervosa or after long-term parenteral alimentation without vitamin supplementation.[2,3] Our patient did not present personality disorder or distorted body self-perception indicating anorexia nervosa. Strict vegetarian diet without anorexia nervosa is an exceptional cause of vitamin B1 deficiency. In fact, the body stores in normal conditions 25-30 mg of thiamin, mostly in metabolically active organs such as the heart, kidneys, and brain. Due to its rapid turnover, thiamin stock is rapidly exhausted within 2-3 weeks in case of lack of alimentary supply.[1] In the gastrointestinal tract, thiamin absorption is an active mechanism and the mucosal transporters are situated mostly in the duodenum. Threshold of thiamin intestinal absorption is about 10 mg/day, and it decreases in case of malnutrition.[1] Thereby, oral thiamin supplementation is not effective in beriberi and Gayet-Wernicke syndrome.

Complications of thiamin deficiency can be life-threatening as in Gayet-Wernicke syndrome and in wet beriberi (also called Shoshin beriberi). They can also alter patient's functional outcome as in dry beriberi and in rare cases of optic neuritis. In beriberi neuropathy, nerve conduction studies show usually sensory predominant axonal neuropathy.[2-4] Motor symptoms are mostly latent and may be worsened by associated thiamin deficiency-induced myopathy. Acute beriberi neuropathy mimicking Guillain-Barré syndrome (GBS) is rare and must be considered face to person at risk of thiamin deficiency. Our patient's electromyography (EMG) showed some classical finding of GBS such as the presence of partial motor conduction blocks and abnormal temporal dispersion of motor responses.[5] Furthermore, the rapid evolution and the ascension from lower limbs to upper limbs then to face remind GBS natural course.

In the literature, similar cases of dry beriberi mimicking GBS are seldom reported.[3] Koike, et al. found that 7 out of 11 (64%) neuropathies due to thiamin deficiency in patients who had dietary imbalance show acute progression.[3] Nerve conduction study in the same paper revealed sensory and motor neuropathy more marked in the lower limbs and with mixed axonal and demyelinating mechanism.[3,5]

Thiamin plasma level can be assessed by high-performance liquid chromatography conveniently since the 1980's. Nevertheless, thiamin plasma concentration analysis may delay

and patient must be placed on thiamin supplementation without waiting for the result if he matches the clinical feature of vitamin B1 deficiency. As in Gayet-Wernicke syndrome, early treatment is crucial to prevent permanent complications such as residual deficits. Usually, functional recovery is achieved within the 6 months, but sensory symptoms may linger.[4] In our patient, IV immunoglobulins were discussed at the first time, but the history of alimentary imbalance directed the diagnosis to beriberi. Fortunately, the good evolution advocated this diagnosis.

In conclusion, dry beriberi becomes rare at present days. Nevertheless, physicians must recall this diagnosis face to an acute neuropathy, especially in patients with a history of alimentary disorders. Early thiamin supplementation is mandatory for a suitable recovery.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Iranian Journal of Neurology

Neurological Images

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A huge and invasive skull metastasis caused by renal cell carcinoma

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Keywords
Skull; Metastasis; Renal Cell Carcinoma; Neoplasms; Magnetic Resonance Imaging

A 65-year-old man presented by a progressive scalp mass from 9 months before. Physical examination showed a huge mass on his skull (Figure 1) associated with two small swellings in his axilla and flank.

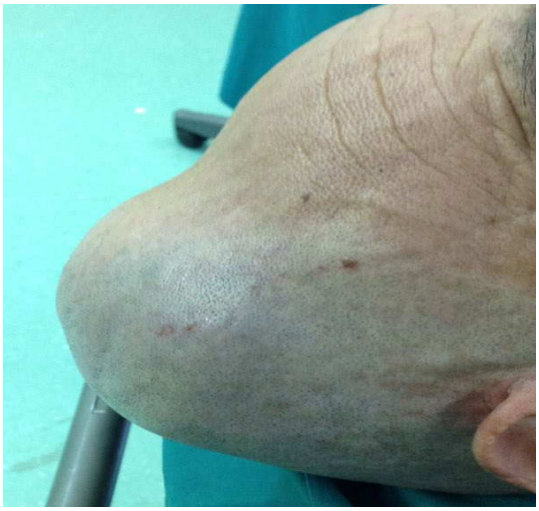

Figure 1. The image of the patient's scalp

Neurological examination was normal. The laboratory data and preoperative evaluation was normal, too. The brain computed tomography (CT-scan) and magnetic resonance imaging (MRI) demonstrated a huge extra-axial mass in right parietal bone resulted to bone destruction and scalp invasion (Figures 2 and 3).

