Iranian Journal of Neurology

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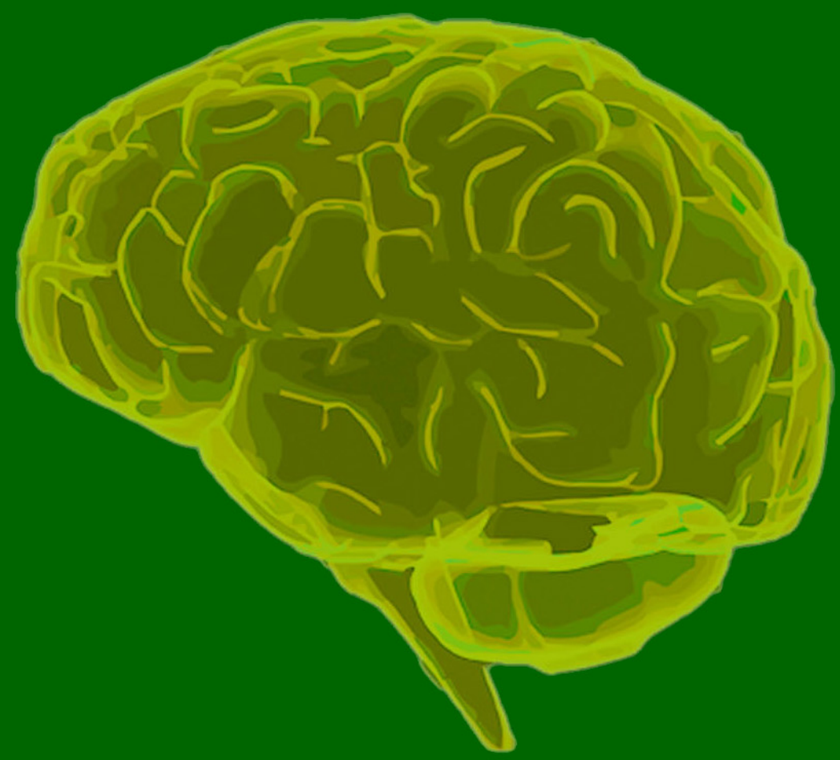

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Iranian Journal of Neurology

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

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Details

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

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Each section of the paper should begin on a new page

The manuscript must include:

Page 1: Title Page

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1. Title page:

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

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Original Paper

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Outcome of subthalamic nucleus deep brain stimulation on long-term motor function of patients with advanced Parkinson disease

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Keywords
Parkinson Disease; Deep Brain Stimulation; UPDRS

Abstract

Background: The objective of our study was to assess Unified Parkinson Disease Rating Scale (UPDRS) score in Parkinson disease (PD) patients who underwent subthalamic nucleus (STN) deep brain stimulation (DBS) 6 years after their surgery and to compare their UPDRS score 6 years after DBS with their score before surgery and 6 months after their operation.

Methods: In this cross sectional study which was carried out at Neurology Department of Rasool-e Akram Hospital, Tehran, Iran, affiliated to Iran University of Medical Sciences between 2008 and 2014, 37 patients with advanced PD were enrolled using non-randomized sampling method. All of the patients underwent STN DBS surgery and one patient died before being discharged, therefore; we started our study with 36 patients. The UPDRS III total score at preoperative state, 6-month follow-up and 6-year follow-up state were compared using repeated-measure analysis of variance.

Results: Thirty-seven patients (26 men and 10 women) with mean age of 50 ± 3 ranging from 32 to 72 years underwent STN DBS surgery. All patients were suffering from advanced PD with mean period of 11.3 ± 1.9 years. All patients except one were followed up for six months. And 14 patients (8 men and 6 women) were included in a six-year follow-up. The UPDRS score measurements before surgery, at 6-month follow-up and 6-year follow-up were 18.22 ± 2.88, 12.80 ± 3.14, 25.0 ± 11.8, respectively. Significant increase in UPDRS score was observed between the preoperative and six-year follow-up period ($P < 0.001$).

Conclusion: In conclusion, this study suggests that total UPDRS score will increase at 5 years following STN DBS and also showed that resting tremor, one of UPDRS sub-scores, will improve over time and the benefit of DBS will be persistent even after 6 years.

Introduction

Parkinson disease (PD) is a disabling neurodegenerative disease that is characterized by resting tremor, rigidity and stooped posture

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and can variably affect the daily function of the patients.[1,2] Levodopa (L-dopa) is known as the best medication for treating PD, yet this medication has many side effects such as dyskinesia if taken for a long period.[3,4] Deep brain stimulation (DBS) is a trending surgical method that has been mostly used in the last two decades due to being less invasive and the fact that it can be performed bilaterally.[5-10] Subthalamic nucleus (STN) stimulation is considered as a major target in PD patients.[11] STN DBS in PD patients has shown to improve motor function and daily activities of the patients in short-term period but there is little evidence that clarifies the role of STN DBS for improving non-motor symptoms.[12,13] Despite lack of evidence, some studies also showed that this method of surgery can have a positive effect on some of non-motor symptoms.[14] There are studies that have shown the effectiveness of STN DBS on motor symptoms of PD patients in short-term period using Unified Parkinson Disease Rating Scale (UPDRS).[15-18] There is limited evidence on the effectiveness of STN DBS in long-term period; however, the study on long-term effectiveness of STN DBS was done in China but it had a small sample size and it has shown improvement only in some aspects of motor function.[19] Since there has been a lack of clinical data on long-term effectiveness of STN DBS on motor symptoms of PD patients, this study aimed to assess UPDRS score in PD patients who underwent STN DBS 6 years after their surgery. In addition we also observed the patients to detect any possible significant improvement by comparing their UPDRS score 6 years after DBS with their score before surgery and 6 months after their operation.

Materials and Methods

In this cross sectional study which was carried out at Neurology Department of Rasool-e Akram Hospital, Tehran, Iran, affiliated to Iran University of Medical Sciences between 2008 and 2014, 37 patients with advanced PD were enrolled using non-randomized sampling method.

All of the patients underwent STN DBS surgery and one of the patients died before being discharged from the hospital due to myocardial infarction; therefore, we started our study with 36 patients.

Patients were included if they improved more than 30% in L-dopa challenge test and were excluded in case of having severe cardiovascular disease, uncontrolled high blood pressure, active ischemic cardiac disease, cerebrovascular accident, cancer and also if they were consuming any anticoagulant drugs.[20] In addition to these criteria, a stable dose of L-dopa was also maintained for at least 2 months prior to the surgery.

The study had the approval from the Institutional Review Board of Iran University of Medical Sciences (approval ID: IR.IUMS.REC1395.8821215181). Written informed consents were taken from all patients. A short-term (6 months) and a long-term (6 years) follow-up were done to evaluate and compare UPDRS score in the patients before and after surgery.

Stereotactic surgery was performed in all of our patients. This operation was done in different steps in order to detect the best point of stimulation in STN. First step was done using stereotactic magnetic resonance imaging (MRI). The surgeons used the MR compatible frame on patient's head and chose the best anatomical point of STN.

The second step was done in the operating room to assess the electrophysiological activity of different nuclei by the means of tetra polar electrodes and to find the best point for inserting the permanent electrodes in STN in the operating room. This procedure was performed under local anesthesia and a trained neurologist was present to assess clinical response to DBS while operating. After determining the optimal track, the corresponding microelectrode was removed and a permanent lead was replaced. Finally, the subcutaneous pulse generator was placed in the pectoralis major muscle after few days under general anesthesia. During the weeks following the surgery, an experienced neurologist programmed the pulse generators.

Short-term follow-up was done in all of our 36 patients. However, in long-term follow-up, 22 patients were excluded from the study due to death or because they were followed up in another center and long-term follow-up was only done in 14 patients.

Postoperative motor performance was evaluated using the UPDRS part III right after the surgery, 6 months after the surgery and also 6 years after the operation.

UPDRS part III measures items such as speech, facial expression, resting tremor, acting tremor, rigidity, finger tap, hand movement, rapid alternating movements, leg agility, rising from the chair, gait, bradykinesia, and posture stability.

Each score is from 0 to 4.[21] Lower scores show better performance.

Preoperative UPDRS III evaluation was also done in the on- and off-medication state. Postoperative scores were only assessed in on-medication state 6 months and 6 years after the surgery.

In this study, all data were analyzed by SPSS software (version 22, IBM Corporation, Armonk, NY, USA). Descriptive analysis of the data with normal distribution is available as means and standard deviation.

The UPDRS III total score at preoperative state, 6-month follow-up and 6-year follow-up state were compared using repeated-measure analysis of variance (ANOVA). The distribution of UPDRS III sub-scores was not normal; therefore, we compared them using the Wilcoxon signed-rank test. We also used repeated-measure ANOVA to compare doses of L-dopa in three phase of our follow-up.

Results

Thirty seven patients (26 men and 10 women) with the mean age of 50 ± 3 ranging from 32 to 72 years underwent STN DBS surgery. All patients were diagnosed with advanced PD with the mean period of 11.3 ± 1.9 years from the onset of the symptoms till the time of surgery. All patients except one, who died from the myocardial infarction, were followed up for six months, and 14 patients (8 men and 6 women) were included in a six-year follow-up.

The UPDRS score measurements were 18.22 ± 2.88, 12.80 ± 3.14, 25.0 ± 11.8 before the surgery, 6 months, and six years after the surgery, respectively which showed significant difference between preoperative score and the score 6 years after the operation (P = 0.033), and also significant increase in UPDRS score was observed between the preoperative and six-year follow-up period (P < 0.001) (Table 1).

Sub-score measurements revealed significant differences between preoperative and six-year follow-up scores of resting tremor (P = 0.020), speech (P = 0.007), rapid alternating movements of the hands (P = 0.011), hand movements (P = 0.010), finger tap (P = 0.009), and facial expression (P = 0.021) (Table 1). Furthermore, significant differences were seen between sub-scores of speech (P = 0.007), rigidity (P = 0.022), rapid alternating movements of the hands (P = 0.003), leg agility (P = 0.028), hand movements (P = 0.005), finger tap (P = 0.001) and facial expression (P = 0.021) between the time points of 6-month and six-year follow-up (Table 1).

We also measured the doses of L-dopa, which our patients were consuming before surgery, in short-term follow-up and in long-term period.

Table 1. Unified Parkinson Disease Rating Scale (UPDRS) scores and sub-scores at different time points and reporting P

Time Scores	Preoperation	Postoperation	6 years after surgery	Before surgery (P)	6 months after surgery (P)
UPDRS (mean ± SD)	18.22 ± 2.88	12.80 ± 3.14	25.00 ± 11.80	0.033	< 0.001
Sub-scores (mean ± SD)					
Speech	1.10 ± 0.70	1.05 ± 0.89	1.90 ± 1.07	0.021	0.021
Facial expression	1.10 ± 0.40	0.97 ± 0.44	1.50 ± 0.75	0.020	0.112
Tremor at rest	1.50 ± 1.90	0.83 ±1.38	0.14 ± 0.50	0.257	0.414
Action or postural tremor of hands	0.54 ± 0.77	0.25 ± 0.50	0.28 ± 0.61	0.505	0.022
Rigidity	3.40 ± 2.60	1.40 ± 2.00	4.20 ± 4.20	0.009	0.001
Finger taps	1.60 ± 1.30	1.25 ± 1.60	3.40 ± 1.90	0.010	0.005
Hand movements	1.41 ± 1.40	1.02 ± 1.44	2.60 ± 1.70	0.011	0.003
Rapid alternating movements of hands	0.83 ± 1.05	0.50 ± 1.02	2.60 ± 1.70	0.077	0.028
Leg agility	2.80 ± 1.70	2.25 ± 1.90	3.50 ± 2.10	0.157	0.206
Arising from chair	0.19 ± 0.40	0.16 ± 0.50	0.50 ± 0.65	0.317	0.132
Posture	0.83 ± 0.50	0.70 ± 0.60	0.92 ± 0.80	0.194	0.053
Gait	0.75 ± 0.69	0.60 ± 0.70	1.00 ± 0.80	0.160	0.190
Postural stability	1.02 ± 0.65	1.00 ± 0.70	1.40 ± 0.85	0.132	0.366
Body bradykinesia and hypokinesia	0.91 ± 0.70	0.63 ± 0.79	1.00 ± 0.87	0.538	0.111

SD: Standard deviation; UPDRS: Unified Parkinson Disease Rating Scale

Table 2. L-dopa dosage in patients at different time points

Follow-up periods	Number of patients	Gender	Age (year) (mean ± SD)	L-dopa (mg/dl) (mean ± SD)
Preoperation (baseline)	36	Men: 26, Women: 10	50 ± 3	1269 ± 114
Six-month (short-term)	36	Men: 26, Women: 10	50 ± 3	783 ± 87
Six-year (long-term)	14	Men: 8, Women: 6	49 ± 8	992 ± 170

The mean L-dopa equivalent doses showed significant decline from 1296 ± 224 mg/d before surgery (baseline) to 783 ± 87 mg/d after DBS in short-term period ($P < 0.005$), but there was no significant difference between the doses of L-dopa consumption in long-term follow-up and short-term follow-up ($P = 0.110$). Furthermore, there was no significant decline between long-term follow up and preoperative doses of L-dopa ($P = 0.530$) (Table 2).

Discussion

The purpose of this study was to assess UPDRS score in patients suffering from PD who underwent STN DBS 6 years ago and to compare UPDRS score 6 years after the surgery with their score 6 months after the surgery and also their score before the STN DBS. We measured their UPDRS score while they were all on medication and according to their UPDRS score after 6-year follow-up, we found that total motor function got worse after 6 years following the operation compared to the score before and 6 months after the surgery. We also compared UPDRS sub-scores in patients 6 years after the surgery with their score in 6-month follow-up and also their pre-operative sub-scores. We found a significant improvement in patients' resting tremor in 6-year follow-up compared to their pre-operative state. We also observed an improvement in the tremor at rest of patients 6 years following the surgery in comparison to their score in 6-month follow-up, although it was statistically insignificant. Total worsening in motor function of the patients in 6-year follow-up compared to their state before surgery was mainly due to their poor score in speech, facial expression, finger taps, hand movements and rapid alternating movements of hands. When we compared sub-scores 6 years after STN DBS with patients' sub-scores 6 months after the surgery, we found that the reason for worse motor status was mainly the poor result in speech, facial expression, rigidity, finger taps, hand movements and rapid alternating movements of hands and leg agility.

We also measured the dosage of L-dopa needed in patients 6 months and 6 years after the surgery and we compared them with the daily doses of the medication needed before the operation and we found that during short-term follow-up, patients' requirement for L-dopa had significantly decreased. However, in a long-term, dose of L-dopa needed in patients had reduced, but it was statistically insignificant.

In a study that was conducted in 2009 on the same patients as the current study, UPDRS score was measured 6 months after STN DBS and the results indicated a significant improvement in UPDRS score in short-term follow-up.[22] In some studies which observed motor symptoms of the patients in 5 years and a few studies which followed the patients more than 8 years, DBS was shown to be beneficial for tremor, rigidity, and bradykinesia but not for axial symptoms.[8,23-27] However, in our study, the efficacy of STN DBS was only persistent for tremor at rest and not for other symptoms.

In another study that was conducted in China, it was shown that in the off-medication state, motor symptoms were significantly improved 5 years following the operation. However, similar to our study, it was implied that with longer follow-up in on-medication state, worsening of motor function is expected due to L-dopa resistance symptoms.[19]

One of our study limitations was small sample size, which could inevitably result in declined statistical power. Furthermore, we lost 61.1% of our patients (22 from 36 patients) in 6-year follow-up and that could also lead to bias. Finally, we could not evaluate UPDRS in off-medication state since patients were unwilling to discontinue their L-dopa.

Conclusion

In conclusion, this study suggests that total UPDRS score will increase at 5 years following STN DBS and the patients' motor function will worsen in log-term follow-up after the operation. Our study also showed that resting tremor, one of UPDRS sub-scores, will improve over time and the benefit of DBS will be persistent even after 6 years.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Original Paper

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Stroke subtypes, risk factors and mortality rate in northwest of Iran

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Keywords
Stroke; Epidemiology; Risk Factors; Iran

Abstract

Background: Stroke is the second most common cause of death and first cause of disability in adults in the world. About 80% of all stroke deaths occur in developing countries. So far, the data on stroke epidemiology have been limited in Iran. Therefore, this study was focused on stroke demographic data, risk factors, types and mortality.

Methods: A retrospective study was done in two university tertiary referral hospitals in Tabriz, northwest of Iran, from March 2008 to April 2013. Patients diagnosed with stroke were enrolled in the study. Demographic data, stroke subtypes, duration of hospitalization, stroke risk factors and hospital mortality rate were recorded for all the patients.

Results: A total number of 5355 patients were evaluated in the present study. Mean age of the patients was 67.5 ± 13.8 years, and 50.6% were men. Final diagnosis of ischemic stroke was made in 76.5% of the patients, intra-cerebral hemorrhage (ICH) with or without intra-ventricular hemorrhage (IVH) in 14.3% and subarachnoid hemorrhage (SAH) in 9.2%. Stroke risk factors among the patients were hypertension in 68.8% of the patients, diabetes mellitus (DM) in 23.9%, smoking in 12.6% and ischemic heart diseases (IHD) in 17.1%. Mean hospital stay was 17.3 days. Overall, the in-hospital mortality was 20.5%.

Conclusion: Compared to other studies, duration of hospital stay was longer and mortality rate was higher in this study. Hypertension was the most common risk factor and cardiac risk factors and DM had relatively lower rate in comparison to other studies. Because of insufficient data on the epidemiology, patterns, and risk factors of stroke in Iran, there is a necessity to develop and implement a national registry system.

Introduction

Stroke is a serious problem world-wide especially in Asia with higher mortality than Europe or North America.[1] It is the most important cause of disability and the second cause of death worldwide. Only one-third of all strokes occur in the developed countries. In the developing countries stroke is a major health issue despite being preventable.[2] It is estimated that about 5.7 million deaths in 2005 occurred that most of

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these deaths (87%) were in low-income and middle-income countries. Nowadays the incidence of stroke in low- to middle-income countries is higher than in high-income countries. Moreover in low to middle-income countries, there are greater mortality rate and a younger age of stroke onset, factors that raise the burden of stroke burden.[3] Stroke constitutes a major global challenge for health policy and healthcare economics. Reducing stroke burden requires extensive knowledge of risk factors and, if applicable, preventive control. In last classification of countries by World Bank, Iran was qualified as a middle-income country,[4] and the stroke prevalence in Iran is significantly higher than the developed countries especially for stroke in young adults.[5,6] In comparison with high-income countries, stroke in young adult is more common in Iran and mortality rate is higher.[7] Fortunately, stroke is a preventable disease and for this purpose, knowledge of risk factors and epidemiology of it within a certain country is an essential step.[8] This study was conducted in order to collect the epidemiological data in patients diagnosed with stroke in order to help the healthcare providers manage stroke more effectively in Iran.

Materials and Methods

This was a retrospective hospital-based, longitudinal study which was performed at the Imam Reza and Razi Hospitals, two major tertiary referral centers in northwest of Iran affiliated to Tabriz University of Medical Sciences, Tabriz, Iran. All patients with the diagnosis of stroke from March 2008 to April 2013 were enrolled. Stroke patients from any subtypes (ischemic, hemorrhagic) were selected based on the patients' data in hospital documents and by using the International Classification of Diseases, 10th edition (ICD-10). All available data including age, gender, duration of hospital stay, discharge state, mortality, risk factors and paraclinical data were sought in especially-designed data matrix. Risk factors for each subtype of stroke were recorded separately. The patients were followed up during hospital stay. Chi-square test and Student's t-test were used to analyze the data. For hospital mortality outcome, a multivariate logistic regression analysis was built with sex and age groups as covariates. A P-value less than 0.05 was considered significant. For statistical analysis, SPSS software (version 18, SPSS Inc., Chicago, IL, USA) was used.

