Journal of Neurological Sciences [Turkish] **33:(3)**# 50; 433-442, 2016
http://www.jns.dergisi.org/text.php3?id=989
Research Article

Course of Migraine with Aura: A Follow-up Study

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Summary

Background: Migraine has a prevalence of between 10-13% worldwide and one-third of the migraine patients complaint aura symptoms. However, the current understanding of the course of migraine with aura still remains uncertain. We aimed to determine the baseline and the time course characteristics of migraine with aura and to assess the evolution of headache frequency, duration and intensity.
Methods: The data of 230 patients were obtained from an electronic headache database retrospectively as a part of the Turkish Headache Database Project, and a latent growth mixture model was used to assess the variables. The frequency (low, medium, and high), duration (short, long) and severity (mild, moderate, and severe) of headaches were analyzed with a three-group model, a two-group-model, and a second three-group model, respectively. The probabilities for each of the subgroups were estimated using the latent growth mixture models.
Results: Unilaterality and dizziness were more likely to be observed in the moderate severity group than the mild severity group (odds ratio [OR]: 3.146, p = 0.007; OR: 2.637, p = 0.047) and vomiting was a rare symptom in the medium group (OR: 0.467, p = 0.017). Within six months follow-up assessments, there were significant recovery rates in terms of headache frequency, duration, and severity (68%, 65%, and 56%, respectively).
Conclusion: Our preliminary results support the importance of using longitudinal studies to reveal the course of migraine. Our findings might guide clinicians to reveal treatment goals and to develop effective treatment strategies.

Key words: Migraine with aura, course, growth mixture models

Auralı Migren Seyri: Takip Çalışması

Özet

Amaç: Migren prevalansı tüm dünyada %10-13 olarak bildirilmektedir ve hastaların üçte biri aura tarif etmektedirler. Fakat auralı migren seyri ile ilgili bilgilerimiz halen kısıtlıdır. Bu çalışmada auralı migren başlangıç ve takip özelliklerinin saptanması ve başağrısı sıklığı, süresi ve şiddetinin takip süresince değişiminin incelenmesi amaçlandı.
Metod: Türkiye Başağrısı Veritabanı Projesi kapsamında oluşturulan elektronik veritabanı retrospektif olarak tarandı. Çalışmaya toplam 230 auralı migren hastası dahil edildi ve değişkenlerin zaman içerisindeki seyrinin belirlenmesi için latent growth mixture modeli kullanıldı. Başağrısı frekansı (düşük, orta, yüksek), süresi (kısa, uzun), ve şiddeti (hafif, orta, şiddetli) sırası ile üç grup, iki grup ve üç grupta model oluşturularak incelendi. Tüm alt grupların olasılıkları latent growth mixture modeli kullanılarak hesaplandı.

Sonuçlar: Unilateral başağrısı ve dizziness orta şiddette başağrılı grupta daha sık gözlendi (odds ratio [OR]: 3.146, p = 0.007; OR: 2.637, p = 0.047) ve kusma orta şiddetli başağrısı grubunda nadir bir semptomdu (OR: 0.467, p = 0.017). Takipler süresi içerisinde başağrısı sıklığı, süresi ve şiddetinde belirgin düzelme izlendi (%68, %65, ve %56 sırası ile).
Tartışma: Bu ön çalışmanın sonuçları migren seyrinin belirlenmesinde izlem çalışmalarının önemini desteklemektedir. Bulgularımız klinisyenlerin etkin tedavi stratejileri geliştirmeleri ve tedavi amaçlarının belirlemelerinde yardımcı olacağını düşünmekteyiz.

Anahtar Kelimeler: Auralı migren, seyir, growth mixture model

INTRODUCTION

Migraine is a common, heterogeneous, neurovascular disorder characterized by moderate to severe headache attacks and a variable prognosis[2]. The prevalence of migraine is estimated to be 10–13% worldwide and approximately one-third of migraineurs experience aura along with other symptoms[18,7,12,16]. According to the International Classification of Headache Disorders (ICHD), a migraine aura is defined as a unilateral and reversible visual, sensory, aphasic, and/or other symptom that develops gradually and precedes the headache attack[10]. The most commonly occurring migraine aura symptoms comprise visual symptoms, followed by somatosensory, motor and speech auras. Although migraine aura commonly precedes the headache attacks, they may also manifest concurrently with headache and aura stem from changes in cortical neuronal depolarization and are propagated by depression spreading throughout the cortices[3].

