Journal of Neurological Sciences [Turkish] **27:(3)**# 24; 292-301, 2010
http://www.jns.dergisi.org/text.php3?id=374

Research Article

Presynaptic Inhibition and Disynaptic Reciprocal 1a Inhibition in Parkinson's Disease, The Effect of The Dopaminergic Treatment

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Summary

Objective: In recent years, increasing number of studies about the spinal cord pathology in Parkinson's disease had been conducted. H reflex investigation is an important choice in the studies dealing with neurophysiological and interneuronal alterations of the spinal cord. The effect of the dopaminergic treatment on the spinal interneuronal reflex pathways is a relatively less investigated issue. This study has been adressed to assess the presynaptic and disynaptic inhibition levels in Parkinson's disease, and the effect of dopaminergic treatment.
Methods: Presynaptic inhibition and dysynaptic reciprocal 1a inhibition is investigated by double stimulation of the tibial nerve at the popliteal fossa and peroneal nerve at the fibular head in patients with Parkinson's disease and also in control subjects for the 1-100 ms conditioning test intervals. The amplitude changes of the test and the conditioned H reflex responses were calculated and compared in the affected and less affected sides in both before and under dopaminergic treatment.
Results: Disynaptic and presynaptic inhibitions existed in all subjects. Disynaptic reciprocal 1a inhibition was shortened only at 2 ms conditioning interval. The conditioned and test H reflex ratio (Hc/Ht) for the 20 ms conditioning test interval (presynaptic inhibition) was significantly smaller in the affected side than the controls (p: 0.046). The percentages of the inhibitions for the 20-10-5-3-2 ms conditioning intervals significantly increased in the affected side under treatment when compared with the ones obtained in the pretreatment period (p: 0.031, 0.027, 0.014, 0.026, 0.037).
Conclusion: Presynaptic inhibition was decreased and disynaptic inhibition duration was shortened in the affected side of the patients with Parkinson's disease, dopaminergic treatment caused significant increases in both periods of inhibition. These findings indicate an abnormal supraspinal influence on the spinal cord in Parkinson's disease, and also the role of some dopa responsive neural mechanisms.

Key words: Presynaptic inhibition, reciprocal inhibition, spinal inhibitory mechanisms, H reflex, Parkinson's disease, dopaminergic treatment

Parkinson Hastalığı'nda Presinaptik İnhibisyon ve Disinaptik Resiprokal 1a İnhibisyonu, Dopaminerjik Tedavinin Etkisi

Özet

Amaç: Son zamanlarda Parkinson Hastalığında spinal kord patolojisi ile ilgili çalışmalara daha fazla rastlanmaktadır. H refleks incelemesi spinal kordaki nörofizyolojik ve internörinal değişiklikleri inceleyen çalışmalarda önemli bir seçenektir. Dopaminerjik tedavinin spinal internöronal refleks yollarındaki etkisi daha az araştırılmış bir konudur. Bu çalışma Parkinson Hastalığında presinaptik ve disinaptik inhibisyon düzeylerini, dopaminerjik tedavinin etkisini incelemek üzere planlanmıştır.
Metod: Presinaptik inhibisyon ve disinaptik resiprokal 1a inhibisyonu Parkinson hastalarında ve normal kontrollerde 1-100 ms intervallerle peroneal sinirin ve tibial sinirin ikili uyarımı ile

araştırıldı. Test ve şartlanmış H refleks yanıt amplitüd değişiklikleri hesaplandı. Dopaminerjik tedavi öncesi ve sonrası etkilenen ve daha az etkilenen taraflarda karşılaştırıldı.
Bulgular: Disinaptik ve presinaptik inhibisyon tüm deneklerde mevcuttu. Disinaptik resiprokal 1 a inhibisyonu etkilenen tarafta daha kısa süreliydi ve sadece 2 ms'lik intervalde vardı. 20 ms'lik interval için şartlanmış ve test H refleks oranı (presinaptik inhibisyon) etkilenen tarafta kontrollere göre anlamlı düşük bulundu (p: 0.046). 20-10-5-3-2 ms'lik intervallerdeki inhibisyon oranları tedavi sonrası etkilenen tarafta tedavi öncesine göre anlamlı artmıştı (p: 0.031, 0.027,0.014, 0.026, 0.037).
Sonuç: Parkinson hastalığında tutulan tarafta presinaptik inhibisyon azalmış, disinaptik inhibisyon süresi kısalmış bulunmuştur. Dopaminerjik tedavi, her iki inhibisyon periyodunda anlamlı artışa neden olmuştur. Bu bulgular Parkinson hastalığında supraspinal etkilerde anormallik varlığını ve ayrıca bazı dopaya cevaplı nöral mekanizmaların rolünü düşündürmüştür.