Results

Medical records from 5355 patients consisting of 2708 (50.6%) men and 2647 (49.4%) women were reviewed. Table 1 illustrates general feature of the study. The mean age of patients was 67.6 ± 13.8 years. Among the patients 7 (0.1%) were in pediatric age group (< 15 years), 414 (7.7%) were young adults (15-45 years), 1587 (29.6%) were middle aged (45-65 years) and 3374 (63%) were older adults (< 65 years). In this study stroke subtypes included ischemic stroke 4096 (76.5%), intra-cerebral hemorrhage (ICH) with/without intra-ventricular hemorrhage (IVH) 764 (14.3%) and subarachnoid hemorrhage (SAH) 495 (9.2%). Conventional risk factors were as follows: hypertension that was the most frequent and recorded in 3686 (68.8%) of patients, diabetes mellitus (DM) in 1278 (23.9%), smoking in 673 (12.6%), hyperlipidemia (HLP) in 613 (11.4%) atrial fibrillation (AF) in 215 (4.0%), familial history of stroke in 69 (1.5%) and congestive heart failure in 74 (1.4%) (Figure 1).

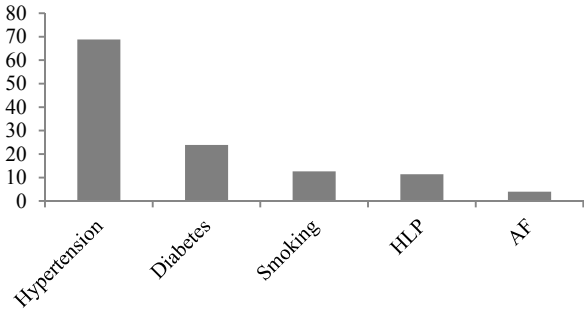

Figure 1. Frequency of risk Factors
HLP: Hyperlipidemia; AF: Atrial fibrillation

In young adults hypertension was less common (29.9%) but smoking was more frequent (15.9%). Hypertension was more common in ischemic stroke patients compared with ICH or SAH patients. Mean hospital stay was 17.3 days which was longer in mortality cases (25.8 days). A total of 1099 (20.5%) patients died during the hospitalization of which 577 (52.5%) were men and 522 (47.5%) women (Figure 2). Mortality rate in hemorrhagic patients was higher than ischemic ones (Figure 3). The mean age in deceased patients was higher than the average age of all patients (69.9 years and 67.6 years, respectively; $P < 0.001$) and the mortality rate in group aged > 65 years was more than twice of the rest (69.9% vs. 33.1%) ($P < 0.001$) (Figure 4).

Table 1. Baseline characteristics of hospital admitted stroke patients in northwest of Iran (2008-2013)

Characteristics	Men (n = 2708)	Women (n = 2647)	Total (%) (n = 5355)
Age (year) (mean ± SD)	65.2 ± 14.6	64.2 ± 15.0	67.5 ± 13.8
Risk factors history [n (%)]			
Hypertension	1691 (62.4)	1995 (75.4)	68.8
DM	558 (20.6)	720 (27.2)	23.9
HLP	242 (8.9)	371 (14.0)	11.4
AF	127 (3.2)	88 (4.8)	4.0
TIA	66 (2.4)	33 (1.2)	2.1
Smoking	573 (21.2)	100 (3.8)	12.6
Ischemic heart disease	460 (17.0)	456 (17.2)	17.1
Familial history of stroke	40 (1.5)	39 (1.5)	1.5
Types of stroke [n (%)]			
Ischemic	2083 (76.9)	2013 (76.0)	76.5
ICH	398 (14.6)	366 (13.8)	14.3
SAH	227 (8.5)	268 (10.2)	9.2
Mortality [n (%)]	577 (21.3)	522 (19.7)	20.5

SD: Standard deviation; TIA: Transient ischemic attack; ICH: Intra-cerebral hemorrhage; SAH: Subarachnoid hemorrhage; DM: Diabetes mellitus; HLP: Hyperlipidemia; AF: Atrial fibrillation

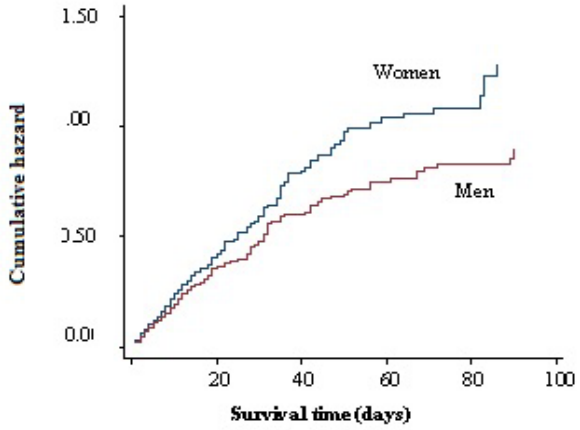

Figure 2. Correlation between gender and mortality

The important results of this study have been summarized in table 1.

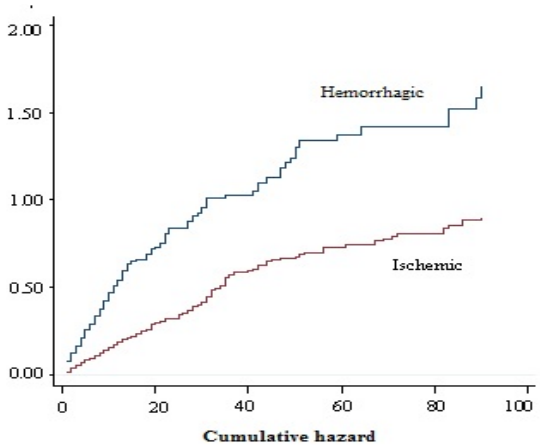

Figure 3. Correlation between type of stroke and mortality

Discussion

In this study the prevalence of stroke among men and women were relatively equal. The mean age of patients was as the same as other studies in Iran[8] and India[9] and Saudi Arabia[10] but slightly higher than Saudi Arabia.[10] The lower mean age in Saudi Arabia might be due to predominance of young age group in that country. Likewise, in developed countries ischemic stroke represents the majority of stroke subtypes, followed by ICH and SAH.[3,11,12]

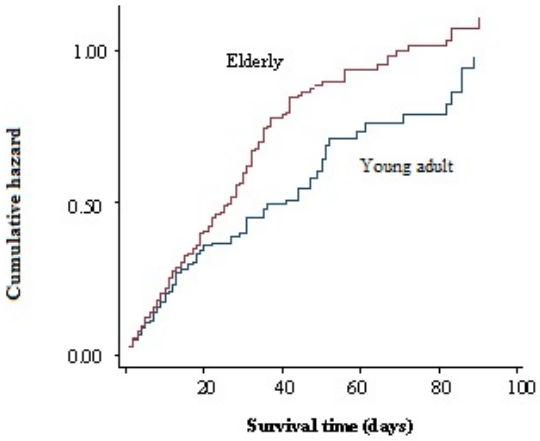

Figure 4. Correlation between age and mortality

The stroke patients age categories in the study with respect to the population in each age category in East Azerbaijan province in 2010 based on national census is shown in table 2. It could be implied that the stroke risk increases with aging and reach the maximum in 9th decade of life in this population that is similar to other studies.[13]

Table 2. Age distribution of the stroke patients admitted to the Imam Reza and Razi hospitals with respect to the population in Tabriz

Age (year)	Men [n (%)]		Women [n (%)]		Total [n (%)]		Ratio***
	Admission*	Population**	Admission	Population	Admission	Population	
10-19	3 (0.10)	291073 (15.40)	3 (0.10)	567741 (30.80)	6 (0.10)	858814 (23.10)	0.004
20-29	37 (1.36)	405376 (21.50)	43 (1.62)	394678 (21.40)	80 (1.49)	800054 (21.50)	0.069
30-39	90 (3.30)	323096 (17.20)	96 (3.62)	318219 (17.30)	186 (3.47)	641315 (17.20)	0.200
40-49	206 (7.60)	232682 (12.40)	225 (8.53)	228377 (12.40)	431 (8.04)	461059 (12.40)	0.640
50-59	415 (15.40)	161438 (8.57)	449 (17.00)	166225 (9.02)	864 (16.20)	327663 (8.79)	1.830
60-69	657 (24.40)	88348 (4.69)	528 (19.90)	95881 (5.20)	1185 (22.20)	184229 (4.94)	4.490
70-79	832 (30.70)	63828 (3.39)	866 (32.70)	62214 (3.37)	1698 (31.70)	126042 (3.38)	9.370
80-89	445 (16.40)	25288 (1.34)	416 (15.70)	25168 (1.36)	861 (16.10)	50456 (1.35)	11.900
≥ 90	23 (0.84)	1604 (0.08)	21 (0.79)	2012 (0.10)	44 (0.88)	3606 (0.10)	8.800
Total	2708	1882031	2647	1842589	5355	3724620	0.140

*Admitted stroke patients to Imam Reza and Razi hospitals, **East Azerbaijan population, ***Calculated by dividing the percent admitted to the hospital to the percent population in each category

This pattern of highly prevalent risk factors is similar to the Arab countries neighboring the Persian Gulf except for a relatively low incidence of DM and cardiac problems in this study.[9,10-14]

This study revealed that hypertension was the most frequent risk factor in all subtypes of stroke across all age groups that was similar to all other epidemiologic studies. Moreover, the risk of hypertension was similar among all the patients with stroke due to either large vessel disease or lacunar infarct, like the Oxfordshire project.[15]

DM is a strong risk factor for stroke,[16] and its prevalence is increasing.[17] Persons with DM have an increased susceptibility to atherosclerosis and atherogenic risk factors, notably hypertension, obesity, and abnormal blood lipids.[18] It is still unclear whether stroke subtype, severity, and prognosis are different in diabetic and nondiabetic patients.[16] In this study, DM was the second most important risk factor but with lower incidence in comparison with other studies.[6] Low incidence of DM as a risk factor probably is due to low incidence of this disease in northwest of Iran in comparison with other places or unawareness of people about their disease.

Cardiac disorders are modifiable risk factors for stroke. Cardioembolic stroke accounts for 14%-30% of all cerebral infarctions.[19] In one study 14% of stroke patients were diagnosed with cardiogenic stroke.[20] Unlike other studies in developed and developing countries cardiac problems had a small role as a risk factor in this study. For example, AF was detected in only 4.0% of our patients in comparison with 8.6% of patients in another study.[6] This is maybe due to incomplete data recording and in-hospital cardiac survey in our centers.

The other important risk factors for ischemic stroke and transient ischemic attack (TIA) are smoking and HLP which are considered as two modifiable risks. The well-known association between smoking and ischemic stroke can be attributed to large-vessel atherosclerosis with stenosis.[21,22]

According to the previous studies, cigarette smoking was correlated with atherosclerotic and cardioembolic types of ischemic stroke.[23] In this study smoking with 12.6% and HLP with 11.4% prevalence, were important risk factors in both ischemic and hemorrhagic strokes.

Stroke incidence increases with a family history of stroke.[6] This fact could be due to a familial association existing with other risk factors for stroke (cholesterol, hyperfibrinogenemia, hypertension, diabetes and etc.),[18] genetic tendency for stroke, a genetic determination of other stroke risk factors, and a common familial exposure to environmental or lifestyle risks,[17] or due to independent factors.[18]

In this study the incidence of family history of stroke was 1.5%, lower in comparison with other studies,[24] and it might be duo to incompetent medical recording in our hospitals. Mean hospital stay was longer than another study in southern Iran,[7] because our centers are referral for 4-5 provinces of Iran and some neighbor countries with many patients with poor prognosis. Our in-hospital mortality rate (20.5%) was higher in comparison with some developed countries (17.5%),[25] and equal to (20.0%) or lower (24.6%) than other studies in Iran.[5,7]

The 30-day mortality rate of stroke patients in North Africa and Arab Middle-Eastern countries, which are socioeconomically similar to Iran, is

lower and reported between 10% and 17.3%.[26] On the other hand unlike most other studies, in this study mortality rate was higher in men than women that can be due to Iranian culture and life style, as women are less involved in stressful situations and consume much less alcohol and cigarettes.

These results can be due to some factors such as absence of primary and secondary stroke units and consequently low rate of thrombolysis and thrombectomy that can influence stroke prognosis.[27] Moreover, incomplete stroke registry system during this study period and low stroke awareness among Iranian general population,[28] that causes the late referral of stroke patients and leads to increased mortality, are other causes.

Conclusion

xDuration of hospital stay was longer and mortality rate was higher in Northwest of Iran than other countries. Among risk factors, cardiac risk factors and DM had lower rate in comparison to other studies probably due to under diagnosis. Generally, the data on the epidemiology of stroke and its pattern and risk factors is scarce in Iran. In order to overcome this incompetency and improve the data recording and outcome of stroke patients, we need to develop systematic recording and registries and provide stroke units.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Evaluation of non-motor symptoms and their impact on quality of life in patients with Parkinson's disease, Isfahan, Iran

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Keywords
Non-Motor Symptoms; Parkinson Disease; Quality of Life

Abstract

Background: Parkinson's disease (PD) is diagnosed on the basis of motor symptoms, but non-motor symptoms (NMS) have high prevalence in PD and often antecede motor symptoms for years and cause severe disability. This study was conducted to determine the prevalence of NMS in patients with PD.

Methods: This cross-sectional study was performed in Isfahan, Iran, on patients with PD. The prevalence of NMS was evaluated by the NMS questionnaire, the NMS scale, and Parkinson's disease questionnaire-39 (PDQ-39). The Mini-Mental Status Examination (MMSE) was used for assessing cognition.

Results: A total of 81 patients, including 60 men and 21 women, were recruited for this study. The prevalence of NMS was 100%, and the most commonly reported symptom was fatigue (87.7%); there was a strong correlation between NMS and the quality of life (QOL) of patients with PD ($P < 0.001$).

Conclusion: This study showed that NMS are highly prevalent in the PD population and adversely affect QOL in these patients. Early diagnosis and treatment can improve QOL and can help in disability management of patients with PD.

Introduction

Although non-motor symptoms (NMS) are common among patients with Parkinson's disease (PD), they are often not well-known in clinical practice.[1] While PD is diagnosed on the basis of motor symptoms, comprising slowness of movement and complications with balance, it is known that NMS are highly prevalent and often amenable to therapy.[2] In fact, studies have demonstrated that NMS of PD, such as sleep disturbances, anxiety, and depression, are more disabling than motor symptoms of PD, deteriorating the quality of life (QOL). NMS are also the most common reason for admission to institutional care.[3]

The pathophysiology of NMS is still poorly understood, and dysfunction of both

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dopaminergic and non-dopaminergic systems seem to be involved.[3] Although the non-motor features of PD are common, these symptoms are not frequently distinguished in clinical practice. It has been found that approximately half of the NMS of PD are not recognized even by neurologists, causing interruptions in treatment and insufficient management. There are precise validated tools available for NMS assessment, such as the NMS questionnaire (NMSQ) and NMS scale (NMSS).[4]

Recognizing the most prevalent NMS in PD and clarifying their clinical features would help in the diagnosis of PD prior to the presence of motor symptoms.[5] To describe the range and prevalence of NMS in patients diagnosed with PD, we enrolled participants in a cross-sectional study by the unified PD rating scale (UPDRS), NMSQ, NMSS, and Parkinson's disease questionnaire-39 (PDQ-39).

Moreover, the Mini-Mental Status Examination (MMSE) and a comprehensive medical history of all patients were taken to detect the correlations between NMS and PD.

Materials and Methods

This observational cross-sectional study was prospectively performed on patients with idiopathic PD (IPD) diagnosed on the basis of the UK brain bank criteria; the patients were recruited by referral from a PD clinic in the Al-Zahra hospital, Isfahan, Iran. Written informed consent was obtained from the patients for the time period of June 2014–June 2015. The Ethical Committee of the Isfahan University of Medical Sciences approved the study (approval code: 294011).

All patients diagnosed with IPD who agreed to participate underwent medical evaluation by a neurologist specialized in movement disorders, and who had a certificate from a MDS-UPDRS training program. Medical students completed the questionnaires by interviewing patients or their care givers. Patients with neurological or systemic diseases that could affect NMS and QOL (disability due to cerebrovascular disease, advanced diabetes mellitus, renal failure, heart failure, hepatic failure, malignancy, severe anemia, pain syndrome) and patients with severe cognitive impairment (MMSE < 19) that could cause unreliable information were excluded from the study.[6]

Demographic data, disease history, and social information were collected by a checklist, the modified Hoehn and Yahr staging.[7] The Unified Parkinson's Disease Rating Scale-part III (UPDRS-III)[8] was used for assessment of motor symptom severity, and NMS were evaluated by the NMSQ,[9] NMSS,[10] and UPDRS I-II. For QOL, PDQ-39[11] was used. UPDRS-IV was used to assess motor complications, and finally, cognitive abilities were investigated with the MMSE.[12]

Questionnaire: 1- UPDRS, which adjusted according to the MDS-UPDRS revision 21, with the method defined by Goetz, et al., was used to evaluate motor and non-motor disability.[13]

2- NMS scale was established and validated for the first time by Chaudhuri, et al. in 2007.[10] The scale evaluates the severity and frequency of NMS occurring in PD in the last month, is relatively easy to apply, takes about 10-15 minutes to complete, and is applied by the physician. The scale contains 30 questions divided into nine domains: cardiovascular (2 items), sleep/fatigue (4 items), mood/cognition (6 items), perceptual problem/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary tract (3 items), sexual function (2 items), and miscellany (4 items).[10]

3- NMSQ, comprising a series of 30 questions, which is a screening tool for evaluating NMS, and is not used as a rating scale.[9]

4- PDQ-39 is used as a reliable and valid tool for the assessment of QOL in PD patients, with 8 discrete scales: mobility (10 items), activities of daily living (ADL) (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognitions (4 items), communication (3 items), and bodily discomfort (3 items).

Patients are asked to select one of 5 responses on a scale (never, occasionally, sometimes, often, always) for each event.[11]

The 5-MMSE questionnaire contains 11 questions that measure five aspects of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30, takes only 5-10 minutes to administer, and is consequently practical to use in clinics as a routine tool. The Persian version of the MMSE was used in this study, which has been validated for our society, based on age and education.[12,13]

All data were analyzed using the SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Quantitative demographic characteristics were expressed by mean ± standard deviation (SD), and qualitative data were shown as percentage. To compare means of

two normally distributed data, Student's t-test was used, and for non-normally distributed data, the Mann-Whitney test and U-test were used. For comparisons of correlations between two groups, chi-square and Fisher's exact tests were used, and Spearman's rank correlation coefficient was applied to evaluate the associations among variables.

The total scores of UPRDS (I through V, I plus II, and total), PDQ39 (total number and each section), NMSS (total number and each domain), NMSQ total numbers, and total MMSE were calculated by summating items. A P value of < 0.05 was considered to be statistically significant.

Results

Patient characteristics: Eighty-one (n = 81) Isfahanian patients with PD, including 60 men and 21 women, with mean age of 62 ± 12 years (range 36 to 83 years) and mean disease duration of 6.1 ± 5.0 years (range 3 months to 20 years), enrolled in this study. Table 1 summarizes their demographic data and clinical characteristics. Disease severity evaluated by Hoehn and Yahr staging[7] demonstrated that the highest proportion of patients were in stage 2 (n = 32, 39.5%), while the lowest proportions were in stages 4 and 5, with 4 patients in each of those stages. The mean score of UPDRS was 57.2 ± 26.0. The mean scores of motor symptoms and NMS of patients were 37.2 ± 20.0 and 20.1 ± 10.0, respectively.

The mean MMSE score was 25 ± 5 (range 17-30). The most prevalent MMS score was 30 (18.7%), and there was not any correlation between disease duration and cognitive impairment (P = 0.607).

NMS: All 81 patients (100%) had at least one non-motor symptom based on NMSS. The mean total score of the NMSS was 37.03 ± 22.51 with a range between 1 and 96. Among the domains of NMS, the highest percentages were seen in the domains of sleep/fatigue (87.7%). The lowest percentages were those from perception/hallucinations domain (34.6%). These results are demonstrated in table 2. The most frequently (> 60%) reported symptoms were fatigue (74.1%), constipation (67.9%), anxiety (65.4%), and short term memory loss (60.5%). Gastrointestinal tract and sexual function were significantly more prevalent in men (74% and 75%, respectively) than in women (26% and 25%, respectively) (chi-square test, P < 0.020). There were no differences between genders for the remaining NMS domains. Detailed frequencies of NMS are shown in table 3.