The history of migraine, particularly for migraine with aura (MwA), has yet to be sufficiently characterized. A majority of studies have found favorable outcomes for the long-term prognosis of MwA; 23–56% of migraine patients have been reported to be attack-free at follow-up visits[1,5,6,20]. The characteristics and symptoms associated with migraine could have prognostic value for the course of the disease. For instance, one follow-up study reported that patients with a high baseline frequency of migraine and age of onset younger than 20 years are associated with a poor prognosis[17]. In contrast, male gender, visual auras, and the late onset of MwA are predictors of a good prognosis[6].

Although there is a relatively high frequency of favorable outcomes observed in migraine patients, a considerable proportion of this population exhibits increases in the frequency and chronification of headaches over time. Population-based studies have estimated that the prevalence of chronic migraine (CM) is 1–3% and CM patients are associated with a higher degree of disability[18,7,4]. Moreover, an increasing amount of evidence indicates that there is a risk of ischemic cerebrovascular and coronary artery diseases among this population, particularly for patients with MwA[15,8]. Thus, an evaluation of the course of MwA will aid in the prediction of chronicity-related factors as well as provide clues regarding the pathophysiology of this disease.

This study was conducted as part of the Turkish Headache Database Project, and our data are the preliminary findings of follow-up assessments. We investigated the baseline phenotypic features and the time courses of patients with MwA in terms of potential predictors for their prognosis using the latent growth mixture method (LGMM) to examine longitudinal data. To the best of our knowledge, this study is the first to analyze MwA patients using this methodology, which allows for the identification of homogeneous subpopulations rather than meaningful

groups or classes within a larger heterogeneous population.

MATERIAL AND METHODS

The study population (n = 230) was composed of patients admitted to the Mersin University Headache outpatient clinic that were diagnosed using ICHD-II criteria[11]. All data were collected from an electronic headache database as a part of the Turkish Headache Database Project. Patients who fulfilled the ICHD-II criteria for MwA or probable MwA were recruited. An experienced headache specialist examined all patients, and those with more than one follow-up visit were included in the study. Patients with primary and secondary headaches other than MwA were excluded because the effects of the clinical variables could not be precisely evaluated for patients without pure migraine. The patients were assessed monthly during the eight-month treatment period and throughout the one-year follow-up period. After collecting sociodemographic data, a detailed headache history was obtained that included headache frequency, duration, and severity; comorbidities; headache characteristics and localization; and any associated symptoms in order to determine the course of the disease over time. Headache severity was evaluated using the Visual Analog Scale (VAS).

Institutional Review Board Approval- The Human Ethical Committee of Mersin University (MEU.0.01.00.06/265, 20.10.2008) approved this non-profit study and patients were provided written informed consent prior to participation.

Statistical analysis

The modeling of the LGMM includes model building, testing of the model terms and risk factors, and estimation of the membership in each group for every patient. The model included risk factors and time-dependent covariates because, although risk factors and time-stable covariates may impact group memberships, time-dependent covariates affect observable behaviors[13]. A plugin for the STATA MP/11 package was applied to define the developmental trajectories separately for the severity, frequency, and duration of the headaches. This approach is a group-based mixture modeling technique that combines the latent growth curve and mixture modeling and may be more useful in situations in which both the number and structure of the trajectories are unknown[19].

Using all available baseline data from the 230 MwA patients, growth trajectory models were fitted using maximum likelihood methods that allowed for incomplete data. Because the data included psychometric scales and frequencies, the estimation of the trajectories was accomplished using the censored normal (CNORM) and zero-inflated Poisson (ZIP) models, respectively. A similar statistical methodology was used in our another recent study as well[21]. A series of models that included two to four subgroups with varied modeling terms were examined and compared to a one-group model, and the parameter estimates for the linear, quadratic, and cubic modeling terms for each subgroup were tested for each trajectory. In the second stage of the procedure, a multiple logistic regression analysis was applied to determine the odds ratios (ORs) and statistical significance of the univariate effective risk factors. A p value < 0.05 was considered to indicate statistical significance.