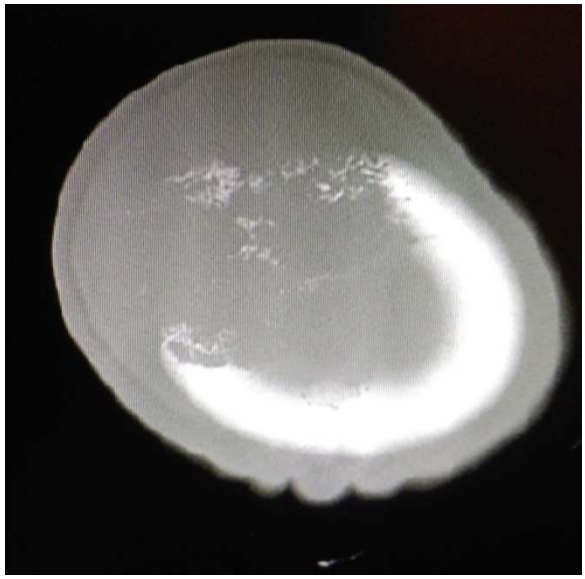

Figure 2. The bone window brain computed tomography (CT-scan)

In surgery, there was a huge oval-shape hemorrhagic and firm mass associated with scalp invasion and bone destruction (Figure 4).

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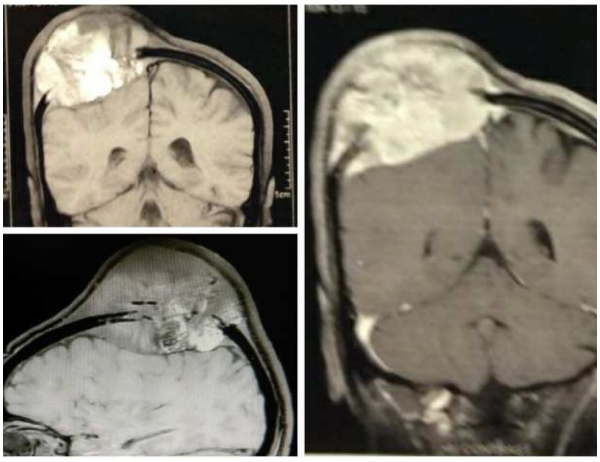

Figure 3. The coronal T1, sagittal FLAIR, and coronal Gd-enhancement T1 image sequences of brain magnetic resonance imaging (MRI)

After skin incision, the mass was dissected from scalp and debulked; parietal craniectomy around the lesion was done; dura was opened and tumor was dissected from neural tissue and was resected totally. Helping synthetic patch and titanium mesh, the dura and skull were repaired. Histopathology revealed renal cell carcinoma (RCC).

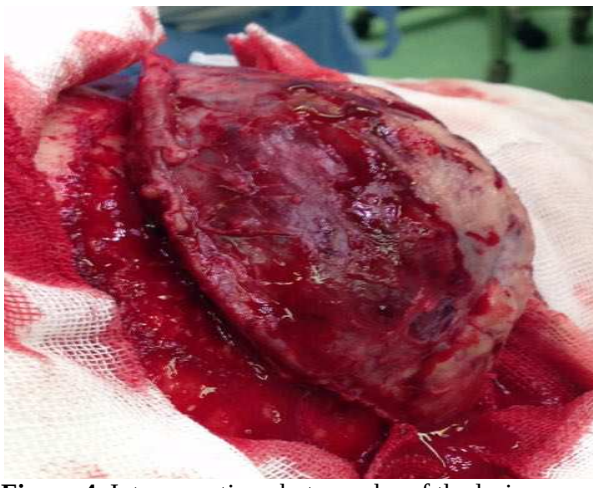

Figure 4. Intraoperative photograghy of the lesion

Sepulveda, et al. reported a 62-year-old man presented with a large expansive and destructive mass within cranial base associated with bilateral internal carotid artery involvement. Incisional biopsy revealed clear cell adenocarcinoma in favor of renal tumor metastasis.[1]