Table 1. Characteristics of patients with Parkinson's disease (PD)

Characteristics	Value
Age (year) (mean ± SD)	62 ± 12
Men (%)	74.1
Education [n (%)]	
Illiterate	24 (29.6)
Primary or/and secondary school	31 (38.3)
High school	16 (19.8)
University graduated	10 (12.3)
Duration of disease (year) (mean ± SD)	6.1 ± 5.0
Smoking (%)	23.5
Comorbidity [n (%)]	
Hypertension	11 (13.6)
Diabetes	9 (11.1)
Ischemic heart disease	5 (6.1)
Hyperlipidemia	6 (7.4)
Hoehn and Yahr stage (%)	
1	29.6
2	39.5
3	14.8
4	4.9
5	4.9
MMSE (mean ± SD)	25 ± 5
MDS-UPDRS (mean ± SD)	57.2 ± 26.0
Part I	9.5 ± 5.0
Part II	10.7 ± 7.0
Part III	35.0 ± 18.0
Part IV	2.3 ± 3.2
Non-motor symptoms total	20.1 ± 10.0
Motor symptoms total	37.2 ± 19.0
Antiparkinsonian medication (%)	
Levodopa	31.3
Dopamine agonist	57.5
Amantadine	54.3
Anticholinergic	52.6
MAO-B inhibitor	32.8

MMSE: Mini-Mental Status Examination; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Scale; SD: Standard deviation; MAO: Monoamine oxidase

NMSQ: The most prevalent "yes" answer in the NMSQ was constipation (71.6%). The rarest symptom was loss of taste/smell (16.7%). Detailed data are provided in table 3.

Between the duration of disease and NMS there was a direct relationship (part I and II UPDRS P < 0.001, NMSS total P < 0.001, NMS-Q total P < 0.018).

NMS and QOL (PDQ-39): The mean PDQ-39 score was 29.51 ± 18.51 and the median was 25. The most prevalent symptom was feeling pain in the body (77.6%) in the body discomfort domain, which was categorized in mobility domain. Also,

there was an association between QOL and the duration of disease, so that as the disease progressed, the QOL worsened. Detailed data are shown in table 4.

Table 2. Frequency of non-motor symptoms (NMS) by domains

Domain	Percentage
Cardiovascular	40.4
Lightheadedness/dizziness during the postural changes	35.8
Fall because of syncope	32.1
Sleep/fatigue	87.7
RLS	54.3
Insomnia	58.0
Excessive day time sleepiness	54.3
Fatigue	74.1
Mood/cognition	84.0
Anhedonia	38.3
Loss of motivation	48.1
Anxiety	65.4
Sadness/depression	58.0
Flat mood	46.9
Lack pleasure	39.5
Perceptual problem/hallucination	34.6
See something others can not	23.5
Believe you are not true	19.8
Double vision	18.5
Attention/memory	71.6
Difficulties to maintain concentration	53.1
Short-term memory problems	60.5
Forget to do daily things	46.9
Gastrointestinal tract	79.0
Drooling of saliva	54.3
Difficulty in swallowing	28.4
Constipation	67.9
Urinary tract	70.4
Urgency	50.6
Frequency (voiding every 2 hours)	48.1
Nocturia	49.4
Sexual function	44.4
Decreased pleasure	40.7
Problem having sex	44.4
Miscellaneous	69.1
Pain	34.6
Smell or taste dysfunction	17.3
Weight change	43.2
Excessive sweating	34.6

NMS: Non-motor symptoms; RLS: Restless leg syndrome

Correlation between QOL and NMS: In this study several questionnaires for assessment of NMS were used, such as UPDRS parts I and II, NMSS, and NMSQ. We assessed correlation between NMS (by this form) and QOL (by PDQ-39), and the results showed strong correlations between them. The P-value for correlation between all NMS questionnaires and QOL was $P < 0.001$. Detailed results are revealed in table 5.

Table 3. Frequency of non-motor symptoms in patients with Parkinson's disease (PD) non-motor symptoms questionnaire (NMSQ)

Variable	Percentage
Loss of taste/smell	16.7
Difficulty in swallowing	25.7
Vomiting/nausea	22.2
Constipation	71.6
Fecal incontinence	22.4
Incomplete bowel emptying	28.6
Urinary urgency	55.3
Nocturia	58.1
Unexplained pain	55.3
Change in weight	42.7
Memory	55.7
Apathy	38.6
Hallucination	21.1
Problems of concentration	41.6
Sadness	63.4
Anxiety	65.6
Change in libido	42.6
Sexual difficulties	43.1
Dizziness	38.0
Falls	45.1
Daytime sleepiness	44.6
Insomnia	50.7
Vivid dreams	40.8
Sleep behavior disorders	47.4
Restless legs	35.6
Edema	28.0
Excessive sweating	38.6
Diplopia	18.9

Correlation between QOL and motor symptoms: We used Hoehn and Yahr staging,[7] UPDRS III for evaluating motor symptoms, and UPDRS IV for motor complications and found correlations between Hoehn and Yahr staging, UPDRS III, UPDRS IV, and UPDRS total and PDQ-39 scale ($P < 0.001$, $P < 0.001$, $P = 0.210$, and $P < 0.001$, respectively).

Hoehn and Yahr[7] and UPDRS part III had the highest correlation in mobility and ADL ($P < 0.001$).

Correlation between NMS and motor symptoms: We found correlations between NMSQ and Hoehn and Yahr[7] ($P = 0.390$), UPDRS III ($P = 0.008$), and UPDRS total score ($P = 0.001$). Also, NMSS total correlated with UPDRS total, and UPDRS part III had a correlation only with domain 4 of NMSS total ($P < 0.001$).

Table 4. Impact of non-motor symptom in quality of life Parkinson's disease questionnaire-39 (PDQ-39)

Dimensions	Mean ± SD	Most finding	Percentage
Mobility	13.5 ± 10.41	Difficulty looking after things	72.7
ADL	7.02 ± 5.78	Difficulty writing clearly	73.9
Emotional well-being	7.83 ± 5.54	Feeling anxious	73.3
Stigma	5.34 ± 6.10	Conceal his/her PD from the others	48.2
Social support	2.22 ± 3.02	Lacked support from his/her partner	41.2
Cognitions	4.67 ± 3.66	Memory deterioration	68.8
Communication	2.60 ± 2.75	Difficulty speech	64.9
Bodily discomfort	4.62 ± 3.13	Feeling pain in the body	77.6

SD: Standard deviation; PD: Parkinson's disease; ADL: Activities of daily living

Correlation between NMS and cognition: Out of 81 patients, 43 had no cognitive impairment (cut-off point 27), 15 of them had minimal cognitive impairment (cut-off point 24), and the remainder had MMSE 19-24. In this study we found correlations between the NMSQ total score, the PDQ-39 total score, and the MMSE, with P-values of 0.011 and 0.015, respectively. However, there was no significant relation between NMSS total score and MMSE (P = 0.175).

Table 5. Spearman's rank correlation coefficient (rs) and P-value between non-motor symptoms scale (NMSS) domains and Parkinson's disease questionnaire-39 (PDQ-39)

NMSS domain	rs	P
Cardiovascular	0.057	0.307
Sleep/fatigue	0.363	0.001
Mood/cognition	0.377	0.001
Perceptual problem/hallucination	0.392	< 0.001
Attention/Memory	0.395	< 0.001
Gastrointestinal tract	0.110	0.163
Urinary tract	0.158	0.080
Sexual function	0.120	0.148
Miscellaneous	0.116	0.150
NMSS total	0.468	< 0.001

NMSS: Non-motor symptoms scale

Correlation between motor symptoms and cognition: Data analysis revealed correlations between motor symptoms and MMSE scores, as the Hoehn and Yahr[7] scores were significantly higher in PD patients with lower MMSE scores (P = 0.004). Also, there was a significant association between UPDRS part III and MMSE scores (P = 0.003).

Discussion

Recently, much has been written about NMS as disabling symptoms of PD that may affect QOL more than motor symptoms.

In about 20% of patients with PD, NMS may be the main presenting features.[14] However, PD is usually diagnosed when motor symptoms appear, which is the time that most dopaminergic neurons are lost, but prior to this time, NMS would not be usually attended by clinicians.

Unfortunately, the situation is worse in developing countries. Most patients seek treatment after they become disabled from their motor symptoms, and NMS impact their QOL but they and their physicians do not pay attention to them.

To the best of our knowledge, this study is the first one on prevalence of NMS in Isfahan. We found high prevalence of NMS in our PD population as 100% of them had at least one NMS, with the most prevalent one being fatigue (87.7%). Most of them had been disabled by their untreated NMS.

Other studies showed the same result: Barone, et al. evaluated 1072 patients and found that nearly all of those patients complained of at least one NMS, where fatigue (58.1%) was the most prevalent one.[15] Li, et al. in China reported the prevalence of NMS 100% in their PD sample, and again, fatigue (76.0%) was the most common NMS.[6]

Another study in Malaysia reported 97.3% NMS prevalence in their PD samples, where gastrointestinal symptoms were more prevalent (76.1%), and among them, constipation was the most common.[16]

In Peru, another study was done where NMSQ was used as the sole assessment tool for NMS, and they reported that 99.3% of their patients suffered from NMS, with depression and sadness being the most common symptoms.[17] Estrada-Bellmann, et al., with the same methodology, showed that fatigue was the most common domain of NMS symptoms in a Mexican sample.[18] Most of these studies showed the same results, but some differences may have occurred because of methodological differences between those studies and this research. Such differences

include inclusion and exclusion criteria, using different questionnaires, racial variably, healthcare facilities, and economic conditions.

As shown in table 2, NMS symptoms had a high prevalence in our sample compared to previous studies. This indicates a lack of sufficient tertiary healthcare in our country, and unfamiliarity of our population with PD. Only when the disease imposes high impacts on their QOL and ADL they seek treatment.

One study in Tehran, Iran, evaluated the QOL of patients with PD and showed that motor symptoms affecting activities of daily life, depression, anxiety, and being woman had impact on the QOL of PD patients, but NMSS and NMSQ were not used in that study and they mostly paid attention to the QOL of patients.

Fatigue is often recognized by patients with PD as one of their most disabling symptoms with the greatest impression on their QOL.[19]

Prevalence of fatigue in PD was reported to be between 33%–78%,[19] but our results showed a higher prevalence (87.7%). Fatigue causes severe disability, although this symptom is one of the most prevalent NMS in PD, but has mostly been neglected by patients and clinicians. Kang, et al. were reported that fatigue can increase risk the risk of developing PD.[20]

The results have shown strong correlations between the duration of disease and NMS as well as PDQ-39, so, NMS begin before motor symptoms. NMS also develop throughout the course of disease and cause disability that adds on to motor symptoms. This is shown by the strong correlations between disease duration and the NMSS mood/cognition, perceptual problem/hallucination, attention/memory, and sexual domains, and similar domains in the NMSQ. Also, there were correlations between motor symptoms and NMS, which again indicate that as disability worsens (indicated by worse by motor symptoms), NMS become worse, too. As most PD drugs improve only motor symptoms, these findings could show why patients' QOL remain poor despite adequate treatment.

Cognitive impairment correlated with NMS and motor symptoms, but disease duration and MMSE score had no association, which may indicate that cognition correlates with disease severity. Thus, patients with more severe PD have worse NMS and motor symptoms, and less cognitive reserve.

We acknowledge that our study has some limits, including low sample size and lack of normal population as controls, however, this study is the first one in Iran that used the following questionnaires: NMSS, NMSQ, PDQ-39, and UPDRS I-IV for assessing NMS.

Conclusion

In conclusion, as with other studies, we found a high prevalence of NMS in our sample. In our opinion, a change in PD criteria may be necessary, such as adding NMS to diagnostic criteria that could help to diagnose PD earlier, and when neuroprotection becomes available, diagnosis in earlier stages may help prevent worsening motor symptoms and disability. Also, faster and more accurate diagnosis and treatment of NMS would improve patients' QOL and prevent disability.

Conflict of Interests

The authors declare no conflict of interest in this study.

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The comparison of anti-seizure and tocolytic effects of phenytoin and magnesium sulphate in the treatment of eclampsia and preeclampsia: A randomised clinical trial

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Keywords
Phenytoin; Magnesium Sulphate; Cesarean Section; Eclampsia; Preeclampsia

Abstract

Background: To date, magnesium sulphate ($MgSO_4$) is the treatment of choice for prevention of seizure in eclampsia and preeclampsia. However, there are some limitations in the administration of $MgSO_4$ due to its tocolytic effects. The aim of this study was to compare the anticonvulsant and tocolytic effects of $MgSO_4$ and another drug, phenytoin, in patients with eclampsia and preeclampsia.

Methods: This clinical trial was conducted on pregnant women hospitalised with eclampsia or preeclampsia, during 2014–2016. The subjects were randomly assigned to two treatment groups using blocking method based on disease (eclampsia or mild and severe preeclampsia). One group received $MgSO_4$ (group M) and another group received phenytoin (group P) as treatment. Each group consisted of 110 and 65 women with mild and severe preeclampsia, respectively (subgroup A), and 25 women with eclampsia (subgroup B). Duration of labor, the number of cesarean sections, convulsions and Apgar scores of infants were compared between the two groups and were considered as treatment outcomes.

Results: Convulsion rate was significantly lower with $MgSO_4$ than phenytoin ($P = 0.001$). No seizure occurred in patients with mild preeclampsia in group P. Duration of stage one of labor ($P < 0.001$) and the number of cesarean sections ($P = 0.040$) were significantly higher in group M. However, one-minute Apgar scores for newborns were higher in women treated with $MgSO_4$ compared to that of phenytoin ($P = 0.001$). Five-minute Apgar was not significantly different.

Conclusion: Although $MgSO_4$ is more effective than phenytoin for prevention of convulsion in eclampsia and severe preeclampsia, phenytoin may be considered for treatment of special conditions such as mild preeclampsia. Due to the tocolytic effects of $MgSO_4$ on increasing the duration of labor, the increased risk of cesarean section and the potential

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for toxicity, physicians should critically consider the best drug according to the condition of the patient.

Introduction

Preeclampsia is a prevalent multisystem disorder. It is associated with systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg after 20 weeks of gestation and occurrence of proteinuria in previously normotensive patients. Severe preeclampsia can damage several organs such as liver, kidneys, clotting system and brain.[1-3] Preeclampsia and eclampsia are the second largest cause of maternal morbidity.[4-6]

Severe preeclampsia without anti-seizure prophylaxis transforms to eclampsia and new-onset generalised seizures occur in eclamptic women.[7] Women with eclampsia should receive anticonvulsant therapy but there is controversy about this choice.[8-10] Anticonvulsant drugs generally used as prophylaxis are diazepam, phenytoin and $MgSO_4$,[7,10] but many studies reported that $MgSO_4$ is the first choice of therapy.[11-13]

Convulsion may occur due to interference in the regulation of cerebral circulation, dysfunction of endothelium and brain edema.[7] $MgSO_4$ stimulates the release of prostacyclin from endothelium and acts as a vasodilator, reducing systemic blood pressure and protecting from cerebral edema.[14-16]

Advantages of $MgSO_4$ therapy are rapid onset of action, easily available antidote (calcium gluconate), lack of sedation and low cost. On the other side, some side effects of $MgSO_4$ can occur in patients such as painful intramuscular administration, flushing and warmth, nausea, vomiting, headache and muscle weakness. Also, dyspnea, chest pain, pulmonary edema, cardiac arrest and respiratory depression due to magnesium toxicity may be seen in $MgSO_4$ therapy.[17] The tocolytic activity of $MgSO_4$ can increase the duration of labor, the number of cesarean section, and post-partum hemorrhage.[9,18,19]

However, some traditional anticonvulsant drugs such as phenytoin are useful as alternatives.[8,9] Phenytoin crosses the blood-brain barrier rapidly. Side effects of phenytoin include dysrhythmia, hypotension fever, skin rash around the eyes and allergy.[5] The aim of this study was to compare the effects of $MgSO_4$ and phenytoin in terms of method and duration of labor and the rate of seizure in patients with eclampsia and preeclampsia.

Materials and Methods

After approval from the ethics committee, the present randomised clinical trial study was conducted on 400 pregnant women admitted with eclampsia, mild and severe preeclampsia to Arash Hospital in Tehran, Iran, during the time period 2014-2016 (clinical trial number: IRCT2016120311020N7).

Primiparous women with mild and severe preeclampsia and eclampsia and ≥ 34-week gestational age were included in the trial. Patients with heart disease, multifetal pregnancy, smokers, drug users and women with hypersensitivity to $MgSO_4$ or phenytoin were excluded. According to the mentioned inclusion criteria, the patients were chosen with random blocking method based on the disease (eclampsia or mild and severe preeclampsia) and were assigned to one of the two treatment groups. One group received $MgSO_4$ (group M) and another group received phenytoin (group P) as treatment. In each group, 110 women with mild and 65 women with severe preeclampsia (subgroup A), and 25 women with eclampsia (subgroup B) were included (Figure 1).

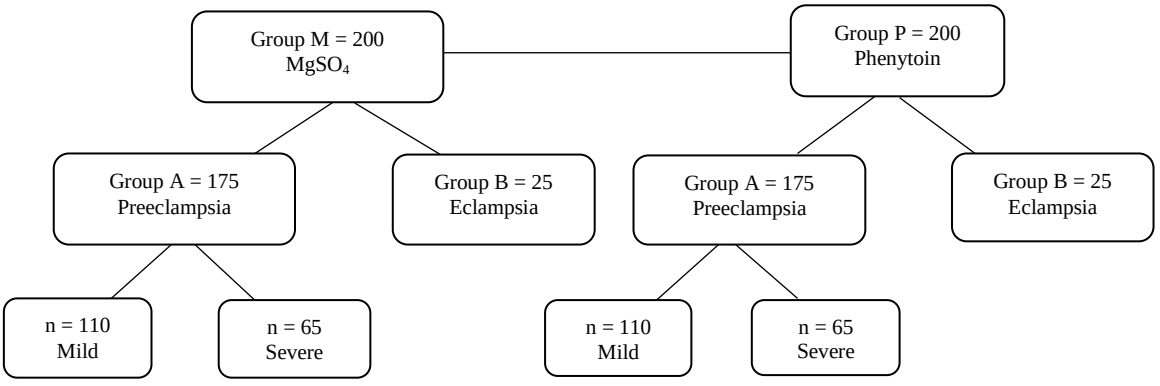

Figure 1. Diagram of the study

Study outcomes, duration of labor, the number of cesarean sections, the number of convulsion events and Apgar scores of infants were compared between groups.

Mild preeclampsia was defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg after 20 weeks of gestation and proteinuria. Severe preeclampsia was defined as systolic blood pressure of ≥ 160 mmHg and/or diastolic blood pressure of ≥ 110 mmHg or when patients with preeclampsia had organ damage such as in liver, kidneys, clotting system, or brain. Eclampsia referred to the occurrence of new-onset tonic-clonic seizures or coma in a patient with preeclampsia.

Group M received the loading dose of 4 g 20% $MgSO_4$ in 100 ml of lactated Ringer's solution intravenously over 20 min, followed by 2 g/hour IV infusion. Patients were monitored every 4 hours regarding the following parameters: presentation of patellar reflex, urine output > 100 ml/4 hours or > 25 ml/hour, and respiratory rate > 12/min. In group P loading dose of 20 mg/kg body weight (maximum 1000 mg) of phenytoin in 100 ml of lactated Ringer's solution was given intravenously slowly over 20 minutes. A maintenance dose of 500 mg was given orally after 10 hours. Therapy was continued for 24 hours post-partum or after the last convulsion following delivery.

The number of convulsions was recorded every four hours and all other laboratory data were recorded every six hours. Complications such as acute renal failure, cerebrovascular accident, and hepatic failure, were also recorded if present. Apgar scores of the fetus at one and five minutes were noted. Duration of labor and the type of delivery were also recorded.