RESULTS

Of the 230 MwA patients, 199 were female (86.5%) and the mean age was 35.97 ± 11.86 years. At baseline, the mean frequency of headaches was 5.65 ± 3.65 days per month, the mean duration of headache was 31.14 ± 26.92 hours, and the mean severity of headache according to the VAS score was 8.34 ± 1.63. The median number of follow-up visits was four (minimum: 0, maximum: 14); however, only eight observations (baseline and

Visits 1–7) were considered in the LGMM due to the insufficient number of patients after the seventh visit. The means and standard deviations for the outcome variables at these eight time points are provided in Table 1. If the first six visits are considered, the recovery rates for headache frequency, headache duration, and headache severity were 68%, 65%, and 56%, respectively. The patients who complied with regular outpatient visits had a longer duration of headache attacks (48.4 ± 28.5 hours) than the patients who visited irregularly (33.43 ± 26.81 hours) and those who never came (29.69 ± 26.95 hours; $p = 0.014$).

The three-group model for the frequency of headaches using the quadratic, quadratic, and cubic terms appeared to be a more appropriate representation of the data than the others. The subgroups were categorized as low frequency (Group 1), medium frequency (Group 2), and high frequency (Group 3; Fig. 1). These subgroups did not significantly differ in terms of age, onset, severity, or duration of headaches. During the follow-up period, headache frequency decreased in all groups but the best recovery was observed in Group 2 followed by Group 3 and then Group 1 (94%, 68%, and 15%, respectively).

The two-group model for the duration of headaches with quadratic and quadratic terms appeared to be a more appropriate representation of the data than the others. The subgroups were categorized as short duration (Group 1) and long duration (Group 2; Fig. 2). The groups did not significantly differ in terms of age, onset, frequency, or severity of headaches. Six of the patients who attended the follow-up assessments after Visit 6 were medical refractory patients and the mean duration for this subset of patients did not change throughout the follow-up period. Within the first six visits, there was an 88% decrease in headache duration in Group 1 and a 69% decrease in Group 2.

The three-group model for the severity of headache with quadratic, quadtratic and cubic terms appeared to be a more appropriate representation of the data than the others. The subgroups were categorized as mild severity (Group 1), moderate severity (Group 2), and severe severity (Group 3; Fig. 3). The subgroups did not significantly differ in terms of age, onset, frequency, or duration of headaches. Within the first six visits, Group 3, which was representative of the patients with the most severe headache attacks, exhibited the best response to treatment (100% recovery) followed by Group 1 (38%) and Group 2 (28%).

The ORs of the risk factors are provided in Table 2. Unilaterality was more prominent in the moderate severity group than the mild severity group ($OR_{unilateral}$: 3.146, $p = 0.007$) and the ORs for dizziness were higher in the moderate severity group than the mild severity group ($OR_{dizziness}$: 2.637, $p = 0.047$). Although the ORs for vomiting, throbbing quality, unilaterality, photophobia, and phonophobia were higher in the severe severity group than the mild severity group, no significant differences were observed. Vomiting was rarely observed in the medium frequency group (OR: 0.467, $p = 0.017$) while a long duration of headache was not significantly associated with any risk factors.