Anahtar Kelimeler: Presinaptik inhibisyon, resiprokal inhibisyon, spinal inhibitör mekanizmalar, H refleks, Parkinson Hastalığı, dopaminerjik tedavi

INTRODUCTION

The symptoms of Parkinson's disease (PD) start with the loss of dopaminergic neurons up to the % 50 and dopaminergic transmitter decrease in the substantia nigra pars compacta[13,15,28]. Although the Braak staging[5,6] system does not include, recent neuropathological studies have demonstrated early involvement of the spinal cord[4,13,51,52]. Some spinal pathways such as presynaptic inhibition and disynaptic reciprocal 1a inhibition are good candidates to study the alterations occurred in spinal cord in PD as they contribute to the isolation of the appropriate motor neuron pool either by focusing excitatory drives and/or inhibiting the other pools. Studies in humans have confirmed that supraspinal drives to interneurones such as corticospinal, rubrospinal and reticulospinal tracts interposes in these pathways[10,11,21,23,33,42]. Previous studies have shown that spinal inhibitory mechanisms were affected in PD[12,21,26,27,39]. Recent study by Fuentes et al.[16] which has shown that spinal cord dorsal column stimulation led to the functional recovery in the rodents with experimentally induced parkinsonism, has drawn the attention to spinal cord again.

Neurophysiological studies about spinal cord dysfunction in PD have been generally conducted with H reflex examinations. In different studies, the changes on the autogenic 1b inhibition, recurrent inhibition, disynaptic and presynaptic inhibition and H reflex recovery cycle were analysed[12,21,26,27,39,45,50].

There are a few neurophysiological studies about spinal inhibitory mechanisms investigating the effect of the dopaminergic treatment. In this study, presynaptic inhibition and disynaptic reciprocal 1a inhibition is assessed by double stimulation of the tibial nerve at the popliteal fossa and peroneal nerve at the fibular head of patients with PD and control subjects; the effect of the dopaminergic treatment was also questionned.

MATERIAL AND METHODS

11 patients with PD (mean age 63±8.9 ; 50-76) and 11 controls without neurologic and serious systemic or metabolic disease (mean age 61±9.8 ; 47-76) were enrolled to study. We were attentive to the age matching because normal human aging causes increase on the presynaptic inhibition[7,38].

All patients with PD were graded according to the NINDS diagnostic criteria[18,25]; Unified Parkinson's Disease Rating Scale of the UPDRS[36,14] and Hoehn and Yahr stages (H/Y) stages[20,37]

were also determined. Patients were examined for two times: firstly, 18 hours after the last dopaminergic drug administration (newly diagnosed patients were examined before starting treatment) and secondly, under the effect of an antiparkinson treatment. Affected or more affected side and healthy or less affected side examined separately.

Electrophsiological tests and Soleus muscle H-reflex studies:

A Nicolet Viking 4 channel EMG-EP machine was used in electrophysiological assessments. The tibial nerve motor conduction studies, tibial nerve F waves and sural nerve sensory conduction studies were performed in all subjects before the H reflex examinations.

During H-reflex studies, the subjects lyed prone with the head in a neutral midline position and their feet resting freely over the edge of the table in a quiet room. The soleus H reflex was evoked by stimulating tibial nerve through monopolar electrode (1 ms rectangular pulse). The reflexes were recorded by disc electrodes placed over the soleus muscle, using a gain of 1000-4000 μV and a filter of 10 Hz to 10 kHz. The reflex response was measured as the peak-to-peak amplitude. The size of the H reflex was kept at % 15-25 of the maximal motor response and this stimulation strength and motor response was checked and kept constant during the examination[8,40].

The soleus H reflex was conditioned by stimulation of the common peroneal nerve (CPN). The CPN was stimulated (rectangular 0.5 ms pulse) by bipolar surface electrodes placed distal to the neck of the fibula. The stimulus strength adjusted to the level slightly above (%105) the motor response treshold[8,9,41]. Test and conditioning stimulus interval was ranged between 1-100 ms (1-2-3-5-10-20-30-40-50-60-80-100 ms). Each stimulation and measurement was performed every 5s. The percentage of each conditioned soleus H reflex amplitude (Hc) to the preconditioned soleus H reflex amplitude (Ht) was calculated.