All data analyses were conducted using SPSS for windows (version 16, SPSS Inc., Chicago, IL, USA). Descriptive statistics for continuous variables were presented as mean ± standard deviation and for categorical variables as numbers (percentage). The baseline characteristics of the two groups were compared using an independent t-test for continuous variables and the chi-square test for categorical variables. Moreover, the convulsions were compared between the groups using chi-square test. All statistical tests were two-sided and the level of statistical significance cut-off was set at 0.05. All analyses were performed on an intent-to-treat basis. The conduct and analysis of the trial strictly adhered to the 2010 CONSORT guidelines.

Results

The mean age of patients in the group M was 27.4 ± 5.9 and in the group P was 27.5 ± 5.7. In the group M, the mean body mass index (BMI) was 24.38 ± 2.72 and in group P it was 24.68 ± 2.74. The differences between the two groups in mean age (P = 0.920) (Table 1) and mean BMI (P = 0.270) (Table 1) were not significant. Also, there was no statistically significant difference between group M (36.25 ± 1.18) and group P (36.45 ± 1.07) in mean gestational age (P = 0.120) (Table 1).

The number of convulsion attacks in patients allocated in $MgSO_4$ group was 0, and in patients treated with phenytoin was 10 (seven convulsions in patients with severe preeclampsia and three convulsions in patients with eclampsia). $MgSO_4$ was significantly more efficient than phenytoin for convulsion prevention (P = 0.001) (Table 2).

Duration of stage 1 of labor was significantly longer in group M (294.4 ± 103.2 min) compared to group P (258.80 ± 101.01 min, P < 0.001) (Table 2).

Duration of stage 2 of labor was also longer in group M (48.18 ± 16.05 min) compared to group P (46.21 ± 15.20 min), but the differences were not statistically significant (P = 0.200) (Table 2). The rate of cesarean section was significantly greater in group M (45%) compared to group P (35%) (P = 0.040). $MgSO_4$ induced longer labor and increased the rate of cesarean sections in comparison to phenytoin.

There was a statistically significant difference in one-minute Apgar score between group M (8.57 ± 1.50) and group P (8.06 ± 1.66) (P = 0.001) (Table 2) but there was no significant difference in the five-minutes Apgar score (P = 0.340) (Table 2). The one-minute Apgar score for newborns was higher in group M but finally, it was same in both groups.

Table 1. Baseline characteristics

Baseline demographics	Group M (n = 200)	Group P (n = 200)	P
Age (years) (mean ± SD)	27.40 ± 5.90	27.50 ± 5.70	0.924
Body mass index (kg/m^2) (mean ± SD)	24.38 ± 2.72	24.68 ± 2.74	0.273
Gestational age (weeks) (mean ± SD)	36.25 ± 1.18	36.45 ± 1.07	0.120

SD: Standard deviation

Table 2. Primary and secondary outcomes of study

Outcomes	Group M (n = 200)	Group P (n = 200)	P
Apgar 1 min (mean ± SD)	8.57 ± 1.50	8.06 ± 1.66	0.001
Apgar 5 min (mean ± SD)	9.88 ± 0.40	9.86 ± 0.43	0.340
Duration of stage 1 of labor (min) (mean ± SD)	294.40 ± 103.20	258.80 ± 101.01	< 0.001
Duration of stage 2 of labor (min) (mean ± SD)	48.18 ± 16.05	46.21 ± 15.20	0.200
Rate of cesarean section (%)	45	35	0.040
Convulsion in patients with mild preeclampsia (n)	0	0	0.001
Convulsion in patients with severe preeclampsia (n)	0	7	
Convulsion in patients with eclampsia (n)	0	3	

Discussion

In the present study, seizures were observed in 10 patients in phenytoin group (7 patients in severe preeclampsia subgroup and 3 patients in eclampsia subgroup) and no seizure occurred in $MgSO_4$ group and/or in patients with mild preeclampsia in the phenytoin group after the trial.

$MgSO_4$ is known as a better choice compared to phenytoin for prevention of seizures in patients with eclampsia and preeclampsia.[16,20] However, Slater and colleagues reported 100% treatment success in their study on 26 women with preeclampsia and eclampsia who were given phenytoin.[21] Possible explanations for this inconsistency in studies may be the administration of different doses of phenytoin. In a study by Robson, et al., three women had seizures despite receiving therapeutic levels of phenytoin.[22] Appleton, et al. explained that therapeutic threshold of phenytoin in non-pregnant patients and pregnant women with preeclampsia may be different.[23]

In the present study, both the rate of cesarean section and duration of labor in $MgSO_4$ group were significantly higher than phenytoin group. Our study showed that the tocolytic effects of $MgSO_4$ are considerably higher compared to that of phenytoin, but $MgSO_4$ is also more effective than phenytoin in the prevention of convulsions.

Our results are in accordance with many previous researches that reported a statistically significant increase in the duration of labor and the rate of cesarean section in patients treated with $MgSO_4$ compared to phenytoin.[5,24,25] In contrast, Belfort, et al. showed that $MgSO_4$ is a weak tocolytic drug and labor duration does not appear to be affected by its administration.[26] Moreover, some studies, reported no tocolytic effects for $MgSO_4$ in women with preeclampsia.[18,27,28]

Phenytoin induced more rapid cervical dilation than $MgSO_4$ and did not increase the duration of labor.[25] Patients treated with phenytoin had significantly less postpartum hemorrhage,[5,29] and less time was required to regain consciousness compared to patients treated with $MgSO_4$.[5]

Therefore, phenytoin can decrease the need for skilled workers in the delivery room. It might be important for hospitals in the low- and middle-income countries with a high prevalence of patients with preeclampsia and eclampsia and insufficient facilities. Phenytoin can be helpful for hospitals that experience increased bed turn-over in those countries.

Because of the intensive care requirement for maternal monitoring during intravenous infusion of $MgSO_4$ or risk of toxicity, particularly where the capacity of maternal monitoring is limited, phenytoin seems to have practical implications.

The present study showed that one-minute Apgar score was lower in phenytoin group but five-minute Apgar score did not differ significantly. Roy, et al. showed that infants born in $MgSO_4$ group had higher Apgar scores compared to phenytoin group, but the results were not statistically significant.[5] Phenytoin does not have a significant effect on Apgar score.

Conclusion

Although $MgSO_4$ is apparently a better choice than phenytoin for the prevention of seizure in eclampsia and severe preeclampsia, phenytoin can be considered for treatment in specific conditions such as mild preeclampsia, owing to its lower risk of convulsion. Phenytoin can be practically implicated in low- and middle-income countries where the capacity for maternal monitoring is limited, considering the potential for toxicity of $MgSO_4$ when administered without intensive care. Further studies are recommended with larger sample size and different drug dosage.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Recurrent isolated optic neuritis: A study on 22 patients

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Keywords
Chronic Recurrent Isolated Optic Neuritis; Recurrent Optic Neuritis; Neuromyelitis Optica Spectrum Disorder; Multiple Sclerosis

Abstract

Background: Isolated relapsing optic neuropathy is a recurrent painful optic nerve inflammation without any sign of other demyelinating diseases such as multiple sclerosis (MS) or neuromyelitis optica (NMO) spectrum disorders, and the attacks are purely responsive to steroid therapy.

Methods: Recurrent isolated optic neuritis (RION) was diagnosed in patients who presented with at least two disseminating episodes of optic neuritis, and negative clinical, para-clinical, and radiological features of the demyelinating, infiltrative and vasculitis disorders involving optic nerve. The patients were assigned into two groups, chronic recurrent isolated optic neuritis (CRION) entailing patients with steroid dependent attack of optic neuritis and RION patients without steroid dependent attack of optic neuritis. They were monitored over a median of 4.0 ± 2.5 years.

Results: There were 16 women and six men with CRION and RION; with the median age of 31.7 ± 9.8 (29.3 ± 9.7 for women and 37.7 ± 7.7 for men). The women to men ratio was 2.6:1. The mean optic neuritis attack was 2.95 ± 1.32 in total. Eight patients were RION while 14 patients fulfilled CRION criteria and took long term immuno-suppressive drugs. In their follow-up, 4 out of 14 CRION cases (28.5%) showed clinical and concordant para-clinical features of NMO spectrum disorder. The analysis of demographic data showed that the average number of ON attacks in CRION patients (3.79 ± 2.32) was significantly more than the average in patients with RION (2.25 ± 0.46, P = 0.02).

Conclusion: CRION is a disease which requires aggressive glucocorticoid and long-term immunosuppressive therapy to restore visual acuity.

Introduction

Recurrent optic neuritis could be a manifestation of different autoimmune diseases which involve central nervous system. Clinical as well as para-clinical hints may help to achieve the accurate final diagnosis. Recurrent optic nerve inflammation, at least in two disseminated episodes, without any evidence of systemic or central nervous system involvement, is called recurrent isolated optic neuritis (RION).[1-3] If it is steroid dependent or requires continuous corticosteroid to prevent further attacks, it is diagnosed as chronic recurrent isolated optic

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neuritis (CRION).[4-7] Steroid dependency is a crucial point in distinguishing CRION from RION.

A decade ago, Kidd, et al., described CRION syndrome as a unilateral or bilateral recurrent isolated optic neuropathy characterized by painful visual loss in association with inflammatory pathology.[8] Moreover, according to their study, treatment with corticosteroid eliminates pain and improves visual acuity but steroid withdrawal causes tendency to relapse. Long term immunosuppressive therapy is recommended in most cases for preventing steroid side effects.[9-14]

The Patients with CRION and RION should neither have clinical nor para clinical features of demyelinating disorders such as multiple sclerosis (MS) and neuromyelitis optica (NMO), sarcoidosis and systemic autoimmune disease. Testing for anti-aquaporin 4 antibody (anti-NMO) can be helpful in distinguishing NMO spectrum disorders from CRION.[3,15-20]

The accurate diagnosis of optic neuropathy as CRION is important because its treatment, recovery and prognosis are different from those of RION, MS and other demyelinating disorders. Despite MS, optic neuritis resulting from CRION may lead to blindness or sever visual loss.[2,17,21,22]

The present study reports the demographic features and clinical characteristics of some Iranian patients with RION and CRION who referred to our center from different parts of the country.

Materials and Methods

All patients presented with recurrent optic neuritis (at least two episodes) who referred to the MS Clinic at Sina Hospital, the major referral center for demyelinating disorders in Tehran, Iran, between 2003 and 2014, participated in the present study. The diagnosis of optic neuritis had been confirmed by an ophthalmologist as well as a neurologist. The patients were precisely assessed with lab tests and radiological evaluation to exclude those with demyelinating diseases of the central nervous system, and those with infiltrative, inflammatory, granulomatosis and vasculitis disorders involving the optic nerve.

Radiological studies were performed on the patients including orbital magnetic resonance imaging (MRI) and anterior optic pathway with fat suppression, brain, cervical and thoracic MRI and chest X-ray (for the detection of sarcoidosis).

Patients without any evidence of specific lesion on brain and spinal MRI involvement were eligible to enter the study.

Blood sampling for complete blood count (CBC), electrolytes, thyroid function tests (TFT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), anti-double stranded DNA (anti dsDNA), vitamin B12, aquaporin 4-antibody (enzyme-linked immunosorbent assay method) and cerebrospinal fluid (CSF) sampling were obtained from all of the patients.

According to the data obtained from medical history, systemic and neurological examination, radiological, serological and spinal fluid investigation, only the patients with isolated idiopathic recurrent optic neuritis were included in this study.

Demographic findings of these cases, response to the treatment, and disease evolution during the survey were analyzed. The patients had some visits with every 6 months to 1 year interval. In addition, they were visited whenever required and after the attacks.

Recurrent attacks affecting the same eye were considered when there was at least 1-month interval between two attacks.

Results

As indicated in the method, the patients diagnosed with a demyelinating, ophthalmologic, nutritional deficiency, infiltrating and inflammatory systemic disorders causing optic neuropathy, were excluded from the survey; thus only 16 women and 6 men had the criteria for CRION or RION.

Out of 22 patients, 14 clearly fulfilled the diagnostic criteria for CRION (corticosteroid dependency and attack recurring with steroid withdrawal) while the others were RION.

The women to men ratio was 2.6:1. The mean age of the patients was 31.7 ± 9.8 years.

In the women group, the mean age was 29.3 ± 9.7 while it was 37.7 ± 7.7 for men, suggesting no significant statistical difference between the two groups (P = 0.07). The most prevalent age of onset was in the third and fourth decades of life with 54% and 27% for each decade respectively, with the age range of 9-45 years.

A total number of 54 attacks were recorded for all patients. The mean recurrence of attacks was 2.95 ± 1.32 (median 3) which showed no significant difference between the both genders (P = 0.54).

Table 1. Demographic data of patients

Total number	Female	Male	Total	P
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
	16	6	22	
Age at diagnosis (year)	29.3 ± 9.7 (29.0)	37.7 ± 7.7 (39.5)	31.7 ± 9.8 (31.0)	0.07
Age of onset (year)	26.4 ± 11.2 (26.8)	35.8 ± 7.2 (37.0)	29.1 ± 10.9 (29.9)	0.07
Number of attacks	3.06 ± 1.76	3.67 ± 2.65	2.95 ± 1.32 (3.0)	0.54
Duration of disease (year)	5.99 ± 3.60 (5.7)	6.91 ± 3.10 (6.0)	6.24 ± 3.43 (6.0)	0.57

SD: Standard deviation
P of < 0.05 are considered significant

The maximum number of episodes was 9 times in two patients; three patients experienced 4 attacks and it was less than 4 for the others. Four patients experienced bilateral simultaneous optic neuritis in one episode during the course of their disease. One patient had simultaneous bilateral optic neuritis at the onset and two further times during the follow-up. The demographic data is shown in table 1.

The demographic data is presented in detail for each group in table 2. Comparison of age of onset, duration of disease and follow-up between CRION and RION revealed no significant differences between the two groups, but the number of attacks was more in CRION before the beginning of treatment, compared to RION cases and the difference was significant (P = 0.02).

MRI, CSF, and serologic test findings: The CSF analyses for cell count, protein and glucose were normal in all patients, and oligo clonal band (OCB) was negative in all patients except for one who showed just one unmatched band in CSF.

Para clinical tests for vasculitis/autoimmune disorders were negative in all patients.

Three patients had nonspecific T2 hyper intense lesions in white matter on brain MRI, the number of these T2 nonspecific brightness lesions remained unchanged during the brain MRI follow-up in the next 6 months and the following year. Spinal cord MRI was negative in all patients at the first evaluation.

NMO antibody was negative during the first evaluation in all patients.

Clinical course of the disease: In the RION group, all patients responded completely to intravenous corticosteroid during their attacks and after tapering corticosteroid, they remained free of exacerbation for a mean time of two-year follow-up.

Table 2. Demographic data of each group

Variable	CRION	RION	Total	P
	Mean ± SD	Mean ± SD	Mean ± SD	
Age at diagnosis (year)	35.90 ± 3.40	34.00 ±6.60	31.70 ± 9.80	
Male	44.70 ± 9.90	39.00 ± 9.90	37.70 ± 7.70	0.72
Female	32.40 ± 13.40	32.00 ± 4.90	29.30 ± 9.70	
Age of onset (year)	29.30 ± 12.60	28.70 ± 7.20	29.10 ± 10.90	
Male	37.00 ± 6.50	33.50 ± 10.60	35.80 ± 7.20	0.90
Female	26.20 ± 13.40	26.70 ± 5.70	26.40 ± 11.20	
Duration of disease (year)	6.70 ± 4.07	5.43 ± 1.80	6.24 ± 3.43	
Male	7.75 ± 3.59	5.25 ± 1.06	6.91 ± 3.10	0.55
Female	6.29 ± 4.36	5.50 ± 2.07	5.99 ± 3.60	
Number of attacks	3.79 ± 2.32	2.25 ± 0.46	2.95 ± 1.32	
Male	4.25 ± 3.20	2.50 ± 0.70	3.67 ± 2.65	0.02
Female	3.60 ± 2.06	2.17 ± 0.40	3.06 ± 1.76	
Duration of follow up (year)	4.32 ± 2.91	3.35 ± 1.31	4.00 ± 2.54	0.54
Male	7.00 ± 3.55	4.75 ± 0.35	6.25 ± 2.99	
Female	3.25 ± 2.01	2.80 ± 1.09	3.10 ± 1.73	
Number of patients	14	8	22	
Male	4	2	6	
Female	10	6	16	

CRION: Chronic recurrent isolated optic neuritis; RION: Recurrent isolated optic neuritis; SD: Standard deviation;
P-value of < 0.05 is considered significant.

Table 3. Neuromyelitis optica spectrum disorder (NMOSD) cases

	Case 1	Case 2	Case 3	Case 4
Gender	Man	Man	Woman	Woman
Age of onset (year)	45	29	42	26
Duration disease (year)	13	5	8	4
Interval between disease onset and final diagnosis of NMOSD (year)	10	1	6	2
MRI positive findings	LETM	LETM	LETM	Periaqueductal hyperintensity
NMO antibody	Positive	Positive	Positive	Positive
Optic neuritis episodes	9	3	4	4

NMOSD: Neuromyelitis optica spectrum disorder; LETM: Longitudinally extensive transverse myelitis; MRI: Magnetic resonance imaging

In the CRION cases, two patients had one episode of optic neuritis who needed to be treated with plasma exchange in addition to the intravenous corticosteroid [one of them developed Neuromyelitis optica spectrum disorder (NMOSD) later]. After initiating the long-term immunosuppressive treatment (13 patients received azathioprine and only one patient received low dose prednisolone), patients were evaluated for their response to drug and disease status in regular visits of every 6 months.

Four out of fourteen CRION cases developed NMO spectrum disease during follow-up course (Table 3); three of them presented paraplegia and spinal cord syndromes, with extensive cord lesions compatible to NMO spectrum disorders. Anti-aquaporin 4 was positive in these three patients. In the other patient, follow-up MRI revealed periaqueductal hyper intensity in the brain and positive NMO antibody in the serum.

The mean years between the onset of recurrent ON and final diagnosis was 4.75.

Discussion

The prevalence of demyelinating disorders including MS is increasing. Although optic neuritis is one of the most common presenting symptoms in MS and NMO, there are still a small number of patients without any definite diagnosis even with the recurrence of the symptoms.[23-25] RION and CRION are associated with those patients who manifest recurrent optic neuritis without a definite diagnosis of any other demyelinating diseases such as MS or NMO. They are more prevalent in women and may develop to other typical demyelinating diseases over time. Four of our cases developed NMOSD which is concordant with other studies.[20,26,27] Except these converted cases, other CRION patients remained responsive to steroids and immunosuppressive therapy like the previous observations made on CRION.[6,11] Only two of our patients had recurrent episodes with less favorable responses to treatment.

Similar to the report presented here, other studies showed that the prevalence of CRION and RION is relatively higher among women.[1,2,11,22,28] The strong point of this study is the comparison made between RION and CRION cases with respect to the age of onset, sex superiority, rate of attacks and disease conversion. Since the risk of blindness is high among CRION cases, recognition of this disease is of considerable importance.

Other probable differential diagnoses were also made in the present study. In contrast to studies conducted by Myers, et al.[11] and Lin, et al.[29] there were not any evidence of vasculitis disorders or granulomatous diseases in the cases of the present study; moreover, no abnormality was found in the screening serologic test performed for autoimmune disorders, suggesting the presence of autoimmune optic neuropathy in the absence of systemic autoimmune process.[30]

Brain MRIs were normal except for three patients who had non-specific white matter lesions. This finding is compatible with the findings of other studies about brain MRI in CRION.[8,20,26,31] Besides, except for one patient, OCB was negative.