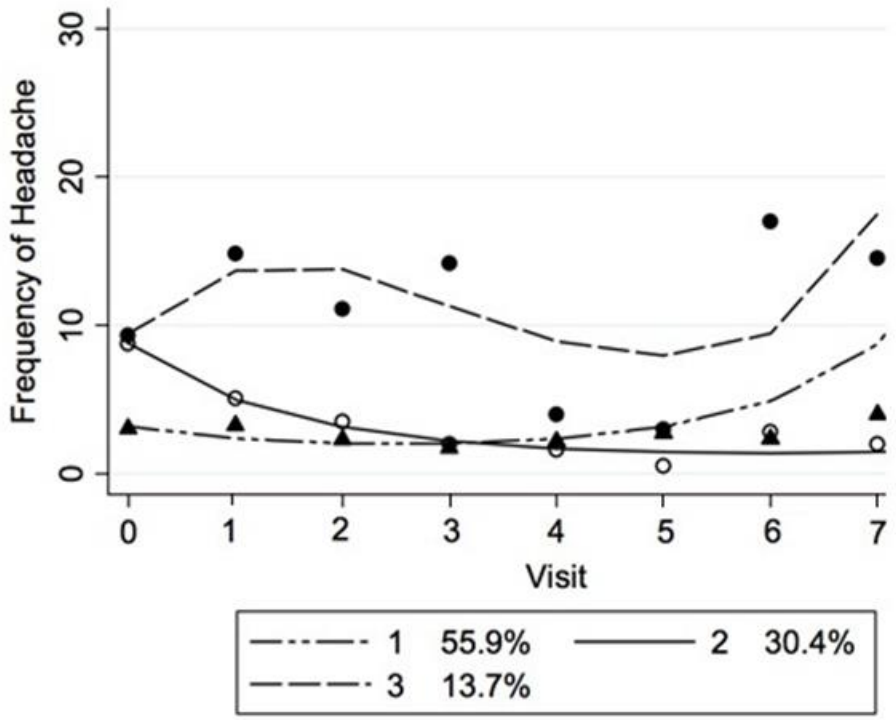

Figure 1: *Time course for headache frequency in MwA*

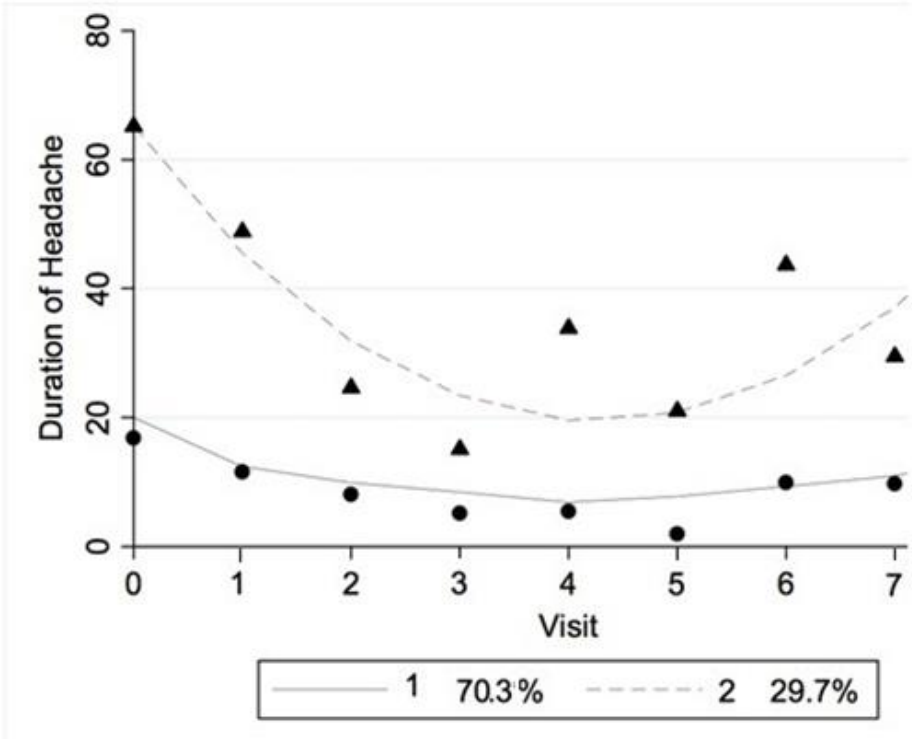

Figure 2: *Time course for headache duration in MwA*

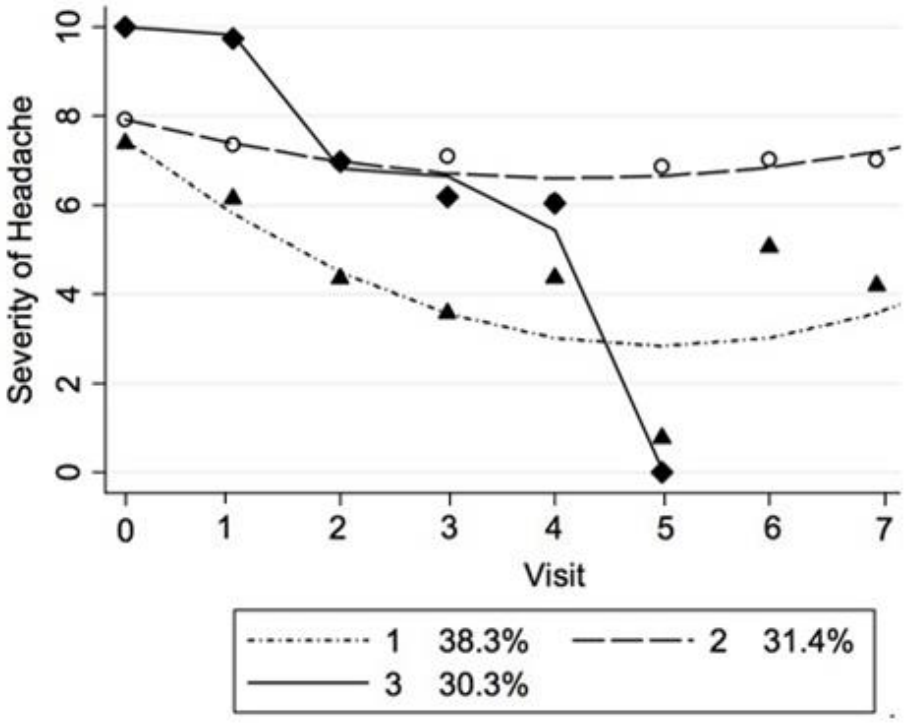

Figure 3: *Time course for headache severity in MwA.*

Table 1. Mean and Standard deviations for headache characteristics of patients at baseline and following 7 visits

	Severity (VAS)	Frequency (days/ month)	Duration (hours)
ine	8.34±1.63	5.65±3.65	31.14±26.92
l	7.20±1.73	5.84±6.00	25.95±25.73
2	5.70±2.29	3.97±4.22	15.39±14.42
3	5.43±2.54	4.96±8.01	9.18±11.11
4	5.35±2.02	2.36±1.78	17.78±25.97
5	3.70±3.86	1.80±2.29	10.80±16.16
6	6.67±1.21	7.33±11.2	30.50±25.23
7	6.40±1.52	7.80±9.88	20.20±29.23

Table 2. Odds ratios and statistical significance of risk factors for severity, frequency and duration subgroups obtained in LGMM. Group 1 was used as reference category for each comparison.

	Severity				Frequency				Duration	
	2 (n=39)		3 (n=81)		2 (n=80)		3 (n=11)		2 (n=74)	
	OR	P Value	OR	P Value	OR	P Value	OR	P Value	OR	P Value
Female	1.565	.483	2.222	.125	1.076	.875	.631	.614	1.724	.295
Age	.999	.934	1.010	.447	1.017	.211	1.027	.350	1.025	.067
Nausea	.510	.224	.497	.091	1.433	.365	1.528	.632	1.397	.402
Vomitting	1.861	.142	1.675	.119	.467	.017	.743	.654	1.616	.128