Rekhi, et al. reported a 15-year-old girl presented with a painless swelling in the occipital region. She had a history of excisional biopsy with a diagnosis of an alveolar soft part sarcoma. The lesion recurred within one month. CT-scan revealed a vascular destructive skull mass compressed the cerebellum. Metastatic RCC was ascertained after excisional biopsy and systemic work up.[2]

Yeh, et al. presented an 80-year-old man admitted for an incidental mass on the left parietal. The CT-scan revealed a destructive soft tissue lesion in the left parietal with intracranial and scalp invasion. Needle biopsy demonstrated metastatic RCC.[3]

Koutnouyan, et al. reported a 33-year-old woman who was referred for a mass in forehead region as a benign lesion. Because of intraoperative severe bleeding and presence of bone erosion, only biopsy rather than resection was done. Histopathology and metastatic work-up demonstrated metastatic RCC.[4]

A metastatic lesion should be in differential diagnosis of a destructive skull lesion with brain and scalp invasion, although it occurs rarely.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Iranian Neurological Events

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The third Iranian and the second joint French-Iranian neuromuscular meeting

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Keywords
Iran; Neuromuscular; Myopathies; Congresses

Neuromuscular disorders constitute a significant proportion of neurologic complaints. However, it has not been very long since they came into focus in Iran. The first specialized meeting on muscle and nerve disorders was held in Isfahan, 2010. The second gathering took place soon after in Tehran 2011 as a joint program with French experts.[1] Kerman was the third place to contribute to neuromuscular disorders education by holding the first myology winter school in 2015.

December 24th and 25th, 2016, Dr. Shahriar Nafissi and Dr. Farzad Fatehi from Iran (Tehran University of Medical Sciences) and Professor Shahram Attarian from France (Aix-Marseille University) coined another educational event in Iranian neuromuscular calendar. The third Iranian and the second joint French-Iranian neuromuscular meeting on myopathies and neuromuscular junction disorders was held in Tehran, Shariati Hospital with the presence of renowned Iranian and French neuromuscular specialists (Figure 1).

A part of this program was supported by a grant from the Campus France in Jundishapur project in Iran, which aims to stablish high-quality scientific cooperation between French and Iranian researchers.

Figure 1. The group of Iranian and French neuromuscular experts

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Figure 2. Quantitative electromyography (EMG) workshop by Professor Pouget

Esteemed French guests were Jean Pouget, Shahram Attarian, Jean Mark Leger, Andoni Urtizbera, Emilien Delmont, and Emmanuelle Campana-Salort. About 200 neurologists, physiatrists, and genetists from all over Iran participated in the meeting. The program was divided into two days. The first day was devoted to neuromuscular junction disorders with a particular focus on myasthenia gravis and its novel treatment approaches and also covering congenital myasthenic syndromes (CMS), Lambert-Eaton myasthenic syndrome (LEMS), and Botulism. The second day was designed to address myopathic disorders, and everybody could take advantage of various lectures on inflammatory and metabolic myopathies highlighting the judicious use of diagnostic techniques namely muscle magnetic resonance imaging (MRI), muscle pathology and electromyography (EMG). GNE myopathy was discussed in a separate section as a comprehensive report of Iranian affected patients. Important metabolic myopathies namely Pompe disease, lipid storage, and mitochondrial myopathies were also entailed. Apart from lectures, at the end of each day of the meeting, three challenging neuromuscular patients were introduced and Iranian and French experts discussed them from different perspectives, suggesting additional evaluations and treatments where needed.

Interactive EMG workshops made the meeting further distinctive. Workshops on single-fiber EMG (by Professor Attarian and Dr. Nafissi) and quantitative EMG (by Professor Pouget) (Figure 2) made everybody stuck in place to the last minutes of the meeting.

The key objectives of the program were to:

- Promote collaborations and joint research programs between Iranian and French neuromuscular experts.
- Give a thorough and concise report of myopathies and neuromuscular junction disorders in Iran.
- Share updates on different aspects of myopathies and neuromuscular junction disorders.

Conflict of Interests

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