Although the patients with NMOSD or MS were excluded before the beginning of the study, during the follow-up, some of the CRION cases converted to NMOSD. This conversion was also observed in other studies.[20,26,27] Alongside the risk of conversion to MS and NMOSD, the higher rate of ON attacks and their severity in the CRION patients, predispose the optic nerve to an axonal damage. Optical coherence tomography (OCT) is a useful method to document this effect. With respect to two patients in CRION group, the optic neuritis attacks did not respond well to the treatment in the acute phase. As stated in the survey performed by Petzold and Plant,

prognosis of recovery from optic neuritis is poorer among NMO and CRION cases compared to those with MS.[2]

The CRION cases in the present study (except for two cases who finally converted to NMOSD) were well controlled during the long term immunomodulatory treatment similar to the other studies.[6,11] In addition to reports about azathioprine and methotrexate, cyclosporine, alkylating agents such as cyclophosphamide and chlorambucil, and intravenous immunoglobulin (IVIG) were among the choices of treatment.[11,14,22] A case series of patients with RION reported failure of rituximab in controlling attacks in one patient, but a potent effect was reported for natalizumab on another patient.[32] Thereafter, it can be concluded that due to the small data which is presented specially on more aggressive treatments, judgment about the choice of treatment is challenging.

The significant difference observed in the present study between CRION and RION in terms of means of ON attacks may be due to the higher number of attacks in CRION cases before the initiation of the therapy.

Limitation: Unfortunately, there was no OCT data of the patients, which could add documentary information about optic nerve and retinal damage in both groups. The cell-based assay anti-NMO technique does not exist in Iran; therefore, we had to utilize enzyme-linked immunosorbent assay (ELISA) technique. It is hoped that future studies apply this novel method instead.

Antibody against myelin oligodendrocyte glycoprotein is introduced as a diagnostic marker and can be used as a prognostic factor in patients with a seronegative anti-NMO, facilitating diagnosis of a subgroup of NMOSD. However, this method was not employed it in this study; it would be one of the prospective issues in further studies.

Conclusion

Early immunomodulatory treatment is recommended to prevent further optic neuritis attacks and consequent axonal damage. Isolated optic neuritis may be dependent on steroids and should be followed and managed properly.

These patients may fulfill the criteria for NMO or MS, but most of them remain isolated even after several years. Early proper treatment with steroids or cytotoxic agents is recommended to prevent further optic neuritis attacks and consequent axonal damage.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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Bimelic symmetric Hirayama disease: Spectrum of magnetic resonance imaging findings and comparative evaluation with classical monomelic amyotrophy and other motor neuron disease

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Keywords
Monomelic Amyotrophy; Wasting; Lamino-Dural Space; Anterior Horn Cells; Amyotrophic Lateral Sclerosis

Abstract

Background: The aim of the study was to evaluate the magnetic resonance imaging (MRI) findings in bilateral symmetrical Hirayama disease and find out MRI features which are probably more indicative of symmetrical Hirayama disease, thereby help in differentiating this entity from other motor neuron disease (MND).

Methods: This prospective as well as retrospective study was carried out from December 2010 to September 2016 in a tertiary care center of northeast India on 92 patients with Hirayama disease. Only 19 patients having bilateral symmetric upper limb involvement at the time of presentation were included in this study sample.

Results: Nineteen patients, who constituted 20.6% of 92 patients of clinical and flexion MRI confirmed Hirayama disease were found to have bilateral symmetrical wasting and weakness of distal upper limb muscles at the time of presentation. Mean ± standard deviation (SD) age of onset of the disease process was 21.7 ± 3.8 years with mean ± SD duration of illness of 3.6 ± 1.3 years. MRI revealed lower cervical cord flattening in 13 (68.4%) patients which was symmetrical in 6 (31.6%) patients and asymmetrical in 7 (36.8%) patients. In the majority of these patients, T2-weighted images (T2WI) cervical cord hyperintensities were found extending from C5 to C6 vertebral level. Seven (36.8%) patients in our study showed bilateral symmetric T2WI hyperintensities in anterior horn cells (AHC).

Conclusion: Bilateral symmetrical involvement of Hirayama disease is an uncommon presentation. Symmetrical cervical cord flattening, T2WI cord

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and/or bilateral AHC hyperintensities were the major MRI findings detected. Flexion MRI demonstrated similar findings in both bimelic amyotrophy and classical unilateral amyotrophy. However, flexion MRI produced some distinguishing features more typical for bilateral symmetrical Hirayama disease which help to differentiate it from other MNDs.

Introduction

Hirayama disease was initially described by Hirayama, et al.[1] in 1959 in a Japanese patient with atrophy of the distal upper limb also known as juvenile muscular atrophy of distal upper limb extremity[2] or monomelic amyotrophy.[3] Hirayama disease is characterized by insidious onset of asymmetric oblique amyotrophy characterized by wasting and weakness of distal muscles of upper extremity, predominantly affecting small muscles of hand in young (men > women) due to involvement of C7, C8 and T1 segmental myotomes with sparing of brachioradialis and proximal muscles of upper limb innervated by C5-C6 myotomes.[1] Affection of lower limb muscles is very rare.[4,5]

Unilateral presentation is the most common in Hirayama disease, though few cases with asymmetrical involvement and rarely bilateral symmetrical involvement have been reported in literature.[6,7] Various literatures have reported different pattern of disease onset and progression. The most rare type is bilateral symmetrical involvement which is seen in only 3.1% of Hirayama disease and which has an association with high level of serum immunoglobulin E.[8-10] The bilateral symmetric Hirayama disease should be differentiated from diseases like other motor neuron diseases (MNDs), syringomyelia, spinal cord tumor, poliomyelitis, toxic neuropathies and traumatic myelopathy. These disorders can be differentiated from bilateral Hirayama disease with clinical, imaging features and genetic testing;[11] whereas syringomyelia, spinal cord tumor or other space occupying lesions can be detected by spinal magnetic resonance imaging (MRI).

We aimed to evaluate the MRI findings in bilateral symmetrical Hirayama disease and find out MRI features which help to differentiate this condition from other MNDs.

Materials and Methods

Our data analysis was designed and the results were tabulated in keeping with a similar study by Pradhan, et al.[6] including a large sample of symmetrical disease. We have compared our results with study conducted by Pradhan, et al.[6] and other similar literatures in the past.

After approval from the institutional ethics review committee, a hospital-based cross-sectional study was conducted. Based on the clinical and flexion MRI criteria, a total of 92 patients with confirmed Hirayama disease were evaluated from December 2010 to September 2016 in a tertiary care center of northeast India. Out of 92 confirmed cases with Hirayama disease, only 19 patients had bilateral symmetrical weakness and wasting of distal upper limbs muscles at the time of presentation and were included in this study. All these patients were assessed through clinical, electrophysiological and radiological evaluation. Informed consent was obtained from patients prior to MRI scan.

Patient selection: We included patients in whom flexion cervical spine MRI was performed. MRI scan was performed using 1.5 Tesla Siemens Magnetom Avanto B15 (Siemens Medical Systems, Erlangen, Germany). Motor and sensory nerve conduction velocities (NCS) and compound muscle action potential (CMAP) amplitudes of median and ulnar nerves were measured in the affected upper limbs.

MRI protocols in patient with Hirayama disease: Imaging of cervical spine was initially performed with patient in neutral supine position with routine sagittal T2- and T1-weighted spin-echo, sagittal and coronal short tau inversion recovery (STIR), and axial T2, T1-weighted fast spin-echo and axial 2D T2-weighted gradient-echo (GRE, Me-2D) sequences. Sagittal spin-echo T1WI were acquired with 450-500/9-15 (repetition time/echo time) while sagittal T2-weighted images (T2WI) were obtained with 4000-4600/110-120 (repetition time/echo time) with 3 mm slice thickness. Axial 2D T2-weighted GRE image was obtained with 650-750/24-32 (repetition time/echo time) with flip angle of 24° to 28°. Flexion MRI of the cervical spine was obtained in 30-40 degree neck flexion. Post-gadolinium fat suppressed sagittal and axial T1WI of cervical spine were obtained in neck flexion with slice thickness of 3 mm.

Image analysis: MRI scans were analyzed for cervical curvature, cord flattening, cord atrophy, T2WI cord or anterior horn cells (AHC) hyperintensities. The maximum forward shifting of posterior dural sac or lamino-dural space (LDS) was measured in midline on post-gadolinium fat

suppressed sagittal T1WI on flexion MRI. Besides anterior-posterior (AP) and transverse (TR) diameter of cervical cord was also obtained in axial images both in neutral and flexion MRI at the site of maximum forward shifting of posterior dural sac. The spinal canal diameters were measured both in neutral and flexion sagittal MRI images. The cervical spinal canal diameter on flexion MRI was measured at the maximum site of posterior dural sac forward shifting. In order to standardize measurement method and to minimize measurement error, each parameter was measured by two radiologists working independently.

Data were presented in terms of percentage, mean and standard deviation (SD). Calculations were done using SPSS software (version 16, SPSS Inc., Chicago, IL, USA).

Results

Out of 92 patients with clinical and MRI confirmed Hirayama disease, 19 patients (20.6%) had bilateral symmetrical wasting and weakness of distal muscles of upper limbs at the time of presentation. The mean age ± SD at the time of presentation and the onset of disease process was 21.7 ± 3.8 and 18.2 ± 3.0 years, respectively. The mean ± SD duration of the disease process was 3.6 ± 1.3 years. The man to women ratio was 18:1. Initial onset of disease process was bilateral symmetrical in 8 (8.7%) patients, initial unilateral amyotrophy progressing to bilateral amyotrophy in 11 (11.9%) patients and unilateral amyotrophy in 73 (79.3%) patients in our study sample of 92 patients. The time taken to affect the opposite upper limb was 1.2 ± 1.2 years in those patients with initial onset of unilateral amyotrophy.

Seven out of 8 patients with initial onset of symmetric disease were clinically suspected to be motor neuron disease and another one patient was toxic myelopathy. Initial unilateral amyotrophy progressed to bilateral amyotrophy in 11 patients clinically suspected to be Hirayama disease (Table 1).

All 19 (100%) patients had hand muscles wasting (Figure 1) and 6 (31.6%) patients also had wasting of forearm muscles. Sixteen (84.2%) patients had cold paresis in hands and 15 (78.9%) patients had hyperesthesia and fasciculation. Deep tendon reflexes of upper limbs were absent/hypoactive in 11 (58%), normal in 4 (21%) and brisk/hyperactive in 4 (21%) patients. The C7, C8 and T1 myotomes were involved in all 19 patients on NCS and electromyogram (EMG).

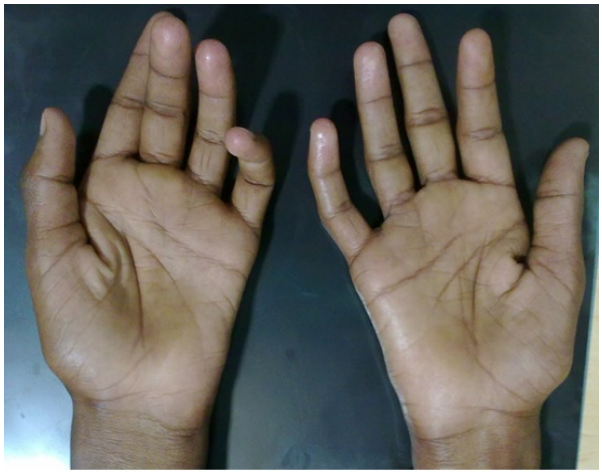

Figure 1. A 25-years old man with bilateral symmetrical wasting and weakness of hand muscles on examination showing flattened thenar and hypothenar eminences

MRI revealed abnormal cervical curvature in 14 (73.7%) patients. Lower cervical cord flattening was noted in 13 (68.4%) patients which was symmetric in 6 (31.6%) patients and asymmetric in 7 (36.8%) patients. Seventeen (89.5%) patients had focal lower cervical cord atrophy, where cord atrophy extended from C5 to C6 vertebral level in 11 (57.9%) patients, C5 to C7 level in 5 (26.3%) patients and C6 to C7 vertebral level in 1 (5.3 %) patient (Table 2).

Thirteen (68.4%) patients showed T2WI hyperintensities in lower cervical cord, which extended from C5-C6 vertebral level in 6 (31.68%) patients, C5-C7 in 5 (26.3%) patients, C6-C7 in 1 (5.3%) patient and C5-T1 vertebral level in another 1 (5.3%) patient (Table 2). T2WI hyperintensities in bilateral AHC giving 'eye of snake' appearance was demonstrated in 13 (68.4%) patients, where bilateral symmetrical AHC hyperintensities was seen in 7 (36.8%) patients (Figures 2 and 3), bilateral asymmetrical AHC hyperintensities, more pronounced in right AHC in 5 (26.3%) patients (Figures 4 and 5), and bilateral asymmetrical AHC hyperintensities, more pronounced in left AHC in 1 (5.3%).

Flexion cervical MRI showed loss of dural attachment, forward shifting of posterior dural sac and post-gadolinium enhancing posterior epidural crescent shaped component due to engorged epidural venous plexus in all (100%) patients. The location of enhancing posterior epidural space component varied from C3 to T6 vertebral level, where 9 (47.4%) patients had in cervical region and 10 (52.6%) patients in cervico-dorsal region (Figures 3 and 6).

Table 1. Summary of 19 patients with bilateral symmetric Hirayama disease at the time of presentation

Case no	Age at presentation (years)/gender	Age at onset (years)	Side of initial affection	Time to affect opposite upper limb (years)	Focal cervical cord atrophy	Cord flattening	Level of T2WI cervico-dorsal cord hyperintensity	T2WI hyperintensities in AHC	Extension of enhancing posterior epidural component on flexion MRI	Associated disco-osteophytic lesion	Prominent epidural flow voids	LDS distance	Ratio of LDS/spinal canal diameter in flexion MRI	Ratio of AP/TR cord diameter during flexion MRI	Ratio of AP/TR cord diameter during neutral MRI
1	25/Man	19	Bilateral upper limbs	-	C5-C6	Symmetrical	C5-C7	Bilateral symmetrical	C5-D2	Yes	No	4.4	0.39	0.37	0.48
2	30/Man	23	Right upper limb	4	C5-C6	Asymmetrical	C5-C6	Bilateral asymmetrical, more on right side	C5-D1	Yes	No	4.8	0.36	0.43	0.49
3	19/Man	16	Left upper limb	2	C5-C7	Asymmetrical	No	No	C5-D5	No	Yes	5.8	0.42	0.22	0.32
4	18/Man	14	Bilateral upper limbs	-	C5-C7	Symmetrical	C5-C6	Bilateral symmetrical	C4-C6	No	No	3.5	0.27	0.32	0.41
5	19/Man	16	Right upper limb	2	C5-C7	No	No	No	C5-D5	No	Yes	9.8	0.71	0.31	0.45
6	16/Woman	14	Bilateral upper limbs	-	C5-C7	Symmetrical	C5-C7	Bilateral symmetrical	C4-C6	Yes	No	4.8	0.44	0.27	0.38
7	24/Man	19	Bilateral upper limbs	-	C5-C6	Symmetrical	C5-C7	Bilateral symmetrical	C5-C7	No	No	4.8	0.37	0.28	0.37
8	23/Man	20	Bilateral upper limbs	-	C5-C6	Symmetrical	C5-C6	Bilateral symmetrical	C5-C7	No	No	3.0	0.24	0.23	0.29
9	21/Man	18	Bilateral upper limbs	-	C6-C7	Symmetrical	C5-C7	Bilateral symmetrical	C4-T1	No	Yes	7.1	0.5	0.22	0.28

10	18/Man	16	Bilateral upper limbs	-	C5-C6	No	No	No	C5-C7	No	No	5.2	0.38	0.23	0.29
11	17/Man	14	Left upper limb	2	No	Asymmetrical	C5-C6	Bilateral asymmetrical, more on left side	C5-C7	No	Yes	4.7	0.35	0.28	0.31
12	19/Man	15	Right upper limb	3	C5-C6	No	C6-C7	Bilateral asymmetrical, more on right side	C4-C6	Yes	No	4.3	0.31	0.26	0.29
13	21/Man	19	Right upper limb	1	No	No	C5-T1	Bilateral asymmetrical, more on right side	C5-C7	No	No	6.1	0.42	0.34	0.38
14	21/Man	18	Right upper limb	1	C5-C6	Asymmetrical	No	No	C3-T2	No	Yes	8.4	0.69	0.21	0.32
15	20/Man	17	Right upper limb	2	C5-C6	Asymmetrical	No	No	C5-T1	No	No	5.2	0.46	0.35	0.46
16	26/Man	22	Right upper limb	2	C5-C7	Asymmetrical	C5-C7	Bilateral asymmetrical, more on right side	C5-T2	Yes	No	4.79	0.41	0.23	0.36
17	28/Man	24	Bilateral upper limbs	-	C5-C6	No	C5-C6	Bilateral symmetrical	C5-T6	No	No	3.9	0.29	0.27	0.35
18	25/Man	21	Right upper limb	2	C5-C6	No	C5-C6	Bilateral asymmetrical, more on right side	C4-C7	No	No	4.1	0.34	0.24	0.37
19	23/Man	20	Left upper limb	1	C5-C6	Asymmetrical	No	No	C5-T3	Yes	Yes	4.59	0.37	0.33	0.43

T2WI: T2-weighted image; AHC: Anterior horn cells; LDS: Lamino-dural space; AP: Anterior-posterior; TR: Transverse; MRI: Magnetic resonance imaging

Table 2. Magnetic resonance imaging (MRI) findings in 19 patients with bimelic symmetric Hirayama disease

MRI finding	n (%)
Abnormal cervical curvature	14/19 (73.7)
Cord flattening	13/19 (68.4)
	Symmetrical 6/19 (31.6)
	Asymmetrical 7/19 (36.8)
Location of cord atrophy	C5-C6 = 11/19 (57.9)
	C6-C7 = 1/19 (5.3)
	C5-C7 = 5/19 (26.3)
T2WI cord hyperintensity	C5-C6 = 6/19 (31.7)
	C6-C7 = 1/19 (5.3)
	C5-C7 = 5/19 (26.3)
	C5-D1 = 1/19 (5.3)
AHC hyperintensities	13/19 (68.4)
	Symmetrical 7/19 (36.8)
	Bilateral asymmetrical more on right 5/19 (26.3)
	Bilateral asymmetrical more on left 1/19 (5.3)
Level of enhancing epidural component extension	Cervical 9/19 (47.4)
	Cervico-dorsal 10/19 (52.6)
Flow voids in epidural component	6/19 (31.6)
Associated disco-osteophytic lesions	6/19 (31.6)

T2WI: T2-weighted image; AHC: Anterior horn cells; MRI: Magnetic resonance imaging

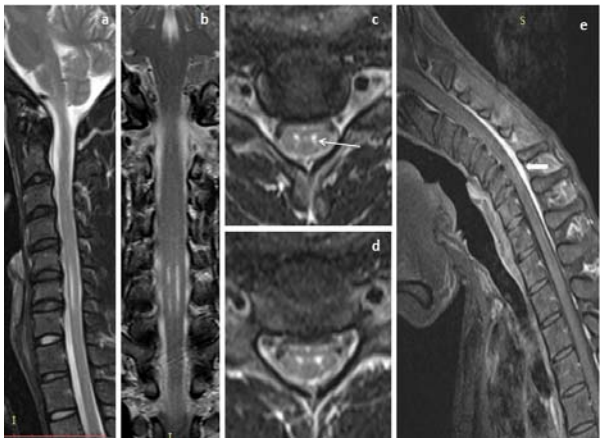

Figure 2. The same patient in figure 1, neutral position sagittal and coronal T2WI MRI images (a, b) showed segmental hyperintensities in lower cervical cord extending from C5 to C7 vertebral level, axial T2WI (c, d) showed symmetrical hyperintense signal in AHC (white arrow), post-gadolinium fat suppressed flexion MRI image (e) showed enhancing crescent shaped posterior epidural lesion extending from C4 to T2 vertebral level (block arrow)

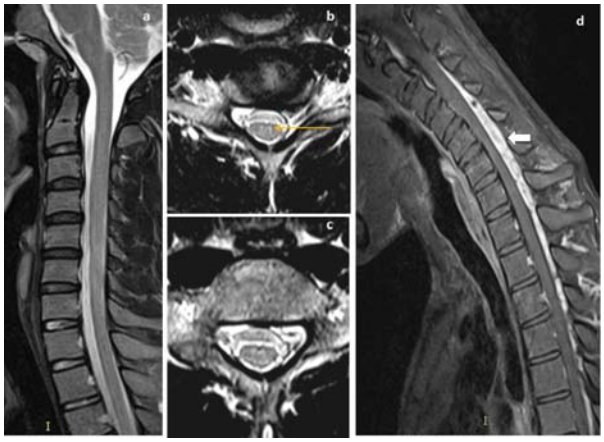

Figure 3. In a 19-year old man, neutral MRI sagittal T2WI (a) showed normal appearance of cervical cord without cord hyperintensities, axial T2WI (b, c) showed bilateral symmetrical faint T2W hyperintensities in AHC of lower cervical cord (yellow arrow), post gadolinium sagittal T1W flexion MRI image (d) showed enhancing posterior epidural lesion extending from C3 to T3 vertebral level (block arrow)

More common location of enhancing epidural component in C5-C7 vertebral level in 5 (26.3%) patients and C4-C6 vertebral level in 3 (15.8) patients. Prominent cerebrospinal fluid flow voids were noted within the enhancing posterior epidural component in 6 (31.6%) patients. Six (31.6%) patients with symmetrical Hirayama disease had also cervical disco-osteophytic bulges (Table 2).