Throbbing	1.922	.197	1.045	.917	1.540	.259	1.393	.693	1.148	.727
Unilateral	3.146	.007	1.009	.979	.839	.580	1.192	.791	.920	.793
Photophobia	1.696	.395	1.151	.738	.840	.661	2.299	.226	1.719	.209
Phonophobia	.891	.860	1.702	.280	1.200	.688	.649	.664	.564	.224
Dizziness	2.637	.047	.692	.454	1.179	.692	.463	.442	.407	.061

Table 3. Mean and Standard deviations of the subgroups at different time points

	Groups	Visit1 Baseline	Visit2 Visit 1	Visit3 Visit 2	Visit4 Visit 3	Visit5 Visit 4	Visit6 Visit 5	Visit7 Visit 6	Visit8 Visit 7
Duration	Group 1 (n= 152)	14.88±12.02	10.70±9.19	7.17±5.88	5.23±4.43	5.50±5.04	1.80±3.03	7.50±3.50	11.00±1.40
	Group 2 (n= 75)	64.08±16.59	47.17±26.39	24.58±15.67	14.88±15.24	34.17±33.99	19.80±19.39	42.00±22.97	36.33±39.57
Frequency	Group 1 (n= 139)	3.05±1.44	3.53±1.85	2.30±1.17	1.80±1.03	2.16±0.75	2.60±2.90	2.33±1.52	4.00±4.24
	Group 2 (n= 80)	9.65±2.06	5.07±2.73	3.76±2.71	2.00±1.51	1.60±0.89	0.50±0.57	3.00±0.00	2.00±0.00
	Group 3 (n= 11)	9.36±2.69	15.22±9.83	11.20±7.56	14.16±12.43	4.00±3.46	3.00±0.00	17.00±8.38	14.50±4.80
Severity	Group 1 (n= 106)	6.96±1.18	5.92±0.97	4.26±1.99	3.70±2.26	4.33±1.03	0.75±1.50	5.00±0.00	4.00±0.00
	Group 2 (n= 39)	8.61±0.75	7.78±1.22	7.44±1.13	7.11±1.76	6.17±2.63	6.80±2.77	7.00±1.00	7.00±0.81
	Group 3 (n= 82)	10.00±0.00	9.67±0.71	7.00±1.80	6.00±2.20	6.00±1.40	NC	NC	NC

DISCUSSION

Identification of the outcome in MwA patients may provide some clues regarding the pathophysiology of this disease as well as new modalities for management. MwA is considered a risk factor of cerebrovascular and coronary artery disease[15,18,9] but the mechanisms underlying this relationship remain unknown. Thus, a determination of the course of MwA may aid in the further characterization of the disease.

This study was part of the Turkish Headache Database Project, which analyzed the data of MwA patients who attended a tertiary headache clinic over an eight-month treatment period. The most common form of auras was visual followed by sensorial. There were significant improvements in all headache parameters during the six visits of the follow-up period in terms of the frequency, duration, and severity of headaches (68%, 65%, and 56%, respectively). Our findings are compatible with those of previous studies[6,20]. Furthermore, they indicate that

MwA is a treatable disorder and that up to 60% of patients may benefit in all aspects with appropriate treatment and close follow-up assessments. These findings can help clinicians and patients establish goals for disease management during follow-up visits.

The three-group model for frequency of headaches with quadratic, quadratic, and cubic terms appeared to be a more appropriate representation of the data than the others. Vomiting was rarely observed in the medium frequency group and most of these patients experienced headaches < 10 days per month at baseline. Groups 2 and 3 exhibited the best recovery (94% and 68%, respectively) while Group 1, which was representative of low-frequent attacks, showed an 18% decrease in the frequency of headaches. These differences may be due to the selection of prophylactic treatment regimens in that group.

To investigate the correlations and course of MwA throughout the follow-up period, a two-group model was selected to analyze the duration of headaches. There were no significant risk factors associated with headache duration but attacks typically lasted 60–80 hours in Group 2, which consisted of patients with longer headache durations. During the follow-up period, the duration of headaches decreased for both groups (Group 1: 88%, Group 2: 69%), which suggests that it is important to determine effective abortive treatment regimens.

A three-group model was used to analyze the severity of headaches and revealed that unilateral pain and dizziness were more prominent in the moderate severity group than in the mild severity group (OR: 3.146, OR: 2.637), which is compatible with previous findings. For example, Kelman reported that the most severe headache attacks were closely related to prominent migraine-associated symptoms[14]. In the present study, patients with the most severe headaches exhibited the greatest response to treatments.

This study had some limitations. First, the duration of the follow-up period was short and the sample size at the follow-up visits may have been insufficient to accurately interpret the prognosis of MwA patients. Second, there was some uncertainty regarding the prognosis of patients withdrawn from the study that could have considerably affected the results. Nevertheless, our findings provide important data regarding the short-term prognosis of MwA patients following treatment at a tertiary headache center. Furthermore, a different type of analysis, the LGMM, was used to independently assess each variable and group and to observe the evolution of each parameter. The follow-up time period was adjucted to be adequate to observe the results in terms of disease management, and our findings revealed favorable treatment responses for each studied parameter, including headache frequency, duration, and attack severity. Furthermore, a higher frequency of headaches and attack severity at baseline were closely related with better disease management.

Abbreviations: ICHD: International Classification of Headache Disorders, MwA: migraine with aura, CM: chronic migraine, LGMM: latent growth mixture model, VAS: visual analogue scale, CNORM: censored normal, ZIP: zero-inflated poisson, OR: odds ratio.

Acknowledgements: Turkish Neurology Society has supported this study database.

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Received by: 27 December 2015
Revised by: 25 March 2016
Accepted: 04 June 2016

The Online Journal of Neurological Sciences (Turkish) 1984-2016
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

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