The mean ± SD, LDS distance was 5.2 ± 1.7 mm at maximum forward shifting of posterior dura from the enhancing engorged epidural venous plexus in posterior epidural space. The ratio of maximum forward shifting of posterior dural sac (LDS)/maximum AP diameter of spinal canal during flexion MRI had an average increment value of 0.41 ± 0.12 mm which resulted in cord compression during flexion MRI.

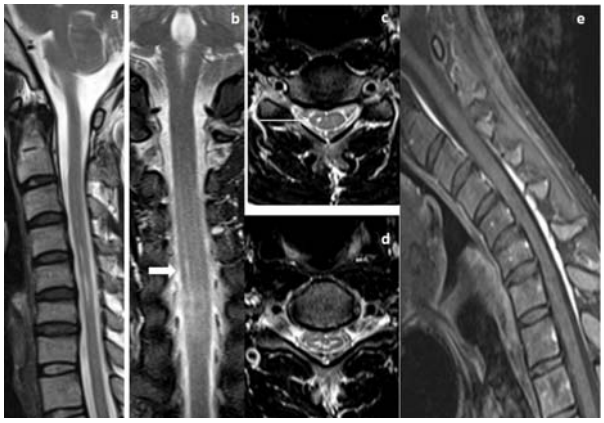

Figure 4. A 17-years old man presented with wasting of bilateral hand muscles. Neural position T2W sagittal and coronal MRI images (a, b) showed segmental hyperintensities in cervical cord extending from C4 to C6 vertebral level, more pronounced in right half of the cord (block arrow), axial T2WI (c, d) showed hyperintensities in bilateral AHC, more pronounced in right AHC and central cord substance (white arrow), post-gadolinium sagittal flexion MRI image (e) showed crescent shaped posterior epidural enhancing lesion with foreword shifting of posterior dural sac

The ratio of AP/TR diameter of cord decreases during flexion MRI because of cord compression and cord flattening.

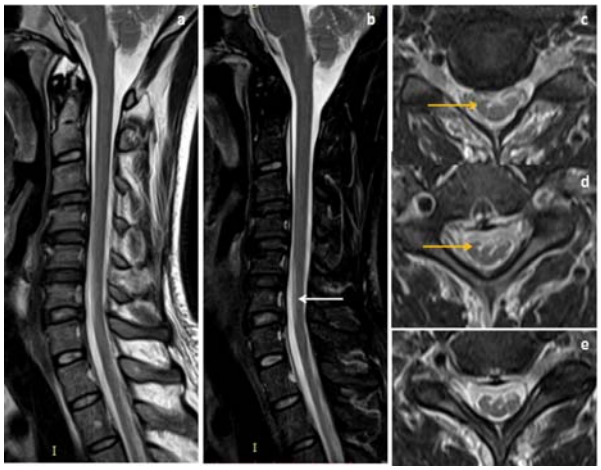

Figure 5. In a 18-years old man neutral MRI sagittal T2W and fat suppressed T2WI (a, b) showed lower cervical cord atrophy with hyperintensities in anterior cervical cord extending from C5 to C7 vertebral level, axial T2WI (c, d and e) showed asymmetrical hyperintensities in AHC (yellow arrows) and anterior cervical cord

The substantial decrement in AP/TR ratio diameter of cord during flexion MRI was 0.28 ± 0.06 (Table 3). Clinical and radiological data of all patients are summarized in table 1.

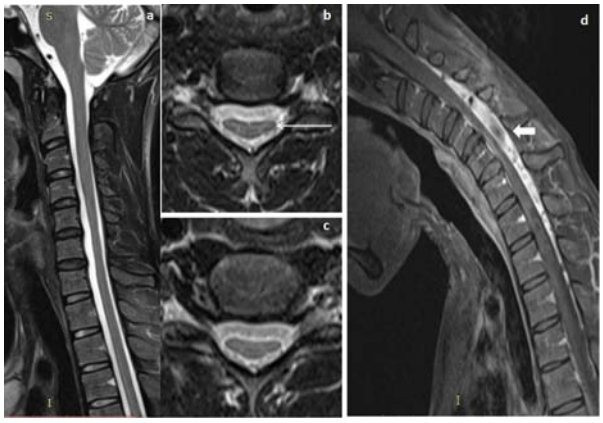

Figure 6. A 21-years old man with bilateral hand muscles weakness, neutral MRI sagittal T2WI (a) showed focal lower cervical cord atrophy without cord hyperintensities. Axial T2WI (b, c) showed anterior flattening of lower cervical cord (arrow), post-gadolinium sagittal flexion MRI T1WI (d) showed anterior displacement of posterior dura matter with enhancing posterior epidural lesion and T1 hypointense cerebrospinal fluid flow voids within (block arrow)

Discussion

The initial symptoms of Hirayama disease are slowly progressing hand weakness and fatigue followed by cold paresis, tremors and atrophy. Asymmetric distribution of symptoms and signs is characteristic, although a bilaterally symmetric form has also been less frequently reported.[6,7,9,12] Segmental C7-T1 myotomes involvement was seen in all cases of our study. The pathology for development of Hirayama disease is thought to be due to compression of lower cervical cord by the posterior dural sac during repeated or sustained neck flexion causing micro-circulatory changes in anterior spinal artery territory which further leads to degeneration of the AHC.[13] Another pathogenetic mechanism cited for development of Hirayama disease is believed to be an imbalance growth between the individual vertebral column and spinal canal contents, leading to abutment of anterior spinal cord against vertebral column and detachment of the posterior dura leading to widened LDS and finally causing microcirculatory disturbances and ischemic changes in the anterior spinal cord.[14-17]

Lehman, et al.[18] found that the median forward shift of posterior dura was 3 mm with mean of 2.7 mm (range 0 to 7 mm) in North American patients with Hirayama disease during flexion cervical MRI. In our study the median foreword shift of posterior dura was 4.8 mm with mean 5.2 mm (range 3 to 9.8 mm) during flexion cervical MRI.

Table 3. Measured parameters during neutral and flexion Magnetic resonance imaging (MRI) in 19 patients of bimelic symmetric Hirayama disease

Parameters	Minimum	Maximum	Mean ± SD
LDS distance (mm)	3.00	9.80	5.2253 ± 1.65862
Spinal canal diameter neutral (mm)	11.10	14.20	12.7158 ± 0.95176
Spinal canal diameter flexion (mm)	10.90	14.60	12.8474 ± 1.08031
AP cord diameter neutral (mm)	3.60	6.40	4.7889 ± 0.84989
TR cord diameter neutral (mm)	10.30	14.60	13.0053 ± 1.06847
AP cord diameter flexion (mm)	3.20	5.60	4.1658 ± 0.73637
TR cord diameter flexion (mm)	12.90	16.10	14.7895 ± 0.80270
LDS/spinal canal diameter flexion	0.24	0.71	0.4066 ± 0.12202
AP/TR cord diameter flexion	0.21	0.43	0.2837 ± 0.06039
AP/TR cord diameter neutral	0.28	0.49	0.3700 ± 0.06782

LDS: Lamino-dural space; AP: Anterior-posterior; TR: Transverse; SD: Standard deviation

Forward shifting of the posterior dural sac is also observed in normal subjects, but without spinal cord compression. The ratio of LDS at maximum forward shift to spinal canal diameter should be increased in Hirayama disease with decreased ratio of AP diameter of spinal cord to transverse diameter of spinal cord in flexion MRI compared to that in neutral position in Hirayama disease. These ratios do not significantly change in normal healthy subjects.[19] In our study sample of 19 patients with bilateral Hirayama disease, the ratio of maximum forward shifting of posterior dural sac (LDS)/maximum AP diameter of spinal canal during flexion MRI had an average increment value of 0.41 ± 0.12 mm which ensured cord compression during flexion MRI.

The ratio of AP/TR diameter of cord during neutral MRI was 0.39 ± 0.07 mm and decreased during flexion MRI because of cord compression and cord flattening with substantial reduction in ratio of AP/TR diameter of cord during flexion MRI (0.28 ± 0.06 mm, Table 3).

Zhou, et al.[20] studied 192 patients with Hirayama disease in mainland China and found bimelic Hirayama disease in 25 patients (13%). In our study, bimelic Hirayama disease was noted in 19 patients out of 92 (20.6%) and initial onset of bilateral symmetric disease was noted in 8 (8.7%) patients followed by initial unilateral amyotrophy which progressed to bilateral amyotrophy in 11 (11.9%).

Pradhan[6] evaluated 11 patients with bilateral symmetric Hirayama disease from North India and observed band like cord flattening on the MRI of all patients (100%) which was symmetric in 7 patients (63.6%) and asymmetric in 4 patients (36.4%). In our study sample of 19 patients, symmetrical and asymmetrical lower cervical cord flattening was noted in 6 (31.6%) and 7 (36.8%) patients, respectively.

Preethish-Kumar, et al.[12] observed bilateral AHC T2WI hyperintensities giving "snake eye" appearance in 65.4% cases in South India, where 57.7% cases showed bilateral symmetrical AHC hyperintensities from. In our study, bilateral AHC T2WI hyperintensities were noted in 68.4% cases, symmetrical in 36.8% cases, asymmetrical with more pronounced signal in right AHC in 26.3% of cases and bilateral asymmetrical hyperintensities more pronounced on left AHC in 5.3% of cases.

Pradhan[6] observed inferior extension of crescent shaped enhancing epidural component during post gadolinium flexion MRI up to the level of T2 vertebral body, however in our study, 10 (52.6%) patients had inferior dorsal extension of enhancing posterior epidural component during flexion MRI, where 2 (10.5%) patients had inferior extension up to T5 vertebral level and 1 patient (5.3%) up to T6 vertebral level.

The typical MRI findings in Hirayama disease may reveal atrophy of lower cervical cord, asymmetric cord flattening, and/or T2WI cord hyperintensities. On neck flexion MRI, anterior displacement of the dorsal dura may be seen with crescent post contrast enhancing venous plexus engorgement in posterior epidural space.[13]

In other MND with spinal cord involvement, progressive neuronal degenerations occur along the corticospinal tract (CST) in the spinal cord. In the most common MND like amyotrophic lateral sclerosis (ALS), the initial MRI findings reveal symmetrical T2WI hyperintensities in anterior lateral column of spinal cord along the CST with preservation of posterior lateral column.[21] It may also show bilateral symmetrical T2WI hyperintensities along AHC giving "snake eye" appearance and in this situation it is difficult to differentiate on conventional MRI from the bilateral symmetric Hirayama disease. However,

flexion cervical MRI helps to differentiate as ALS does not reveal anterior displacement of dorsal dura or enhancing posterior epidural lesion. In patients with ALS, brain MRI shows bilateral T2WI hyperintensities extending along CST from centrum semiovale through posterior limb of internal capsule to ventral brain stem.[21,22]

In patients with spinal muscular atrophy (SMA), T2WI cord hyperintensities may be present in AHC of spinal cord associated with denervation atrophy of axial or proximal muscles. Proximal muscles are dominantly affected in SMA compared to distal muscles. However excessive fatty infiltrations of muscle bundles and increased intermuscular fat planes is noted in SMA. Lower limbs are more affected than upper limbs.[23]

As Hirayama disease has a self-limiting course, the treatment is usually conservative. The treatment involves reducing repeated trauma to cervical cord by avoiding repeated neck flexion, use of soft cervical collar during progressive stage of the disease which has shown to arrest the disease progression.[24] Even surgical interventions like cervical decompression and fusion with or without duraplasty or cervical duraplasty with tenting sutures via laminoplasty without cervical fusion may be advocated in selected patients.[25,26]

Hence early recognition of Hirayama disease is necessary since avoiding or limiting neck flexion prevents or arrest further progression of this disease. So, a high clinical suspicion is necessary to diagnose the bimelic Hirayama disease, and include flexion MRI in addition to neutral MRI while imaging such patients. MRI may help in differentiating bilateral Hirayama disease from other MND, syringomyelia and neuropathies.

Both monomelic and bimelic amyotrophy show similar findings during flexion MRI; however, conventional MRI findings of symmetrical lower cervical cord flattening and bilateral symmetrical AHC hyperintensities favor bimelic amyotrophy. In situations like absence of T2WI cord or AHC hyperintensities, radiological differentiation between monomelic and bimelic Hirayama disease is difficult.

Conclusion

Bilateral symmetric involvement in Hirayama disease, an uncommon occurrence, is usually underdiagnosed because of a common understanding that Hirayama disease has unilateral or asymmetric bilateral involvement. Early diagnosis of bilateral symmetrical disease might help in limiting further progression of the disease by simple means such using cervical collar and asking patient to restrict neck flexion movements.

Conventional MRI findings like symmetrical cord flattening/atrophy and symmetrical T2WI hyperintensities in cord and or AHC favor bilateral symmetric Hirayama disease; however it is essentially difficult to differentiate bilateral symmetrical amyotrophy from the more common classical unilateral amyotrophy through imaging only.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Review Article

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Taming Alzheimer's disease, New perspectives, newer horizons

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Keywords
Alzheimer Disease; Amyloid; Biomarkers; Cerebrospinal Fluid; Magnetic Resonance Imaging; Positron Emission Tomography

Abstract
Alzheimer's disease (AD) is the leading cause of dementia. However, current therapies do not prevent progression of the disease. New research into the pathogenesis of the disease has brought about a greater understanding of the "amyloid cascade" and associated receptor abnormalities, the role of genetic factors, and revealed that the disease process commences 10 to 20 years prior to the appearance of clinical signs. This greater understanding of the disease has prompted development of novel disease-modifying therapies (DMTs) which may prevent onset or delay progression of the disease. Using genetic biomarkers like apolipoprotein E (ApoE) ε4, biochemical biomarkers like cerebrospinal fluid (CSF) amyloid and tau proteins, and imaging biomarkers like magnetic resonance imaging (MRI) and positron emission tomography (PET), it is now possible to detect preclinical AD and also monitor its progression in asymptomatic people. These biomarkers can be used in the selection of high-risk populations for clinical trials and also to monitor the efficacy and side-effects of DMT. To validate and standardize these biomarkers and select the most reliable, repeatable, easily available, cost-effective and complementary options is the challenge ahead.

Introduction

Progressively increasing life expectancy and declining fertility rates have led to a steady demographic shift towards the elderly population and consequently the prevalence of neurodegenerative diseases is on the rise. Alzheimer's disease (AD) is the leading cause of dementia and about 0.5% of the global population or 35 million patients are currently afflicted worldwide.[1,2] This number is expected to quadruple by the year 2050, with an attendant huge human and socioeconomic burden.[3] Despite the disconcerting statistics, these are exciting times as we are at the cusp of better understanding of the disease with the promise of novel disease-modifying therapy (DMT). Simultaneously work is in progress on multi-target-directed ligands (MTDLs), hybrid drugs that act simultaneously on multiple targets, leading to greater therapeutic benefit and simplification of therapeutic regimens.

This article though not exhaustive in scope or detail, outlines the purported pathogenesis of the

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disease, the ongoing research in novel DMT drugs targeting different sites, and the role of diagnostics in detecting the disease in a preclinical state, monitoring disease progress and their complementary role in developing DMT.

Pathogenesis of AD

AD is a multifactorial disease and knowledge of the pathogenesis of AD is essential for understanding the role of diagnostics in its detection, monitoring and development of novel DMT. AD is associated with regional cerebral hypometabolism, extracellular Aβ plaques, intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau, neuroinflammation and oxidative stress, loss of synaptic connections, neural death and atrophy and resultant clinical manifestations of AD.[4-7] The progressive accumulation of Aβ and NFT is believed to begin more than 15 (Aβ) to 10 (NFT) years prior to onset of clinical disease.

Deposition of amyloid-β (Aβ) peptide in the brain is considered to represent the primary event in AD[8] and the amyloid precursor protein (APP), a trans-membrane receptor, is central to the pathogenesis though its exact function is unknown. Aβ is generated by sequential proteolytic cleavage of APP by β-secretase or B-site APP cleaving enzyme (BACE)-1 from within and by γ-secretase from outside the membrane. When normally soluble Aβ peptides attain a definite level, they become insoluble, misfold and aggregate into Aβ plaques. These plaques are composed of insoluble peptides, generally 42 amino acids in length ($A\beta_{1-42}$) and the oligomeric forms of $A\beta_{1-42}$ are thought to have a greater neurotoxic potential than monomers or fibrils.[9,10] Cleavage of APP by the α-secretase followed by γ-secretase generates neuroprotective amyloid precursor protein (APPα).[11]

Apolipoprotein E (ApoE) ε4 allele of ApoE gene encodes the transporter of cholesterol in the brain and is the major genetic susceptibility factor for late-onset AD.[12,13] AD is associated with higher membrane-associated free cholesterol and overall greater brain cholesterol load. Genetic mutations of APP (chromosome 21) or trisomy 21 cause early onset autosomal dominant AD.[14-16] Mutations of presenilin-1, presenilin-2, clusterin (CLU), phosphatidylinositol-binding clathrin assembly protein (PICALM), complement component (3b/4b) receptor 1 (CR1) and triggering receptor expressed on myeloid cells 2 (TREM2) have also been found to be associated with the disease.[17-20] While increased production of Aβ may cause early-onset AD, late onset AD may be caused by impaired Aβ clearance due to interactions with ApoEε4, reduced proteolysis, decreased transport across the blood-brain barrier, or inefficient cerebrospinal fluid (CSF) transport.[21]

Tau binds and stabilizes microtubules and supports axonal transport. Tau interacts with Fyn in the postsynaptic compartment. Fyn phosphorylates the N-methyl-D-aspartate (NMDA) receptor subunit 2B (NR2B) and facilitates its interaction with postsynaptic density protein 95 (PSD95).[22] The NR2B/PSD95 interaction is essential in Aβ-induced neurotoxicity.[23] As increased neuronal membrane cholesterol is an important factor in AD and also causes overexpression of Fyn gene, this could be the link between cholesterol, Aβ and tau.[24]

Casoli, et al. have proposed that mitochondrial DNA mutations are also important factors in AD.[25] The two structural proteins NEDD9 (neural precursor cell expressed, developmentally down-regulated 9) and CASS4 (Cas scaffolding protein family member 4) and the kinase PTK2B (protein tyrosine kinase type 2 beta) apart from their roles in neoplasia, have been found to have a role in inflammation, hypoxia, vascular changes, microtubule stability and calcium signaling, and are relevant in AD.[26]

Altered post-translational modification in the form of autophosphorylation of serine (Ser) and threonine (Thr), blocks the phosphorylation of tyrosine (Tyr) on insulin substrate receptor proteins (IRS) 1 and 2, impairs insulin signaling and leads to diabetes and AD-like complications. O-glycosylation of these Ser and Thr sites prevents phosphorylation and these sites may be targets for future drugs.[27]

Metal dyshomeostasis has also been proposed as a contributing factor to the disease. Herpes simplex virus-1 (HSV) has been investigated as a potential cause of AD with a role of antiviral therapy in future.[28] Deficiency of nutritional factors like docosahexaenoic acid (DHA) and vitamins have also been implicated in the causation of AD and are being investigated.[29] People with higher educational attainment or socioeconomic status have been found to have a greater reserve against AD as do people who exercise regularly.[30-32]

Biomarkers

The inaccessibility of the brain for histopathologic

confirmation and the long preclinical phase, make surrogate markers of the disease that provide a biological measure of the ongoing disease, irrespective of symptomatology, very important. This is especially so with the advances in DMT and hence these have been incorporated into the new diagnostic criteria for AD (albeit for research purposes only). These biomarkers can be genetic (ApoE genotype), biochemical (CSF or plasma) or imaging biomarkers. They have a role not only in early diagnosis and prognosis, but also in selection of subjects for shorter and smaller clinical trials with greater statistical power (selection of inclusion and exclusion criteria), in providing evidence of target engagement and disease-modifying effects of DMT (as surrogate end points) and in monitoring side-effects of DMT.

CSF biomarkers

Due to its direct contact with the brain extracellular space, CSF constituents closely reflect molecular events in the brain. Low CSF $A\beta_{1-42}$ is a sensitive marker of cerebral Aβ deposition but it does not correlate well with duration or severity of disease. Low CSF Aβ is not very specific for AD as it is also seen in frontotemporal dementia (FTD), vascular dementia, Creutzfeldt–Jakob disease (CJD) and dementia with Lewy bodies (DLB). CSF tau (total-tau or t-tau and tau phosphorylated at threonine 181 or p-tau_{181}) is increased in AD and its higher levels correlate with greater cognitive impairment. When $A\beta_{1-42}$ and t-tau are considered together ($A\beta_{1-42}$ to t-tau ratio), the sensitivity and specificity of diagnosing AD is more than 85%.[33] Huded, et al. in a study from southern India also found that p-tau/t-tau and p-tau/Aβ ratio are good indicators of severity of dementia and may help differentiate between mild AD and moderate to severe AD.[34] Different phosphorylated epitopes of tau may also be helpful in distinguishing AD and FTD (p-tau_{231}) or AD and DLB (p-tau_{181}).[35,36]

Levels of orexin (hypocretin), a neuropeptide that regulates arousal, wakefulness and appetite are altered in AD. Liguori, et al. have found that CSF orexin levels correlate with total tau protein levels, sleep impairment and cognitive decline in moderate to severe AD.[37]

Imaging biomarkers

The diagnostic value of imaging in AD is in identifying characteristic topographical, structural and functional alterations in the brain and in differentiating it from other causes of cognitive decline.

Volumetric magnetic resonance imaging (MRI)

AD is characterized by progressive atrophy of the medial temporal lobe (MTL) in a typical sequence: entorhinal complex, followed by hippocampus, amygdala, parahippocampus and posterior cingulate gyrus. Patients with atypical language and visual presentations have left temporal and occipital atrophy, respectively. Volumetric MRI (T1-weighted imaging) has been validated against pathological post-mortem markers such as Braak stages and is the most mature imaging biomarker of disease progression.[38] Savva, et al. in their epidemiological-autopsy study of individuals with and without dementia found that though plaques, tangles and atrophy were all associated with dementia, atrophy was most strongly related to dementia.[39] Progression of whole cerebral and hippocampal atrophy closely matches clinical worsening in AD.[40] Visual evaluation of MTL atrophy vis-à-vis normal ageing has a sensitivity and specificity of around 80%-85%. Paradoxical hippocampal volume loss noted after anti-amyloid immunotherapy is likely due to amyloid removal and fluid redistribution rather than atrophy. Strict standardization is required for manual volumetry and automated software like FreeSurfer, learning embeddings for atlas propagation (LEAP), and QUARC analysis software. Haris, et al. in a small study have shown that T1rho MRI (a technique that can probe the protein content of various tissues) may be useful in the early diagnosis of AD.[41]

Vascular MRI

T2-weighted and fluid-attenuated inversion-recovery (FLAIR) images are used to identify amyloid-related imaging abnormalities (ARIAs, vasogenic edema and microhemorrhages) which are associated with Aβ-lowering drugs.[42] Regulatory authorities require usage of vascular MRI for safety reasons in clinical trials using DMT. The occurrence of ARIAs is dependent on the dose of anti-Aβ drug and ApoEε4 genotype.[43]

Diffusion tensor imaging (DTI) MRI

DTI is based on the directionality of diffusion in the brain parenchyma and is used to assess white matter orientation and integrity using two parameters: fractional anisotropy (a marker of axonal integrity and myelination) and mean diffusivity (marker of cellular integrity). DTI can

supplement volumetric MRI by depicting characteristic disruptions in neuronal connections.[44]

Functional MRI (fMRI)

As the name suggests fMRI provides an insight into cerebral functioning. In this modality, statistical maps of cerebral activation are produced based on changes in regional microcirculation inferred from measuring changes in blood-oxygen-level dependent (BOLD) MR signal. The MRI signal changes because of changes in blood flow, volume and oxyhemoglobin/deoxyhemoglobin ratio induced by external stimuli, specific tasks or drugs. Decreased activity in the hippocampus/MTL and increased activity in the prefrontal cortex is seen during encoding of new information in patients with AD and prodromal AD.[45,46]

Increased activity may be sometimes seen in the MTL in the early stages of the disease and in individuals at genetic risk of AD, and this has been attributed to compensatory mechanisms during hippocampal failure.[47] Apart from the MTL, memory function is also subserved by the "default mode network (DMN)" (precuneus, posterior cingulate, lateral parietal, lateral temporal and medial prefrontal regions).[48] The DMN that normally exhibits beneficial deactivation in healthy subjects, shows increased activity in both preclinical and clinical AD patients.[47-50]

Task-free resting-state fMRI (rs-fMRI)

It is more easily applicable and places less technical demands than activation-task fMRI, especially in severely demented patients. Impaired DMN has been shown even on rs-fMRI and with a direct correlation to disease severity. rs-fMRI has been found to be a stronger classifier than activation-task fMRI in distinguishing risk groups in non-demented adults carrying familial AD genes.[49]

Arterial spin labeling (ASL) MRI

This is an fMRI technique for measuring tissue perfusion using magnetically labelled protons in blood as an endogenous contrast agent. ASL MRI in comparison with perfusion PET was found to be as informative about regional hypoperfusion in prodromal AD and symptomatic AD, with greater resolution and no radiation exposure.[51,52] Although this modality is promising, standardization issues need to be addressed. [18]

Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)

PET involves detection of two oppositely directed annihilation photons generated by positron-emitting radiopharmaceuticals. FDG is a glucose analogue and enters cells by the same transport mechanism as glucose and is phosphorylated to FDG-6-phosphate (FDG-6-P). FDG-6-P does not enter into further enzymatic pathways and accumulates in the intracellular compartment proportional to the glycolytic rate of the cell. While FDG-PET is considered mainly a measure of synaptic activity, BOLD fMRI is indicative of integrated neuronal synaptic activity. The pattern of resting FDG hypometabolism in AD involving the limbic and association areas has been called an "endophenotype" of AD. These hypometabolic areas are highly vulnerable to Aβ deposition and the FDG pattern correlates with histopathology at autopsy.[53] The extent and severity of FDG hypometabolism is predictive of conversion of prodromal AD to AD, and directly correlates with cognitive decline.[54,55]

Amyloid PET

Amyloid PET involves use of Aβ-selective radioligands that bind to fibrillar Aβ.[18] F-FDDNP was the first PET tracer to be used in AD. Although there was higher retention of the tracer in the hippocampus, amygdala and entorhinal cortex of AD patients, it had a relatively high non-specific binding and it also bound tau.[56] The most commonly used tracer has been ^{11}C-PiB (Pittsburgh Compound-B). However newer tracers that do not require a cyclotron like ^{18}F-PiB and florbetaben, florbetapir and flutemetamol are being studied. In positive cases, Aβ deposits in a distribution that follows that of elevated aerobic glycolysis in the resting brain.[57,58] Changes in amyloid PET can be seen as early as changes in CSF Aβ and so both may be used as screening tools, but as CSF Aβ reaches a final level early, amyloid PET is better at detecting cerebral amyloid load.[53] The requirement of assessing disease progression is better served by structural MRI and FDG-PET vis-à-vis amyloid PET as amyloid deposition is an early event accumulating rapidly in the early stages and very slowly in the later stages.[53,56] A direct correlation has been found between APOEε4 and Aβ deposition (as measured with ^{11}C-PiB) and on CSF $A\beta_{1-42,}$ but not on tau or p-tau_{181} levels, suggesting that Aβ initiates the disease.[56] Aβ selective radioligands have also been used to provide

evidence of dose-dependent reduction of Aβ PET signal on treatment with bapineuzumab and gantenerumab; this was however not associated with clinical improvement.[42,59] Another development has been development of tracers directed at NFT: ^{18}F-T-807, ^{11}C-PBB-3.[60,61]

Plasma protein biomarkers

MRI and PET are expensive investigations and CSF studies are invasive, consequently influencing repeatability. Plasma biomarkers have the potential to be easily accessible and cheap markers of disease status. Hye, et al. proposed a panel of plasma proteins as biomarkers that could be used to predict progression of mild cognitive impairment to AD [transthyretin, CLU, cystatin C, A1 acid glycoprotein, complement C4, intercellular adhesion molecule (ICAM)-1, pigment epithelium-derived factor (PEDF), alpha-1 antitrypsin, regulated on activation normal T-cell expressed and secreted (RANTES), apolipoprotein C3] with an accuracy of 87 % as well as proteins associated with greater atrophy [alpha-1 antitrypsin, neuron specific enolase, brain derived neurotrophic factor (BDNF), apolipoproteins (C3, A1, E)] in AD.[62] However, these proteins need to be validated in more longitudinal studies and the issue of specificity addressed as many of these proteins may not be specific to AD. Nevertheless, the concept of a suitable panel of plasma protein and imaging biomarkers for early diagnosis and monitoring progress of AD appears promising.

These biomarkers are summarized in a tabular form in table 1.

Targets for DMT

The various targets of novel DMT can be broadly classified as a) interventions related to Aβ production, aggregation and clearance, b) immunotherapy against Aβ, and c) interventions related to tau hyperphosphorylation.[33]

Interventions related to reduction of Aβ1-42 production, reduction of aggregation and increased clearance

BACE-1 is modified by bisecting N-acetylglucosamine (GlcNAc) and AD patients have increased bisecting GlcNAc on BACE-1. Kizuka, et al. have shown that deficiency of GlcNAc-transferase (GnT)-III, the biosynthetic enzyme for GlcNAc, reduces cleavage of Aβ by BACE-1 resulting in reduced Aβ plaques and improved cognitive function in animal models.[63] Thus, GnT-III and notch-sparing 2nd generation γ-secretase inhibitors (e.g. begacestat, avagacestat, PF-3804014 and NIC5-15) are promising candidates for DMT.[64] Aβ levels can also be reduced by blocking BACE-1 and trials are on anti-β secretase antibodies. Thiazolidinedione antidiabetic drugs (rosiglitazone, pioglitazone) via peroxisome proliferator-activated receptor-γ (PPAR-γ) activation can suppress BACE-1 expression. However, a lack of conclusive beneficial effects and the attendant cardiac risks have led to termination of rosiglitazone trials for AD.[65] The results with pioglitazone in a pilot clinical trial have also been conflicting.[66] Another strategy can be upregulation of α-secretase activity, leading to increased neuroprotective APPα. Though some drugs are undergoing trials, no results are yet available.

As the neurotoxic potential of Aβ oligomers is greater than Aβ monomers or fibrils, antiaggregants like ELND005 (scyllo-inositol), tramiprosate (homotaurine) and PBT2 are also under investigation.[67] Though ELND005 did not achieve the trial endpoints, it did produce changes in CSF Aβ. Similarly, tramiprosate (binds soluble Aβ) and PBT2 (impedes metal-induced oligomerization of Aβ) did not achieve trial endpoints.

Receptor for advanced glycation end-products (RAGE) mediates influx of Aβ and also mediates neuroinflammation and apoptosis, and low-density lipoprotein receptor-related protein 1 (LRP1) mediates efflux of Aβ from the brain. So their inhibitors and activators, respectively are targets of ongoing research.[68,69] An oral RAGE-inhibitor (PF-04494700) has been tried but results were unsatisfactory.[70] Another approach can be specific activation of proteases that degrade Aβ like neprilysin, insulin-degrading enzyme and plasmin.

Immunotherapy against Aβ

Two approaches are being pursued: active immunity (anti-Aβ vaccine) using compounds containing the N-terminal fragment of $A\beta_{1-42}$ or N-terminus mimic peptides (ACC-001, CAD106, V950, AFFITOPE® AD02) and passive immunity using monoclonal anti-Aβ antibody (bapineuzumab, solanezumab).[71,72] Though the clinical efficacy of bapineuzumab has not been consistent, it did demonstrate good tolerability with lowering of CSF p-tau and Aβ on PET. Solanezumab though not associated with ARIAs (amyloid-related imaging abnormalities), was also not found efficacious in mild to moderate AD.

Table 1. Biomarkers for Alzheimer's disease (AD)

Name	Advantages		Disadvantages
APOEε4	Major genetic susceptibility factor for late-onset AD Carrying 1 allele increases risk factor by 2-3 times, 2 alleles increases the risk 16 times		Not diagnostic Genetic studies are expensive
CSF Aβ1-42	Low $A\beta_{1-42}$ is a sensitive marker of cerebral Aβ deposition	When Aβ1-42 and t-tau are considered together (Aβ1-42 to t-tau ratio), the sensitivity and specificity of diagnosing AD is more than 85 %	Invasive procedure Does not correlate well with duration or severity of disease Low CSF Aβ is not very specific for AD as it is also seen in other dementias
CSF tau	CSF tau (total-tau or t-tau and tau phosphorylated at threonine 181or p-tau 181) is increased in AD. Higher levels correlate with greater cognitive impairment Different phosphorylated epitopes of tau maybe helpful in distinguishing AD and FTD (p-tau231) or AD and DLB (p-tau181) p-tau/t-tau and p-tau/Aβ ratio are good indicators of severity of dementia and can differentiate between mild AD from moderate to severe AD		
CSF orexin	CSF orexin levels correlate with total tau protein levels, sleep impairment and cognitive decline in moderate to severe AD		Invasive procedure More studies required
MRI	Atrophy strongly related to dementia and closely matches clinical worsening in AD DTI can supplement volumetric MRI by depicting characteristic disruptions in neuronal connections Decreased activity in the hippocampus/MTL and increased activity in the prefrontal cortex is seen during encoding of new information in patients with AD and prodromal AD in Fmri rs-fMRI has been found to be a stronger classifier than activation-task fMRI in distinguishing risk groups in non-demented adults carrying familial AD genes T2-weighted and FLAIR images are used to identify ARIAs which are associated with Aβ-lowering drugs ASL MRI in comparison with perfusion PET was found to be as informative about regional hypoperfusion in prodromal AD and symptomatic AD, with greater resolution and no radiation exposure	Visual evaluation of MTL atrophy vis-à-vis normal ageing has a sensitivity and specificity of around 80%-85%	Expensive Not yet readily available More studies required and standardization issues need to be addressed
FDG PET	The extent and severity of FDG hypometabolism is predictive of conversion of prodromal AD to AD, and directly correlates with cognitive decline		Expensive Not readily available
Amyloid PET	Changes in amyloid PET can be seen as early as changes in CSF Aβ and so both may be used as screening tools, but as CSF Aβ reaches a final level early, amyloid PET is better at detecting cerebral amyloid load		- The requirement of assessing disease progression is better served by structural MRI and FDG-PET vis-à-vis amyloid PET as amyloid deposition is an early event accumulating rapidly in the early stages and very slowly in the later stages
Plasma protein biomarkers	Potential to be easily accessible, cheap and repeatable		Need to be validated in more longitudinal studies Issues of specificity need to addressed as many of these proteins may not be specific to AD

AD: Alzheimer's disease; MRI: Magnetic resonance imaging; DTI: Diffusion tensor imaging; APOEε4: Apolipoprotein E ε4; CSF: Cerebrospinal fluid; FTD: Frontotemporal dementia; DLB: Dementia of Lewy bodies; MTL: Medial temporal lobe; fMRI: Functional MRI; rs-fMRI: Resting-state functional MRI; FLAIR: Fluid-attenuated inversion-recovery; ARIAs: Amyloid-related imaging abnormalities; ASL: Arterial spin-labeling; FDG: ^{18}Fluoro-2-deoxy-D-glucose; PET: Positron emission tomography

However, these drugs may still have a role in AD prevention. Recent studies have shown that passive immunity achieved by using intravenous immunoglobulin (IVIG) has an acceptable safety profile with encouraging changes in body fluid biomarkers.[73-75]

Interventions targeted to tau hyperphosphorylation and aggregation

Abnormally hyperphosphorylated and aggregated tau causes microtubule instability and axonal transport failure. Abnormal phosphorylation can be decreased by inhibiting tau kinases like glycogen synthase kinase (GSK)-3. GSK-3 inhibitors like valproic acid and lithium have not shown clinical efficacy or improvement in biomarkers. NP031112 (tideglusib), a non-ATP competitive GSK-3 inhibitor has been found to reduce p-tau and Aβ, prevent neuronal death and improve cognition in animals.[76] Methylene blue (Rember™), an anti-tau aggregate and anti-oxidant has also been found to improve cognition in patients with mild to moderate AD.[77]

Bioengineering and gene therapy

Research is also underway in bioengineering techniques using stem cells and gene therapy to induce neurogenesis, angiogenesis, axonal regeneration and neuronal replacement by producing a milieu of Aβ degrading enzymes and neural growth factors.[78]

A number of studies from the Indian subcontinent have shown encouraging results from the use of medicinal herbs and antioxidants in AD in humans and animal models.[79-81]

The various approaches for novel DMT are summarized in table 2.

Table 2. Novel disease-modifying therapy (DMT)

Class of drug/name	Mechanism of action	Special remarks
GnT-III and notch-sparing 2nd generation γ-secretase inhibitors (e.g. begacestat, avagacestat, PF-3804014 and NIC5-15)	BACE-1 is modified by bisecting GlcNAc and AD patients have increased bisecting GlcNAc on BACE-1	
	Deficiency of GnT-III, the biosynthetic enzyme for GlcNAc, reduces cleavage of Aβ by BACE-1 resulting in reduced Aβ plaques	
Anti-β secretase antibodies	Aβ levels can also be reduced by blocking BACE-1	
Thiazolidinedione antidiabetic drugs (rosiglitazone, pioglitazone)	Via PPAR-γ activation can suppress BACE-1 expression	Lack of conclusive beneficial effects and attendant cardiac risks have led to termination of rosiglitazone trials for AD
Drugs upregulating α-secretase activity	Leads to increased neuroprotective APPα	Though some drugs are undergoing trials, no results are yet available
Antiaggregants like ELND005 (scyllo-inositol), tramiprosate (homotaurine) and PBT2	Prevent aggregation of Aβ monomers as neurotoxic potential of oligomers is greater than Aβ monomers or fibrils	-
Inhibitor for RAGE	RAGE mediates influx of Aβ and also mediates neuroinflammation and apoptosis	An oral RAGE-inhibitor (PF-04494700) has been tried but results were unsatisfactory
Activators of receptor for LRP-1	Receptor for LRP-1 mediates efflux of Aβ from the brain	-
Neprilysin, insulin-degrading enzyme and plasmin	Specific activation of proteases that degrade Aβ	-
Active immunity (anti-Aβ vaccine, ACC-001, CAD106, V950, AFFITOPE® AD02)	Using compounds containing the N-terminal fragment of Aβ1-42 or N-terminus mimic peptides	-
Passive immunity (bapineuzumab, solanezumab)	Using monoclonal anti-Aβ antibody	-
Tau kinase inhibitors	Abnormal phosphorylation can be decreased by inhibiting tau kinases like GSK-3	NP031112 (tideglusib), a non-ATP competitive GSK-3 inhibitor has been found to reduce p-tau and Aβ, prevent neuronal death and improve cognition in animals
Methylene blue (Rember™)	Anti-tau aggregate and anti-oxidant	-
Bioengineering techniques using stem cells and gene therapy	To induce neurogenesis, angiogenesis, axonal regeneration and neuronal replacement by producing a milieu of Aβ degrading enzymes and neural growth factors	-
Medicinal herbs and antioxidants in AD (black pepper, Padina gymnospora)	-	-

GlcNAc: N-acetylglucosamine; GnT: GlcNAc-transferase; APPα: Amyloid precursor protein; BACE-1: B-site APP cleaving enzyme; AD: Alzheimer's disease; RAGE: Receptor for advanced glycation end-products; LRP: low-density lipoprotein receptor-related protein 1; GSK: Glycogen synthase kinase; PPAR- γ: Peroxisome proliferator-activated receptor-γ

Conclusion

We have come far in our understanding of the pathogenesis of AD with rapid strides being made in diagnostic modalities to detect the disease at a preclinical stage when novel DMT may be instituted to halt disease progression and also to monitor the effects of these drugs. However, more multi-institutional and longitudinal data is required to validate and standardize these modalities and select the most reliable, repeatable, easily available, cost-effective and complementary options. Synergizing the multipronged efforts of multiple bodies and institutions as represented by AD Neuroimaging Network (ADNI) and Dominantly Inherited Alzheimer Network (DIAN) are the way forward.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Iranian Journal of Neurology

Letter to Editor

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Sarcoidosis limbic encephalitis: A case report

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Keywords
Sarcoidosis; Magnetic Resonance Imaging; Limbic Encephalitis

Sarcoidosis is a rare multisystem chronic granulomatous, with unknown etiology. Neurological involvement in sarcoidosis is rare and occurs in 5 to 15% of cases.[1] Limbic structures involvement in sarcoidosis is unusual and uncommon. Herein, we report a case of limbic encephalitis (LE) as the first manifestation of neurosarcoidosis.

A 39-years-old man with no known past medical history was admitted to our department for short-term memory disorders associated with behavioral type of irritability and agitation behavior occurred 1 month before consultation.

On admission, he was a patient with anxiety and logorrhea, marked disorientation and cognitive impairment with deficit in free recall, difficulty in learning, and calculation deficit with a Folstein Mini-Mental State Examination (MMSE) score of 12/30 which is pathological. In addition, the examination showed an inflammatory flattening of the root of the nose and gynecomastia.

Nasofibroscopie showed inflammatory granulations causing stenosis of nasal cavities and deformed nasal septum. Cerebral magnetic resonance imaging (MRI) showed hyperintensities in right temporoinsular region on FLAIR and T2-weighted images (Figure 1, A and B) and on gadolinium enhanced T1-weigthed images, an enhancement and nodular leptomeningeal thickening in the basilar perimesencephalic cistern extended to the right temporal lobe, hypothalamus, and third ventricle (Figure 1, C and D). Electroencephalogram (EEG) revealed slowing of the basic rhythm with a frontotemporal intermittent rhythmic delta activity predominant in the right. Thoracic computed tomography (CT) scan showed mediastinal and hilar lymphadenopathies without parenchymal lung lesions.

In systemic immunological tests antinuclear antibodies [anti-double stranded DNA (anti-dsDNA), anti-Sjögren's-syndrome-related antigen A (anti-SSA), anti-SSB, and perinuclear anti-neutrophil cytoplasmic (p-ANCA) antibodies] were negative. Histological examination of nasal biopsy showed a granulomatous inflammation made of confluent granulomas with multinucleated giant and epithelioid cells surrounded by a rim of lymphocytes without caseous necrosis favoring the diagnosis of sarcoidosis.

Study of cerebrospinal fluid (CSF) revealed meningitis with 19 white blood cells, of which 75% were lymphocytes, protein level of 0.37 g/l,

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chloride level of 125 mmol/l, and glucose level of 0.51 g/l. CSF cultures were negative.

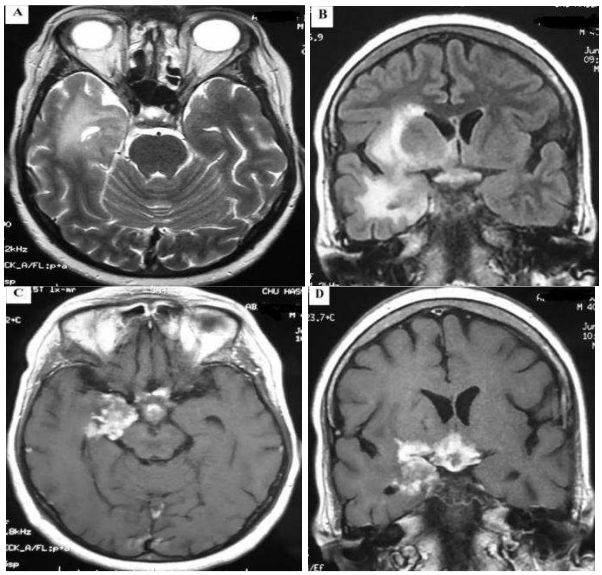

Figure 1. Cerebral magnetic resonance imaging (MRI) showing hyperintensities in the right temporoinsular region associated with an enhancement and nodular leptomeningeal thickening of the basilar peri-mesencephalic citern extended to the right temporal lobe, hypothalamus and walls of the third ventricle. (A) T2-weighted images, (B) FLAIR sequences, (C and D) gadolinium enhanced T1-weigthed images

The dosage of angiotensin converting enzyme in blood was high at 98 IU/l. The hypophysiogramme revealed gonadotropic failure, adrenocorticotropic failure, and thyroid failure with a slight hyperprolactinemia at 76.33 ng/ml.

Serologies of syphilis, human immunodeficiency virus (HIV), and hepatitis B and C were negative as well as herpes simplex virus via polymerase chain reaction (HSV-PCR) in CSF. Assessment of mycobacterium tuberculosis in the gastric lavage fluid and intradermoreaction to tuberculin were normal.

At the end of analysis, a diagnosis of sarcoidosis LE was considered. The patient was treated with pulse intravenous methylprednisolone (1 g/kg/day for 5 days) followed by oral corticotherapy, associated with levothyroxine. The patient's cognitive status improved with a Folstein MMSE score of 23/30 indicating a good clinical response to the oral corticotherapy; although the control EEG was not performed at this time.

LE is histologically defined as an inflammation-degeneration of limbic structures.[2] Clinically, LE is characterized by an acute or subacute onset of short-term memory disorders, psychiatric disorders, confusional state, and temporal lobe or generalized epilepsy.[2,3] Cerebral MRI plays an important role in the diagnosis of LE when it is positive by highlighting hyperintensities in the limbic regions on T2 and FLAIR sequences, such as the internal part of the temporal lobe, hippocampus and amygdala, cingulate gyrus, fornix, and hypothalamus.[3]

Many etiologies have been described in the literature with a predominance of infectious diseases and autoimmune encephalitis or paraneoplasms.[3] Sarcoidosis is one of the uncommon etiologies of LE, and it is few described. The present case described a case of LE as the first manifestation of neurosarcoidosis which is a rare clinical entity. The clinical presentation of our patient was marked by neuropsychiatric and neuropsychological disorders that are the usual manifestations of LE. Although the signal abnormalities of cerebral MRI of the present case were unilateral, presented clinical signs suggested that the cerebral lesions were bilateral but asymmetrical. Functional cerebral imaging [single-photon emission computed tomography (SPECT) and fluorodeoxyglucose-positron emission tomography (FDG-PET)], the most sensitive radiological examination in the diagnosis of LE, should have been performed in our patient which could help to better visualisation of probable asymmetric lesions in the left limbic regions that have not been visualized by the cerebral MRI.[4]

Corticosteroid therapy constitutes the first line treatment of neurosarcoidosis,[5] as the case of our patient. However, in cases of ineffectiveness, intolerance, or contraindications for corticosteroid therapy, immunosuppressive therapy and rituximab may be used as an alternative treatment.[5]

In conclusion, our observation shows the importance to search systematically neurosarcoidosis in the patients with hyperintensities in cerebral MRI on T2 and FLAIR sequences in the limbic regions associated with an enhancement and nodular leptomeningeal thickening.

Conflict of Interests

The authors declare no conflict of interest in this study.

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None.

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Iranian Journal of Neurology

Letter to Editor

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Churg-Straus syndrome: A case report

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Keywords
Churg-Strauss Syndrome; Eosinophilia; Cerebral Infarction; Anticoagulants

Churg-Strauss syndrome is a rare autoimmune disorder characterized by excess circulating, tissue eosinophils, and vasculitis, which affects the lung and skin. The syndrome occurs in patients with a history of asthma or allergy.[1] Neuropathy develops in approximately 3/4 of the patients usually as mononeuritis multiplex. Centrally accentuated antineutrophil cytoplasmic antibody (CANCA) is generally found in more than half of the cases, while central nervous system (CNS) manifestations are relatively unusual and include headache, convulsion, hemiplegia, and brainstem signs.[2]

We report here a 42-year-old man with a history of severe asthma and rhinitis in the past 4 years prior to the first admission. The patient was presented with difficulty in walking and weakness of lower limbs. In addition, he had a history of flu vaccination about 1.5 months before his neurological symptoms. The patient also had a history of skin lesions of hemorrhagic bulla and palpable purpura few days after injection on the lower limbs. At that time, a dermatologist visited the patient and a biopsy was taken with the impression of vasculitis. Eosinophilic dermal infiltration and leukocytoclastic vasculitis (LCV) were demonstrated in the biopsy specimen.

Findings on the first day of admission were as follows: electromyogram/nerve conduction study (EMG/NCS) were compatible with subacute mixed type (demyelination and axonal) of inflammatory polyradiculopathy [Guillain-Barré syndrome (GBS)]. At the complete blood cell (CBC) exam, white blood cells (WBCs) were 14.21 ($10^3/\mu l$) with eosinophilia (40%) (Table 1).

Erythrocyte sedimentation rate (ESR) was 43 and 84 at 1st and 2nd hours, respectively; C-reactive protein (CRP) was negative, and the rheumatoid factor (RF) was ++. In addition, antinuclear antibodies (ANA), anti-cyclic citrullinated peptide (anti-CCP) antibody, cytoplasmic-antineutrophil cytoplasmic antibody (c-ANCA), and perinuclear-anti-neutrophil cytoplasmic antibody (p-ANCA), and anti-phospholipid antibody were found to be negative. Lipid profiles and liver function tests were in the normal range. Brain and thoracolumbar spine magnetic resonance imaging (MRI) results were not significant, except for increased mucosal thickening at both maxillary and sphenoidal sinuses.

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Table 1. Complete blood cell (CBC) results

Variable	Results	Normal range	Unit
WBC	14.21*	4.8-10.8	10^3/µl
RBC	4.96	4.20-6.10	10^3/µl
HGB	13.6	12.0-18.0	g/dl
HCT	39.8	37.0-52.0	%
MCV	80.4	79.0-99.0	femtoliters/cell
MCH	27.5	26.0-32.0	pg/cell
MCHC	34.2	31.5-36.0	g/dl
PCT	0.34	0.12-0.36	%
RDW	14.7	11.5-15.0	%
HDW	2.88	2.20-4.00	g/dl
PLT	459*	130-400	10^3/µl
MPV	7.5	6.4-11.1	femtoliters/cell
PDW	66.1	25.0-75.0	%
NEUT (%)	36.9*	40.0-74.0	%
LYMPH (%)	16.7*	19.0-48.0	%
MONO (%)	4.9	3.4-9.0	%
EOS (%)	40*	0-7	%
BASO (%)	0.3	0.0-1.5	%
LUC (%)	1.3	0.0-4.0	%
NRBC (%)	0	0.0-2.0	%
NEUT	5.24	1.90-8.00	10^3/µl
LYMPH	2.37	1.90-5.20	10^3/µl
MONO	0.69	0.16-1.00	10^3/µl
EOS	5.68*	0.00-0.80	10^3/µl
BASO	0.05	0.00-0.20	10^3/µl
LUC	0.19	0.00-0.40	10^3/µl

*ABN Scattergram

WBC: White blood cell; RBC: Red blood cell; HGB: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PCT: Prolactin count; RDW: Red blood cell distribution width; HDW: Hemoglobin distribution width; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; NEUT: Neutrophil; LYMPH: lymphocytes; MONO: Monocyte; EOS: Eosinophil; BASO: Basophil; LUC: Large unstained cell; NRBC: Nucleated red blood cell

In this admission, intravenous immunoglobulin (IVIG) was administered with the impression of GBS. There was a little improvement but other signs and symptoms appeared progressively in the following year; the symptoms included limb tremor, numbness of fingers, dysarthria, dysphagia, gait impairment, arthralgia, and incontinency.

After 11 months, the patient was admitted again with unilateral sudden visual loss. Clinical examination, according to our last visit, showed bilateral wheezing and fever (38.3 ºC oral). Blood pressure (BP), pulse rate (PR), and respiratory rate (RR) were in normal range. Skin was warm and moist, but no specific lesion was detected. On neurologic examination, there was no response to direct light in the right eye; however, the indirect exam was normal, and there was evidence of central retinal artery occlusion (CRAO) in the right eye, viewed with an ophthalmoscope. Right nasolabial fold was flattened. Muscle force of lower limbs was 4/5, while the upper limbs were normal.

The deep tendon reflex of upper limbs was +++ with obvious rigidity, and the plantar reflex was equivocal. The peripheral blood examination disclosed leukocytosis (WBC: 18.47 10^3/µl) with eosinophilia (23.6%); additionally, the C4 level was low (0.127 g/l with reference range of 0.165-0.380) but C3 and CH50 levels were in the normal range. p-ANCA, c-ANCA, ANA, and anti-double stranded DNA (anti-dsDNA) antibodies were tested again, and found to be negative. Other findings were as: CRP: +++, ESR at 1 hour: 122, RF: ++, prothrombin time (PT): 12.7 s, partial thromboplastin time (PTT): 28.0 s, and international normalized ratio (INR): 1.1.

Cardiac echocardiogram showed ejection fraction of 40-45% as well as anteroseptal hyperkinesia. Both carotids and vertebral arteries were normal in the cervical duplex study. Spiral computed tomography (CT) scan of chest revealed pneumonia and effusion with pleural thickening. Brain MRI findings disclosed diffused symmetrically increased signal intensity at the hemispheric white matter, pons, internal capsule, cerebellar hemispheres, and peduncles bilaterally, showing restricted diffusion on diffusion-weighted images. Mucosal thickening was observed in the maxillary, ethmoidal, sphenoidal, and frontal sinuses (pansinusitis) (Figure 1).

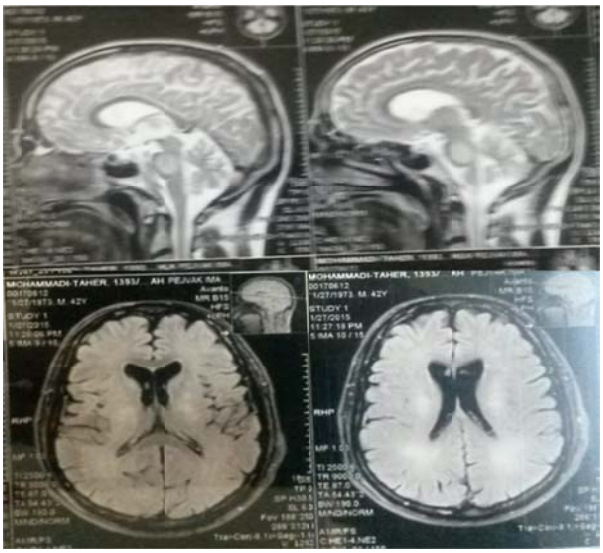

Figure 1. Mucosal thickening in the maxillary, ethmoidal, sphenoidal, and frontal sinuses

The presence of all these findings led to the diagnosis of Churg-Strauss syndrome by American College of Rheumatology (ACR) criteria. The patient was treated with prednisolone (1 mg/kg/day) and cyclophosphamide (150 mg/day). After a month, he came back to the hospital with the complaint of right lower limb pain. This time, we made a decision to keep the patient on warfarin, in addition to previous drugs, and waited to see what would happen later.

Recent studies demonstrated that neurologic manifestations are very interesting in these patients.[2,3] Neurologic manifestations, in a variety of reports, include subarachnoid hemorrhage, intracerebral hemorrhage, cerebral/cerebellar infarct or gliosis, and spinal cord lesion.[4] MRI performed in the first admission showed no abnormalities; nevertheless, there was evidence of peripheral nervous system (PNS) involvement, as misdiagnosed by GBS. However, in the second admission, the brain MRI revealed many hypersingnal foci for vasculitis involvement of the brain parenchyma; indeed, the patient had cerebral/cerebellar infarcts.

The fundamental question that arises here is: what is the possible explanation for these lesions in the brain? It can be due to cardiac embolism, vasculitis, or hypercoagulation. In our patient, we found no cardiac embolism source for his brain lesions, and vasculitis and hypercoagulation remained blameful for CNS manifestation.

He was treated with prednisone (1 mg/kg/day) and cyclophosphamide (150 mg/day), as a usual treatment and standard initial therapy.[5] His signs and symptoms were improved significantly, but the patient experienced a severe attack in less than one month of the therapy, which led to amputation of his leg beneath the knee. At that time, we found out that he may need something more than the usual and standard treatment; therefore, we decided to add warfarin therapy with checking the INR within 2-3 weeks. We followed the patient for about 5 months, and found that he did not experience new attacks after warfarin therapy. Further studies are required to confirm effectiveness of anticoagulation therapy for severe cases of Churg-Strauss syndrome.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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Neurological Images/Videos

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Coiled distal internal carotid artery (ICA) aneurysm in transcranial sonography

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Keywords
Doppler Transcranial Sonography; Aneurysm; Internal Carotid Artery

A 45-year-old man presented with a thunderclap headache. Brain computed tomography (CT) scan without contrast showed massive subarachnoid hemorrhage (SAH). We transferred him to the angiography unit where he was diagnosed with a left (Lt) distal internal carotid artery (ICA) aneurysm. We secured the aneurysm using 8 coils. He was stable the following days.

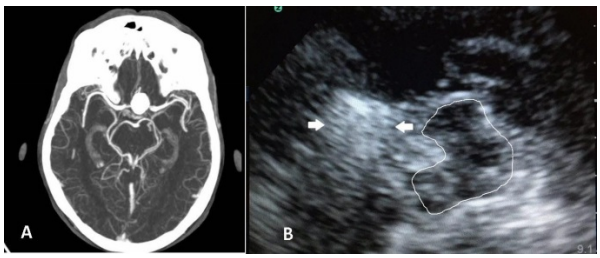

Figure 1. A. Axial brain computed tomography (CT)-angiography showing a giant left (Lt) distal internal carotid artery (ICA) aneurysm. B. Axial transcranial sonogram (mesencephalic level): Butterfly-shaped midbrain was encircled for better visualization (solid lines). Arrows indicate the coiled distal ICA aneurysm.

He was monitored via daily transcranial sonography (TCS) for the potential development of vasospasm. In TCS, the coiled distal ICA aneurysm was visualized as a round hyperechoic mass anterior to the midbrain. There was no aneurysm refilling on consequent evaluations. Unenhanced TCS is proposed as a screening tool for coiled aneurysm refilling.[1]

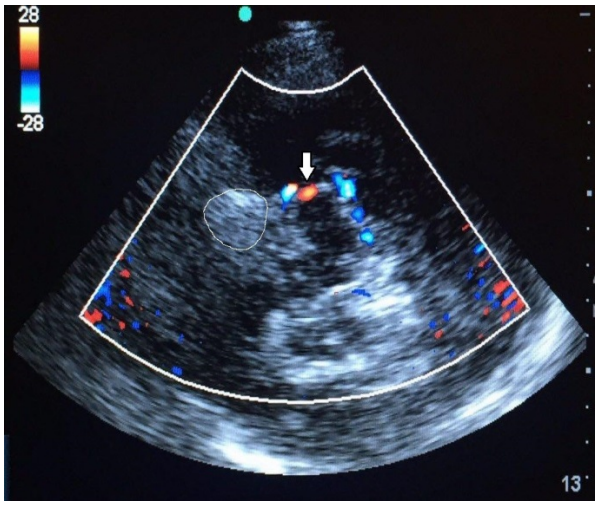

Figure 2. Axial transcranial color sonography (mesencephalic level); coiled aneurysm was encircled. There was no refilling within the aneurysm. Arrow indicates posterior cerebral artery (PCA).

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Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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