This study was approved and reviewed by the local Ethics Committee. Informed consent was obtained from each subject and the study was performed in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Conditioned and test H reflex (Hc, Ht) values and Hc/Ht values (percentage) were measured. The distribution properties were assessed with normal distribution curves and with Kolmogorov Smirnov test. The Hc/Ht % values for each interstimulus interval were analysed with repeated measures of analysis of variance; in pairwise comparisons (within subjects) Bonferroni correction was applied. The values belong to pretreatment and under treatment periods of the patients for each side and the values of the controls were also compared. Correlation analyses were made between the motor UPDRS, H/Y staging values and the percentages of the Hc/Ht amplitudes belong to the pretreatment period of the affected side.

RESULTS

Demographic and neurologic features, motor UPDRS scores and H/Y stages of the patients are shown in Table 1. Nerve conduction studies were all in the normal limits.

Presynaptic inhibition and disynaptic reciprocal 1a inhibition were determined on both sides of the patients with PD and control subjects (Figure 1A-B). By repeated measures analyses and Bonferroni correction (within subjects), this inhibition rates were statistically different and significant at the 10 and 2 ms conditioning test interval in the affected side of the patients in the pretreatment period (p: 0.028 and 0.005); at the 20, 10, 5, 3 and 2 ms in the affected side of the patients under treatment (p: 0.003, 0.003, 0.035, 0.001 and 0.001); at the 20, 10, 3, 2 ms in the good or less affected side (p: 0.02,

0.025, 0.01 and 0.012) in the pretreatment period; at the 20, 10, 5, 3, 2 ms in the good or less affected side of the patients under treatment (p: 0.012, 0,016 , 0.03 and 0.014), at the 20, 10, 5, 3, 2 ms in the control subjects (p: 0.00, 0.026, 0.046, 0.015, 0.019) (see Table 2).

In pairwise comparisons, the inhibition rates which show soleus H reflex amplitude decrease to the conditioning by the peroneal nerve stimulation were less in the affected side of the patients with PD in the pretreatment period (Figure 1A-B); when comparing with the control group, this difference was significant for the 20 ms conditioning test interval (independent student t test, p: 0.046). There was not any significant difference between the values of the less affected side of the patients and the ones of the control subjects in both periods. There was not any significant difference between the values of the both sides of the patients in the pretreatment period.

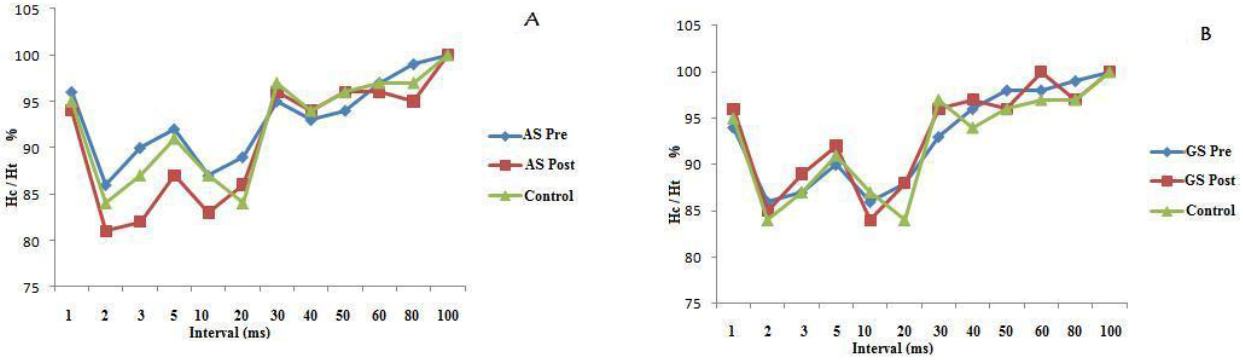

Figure 1: *Graphs shows mean proportions of the Hc/Ht amplitudes in patients with parkinson's disease and controls. Panel A shows to decrease at the presynaptic and disynaptic inhibition levels at the affected side of the patients (AS Pre, diamond) comparing posttreatment values of the same subjects (AS Post, square) and the values of the controls (triangle). Panel B shows graphs of the percentage of the changement in the conditioned H reflexes belong to the good side of the patients (GS Pre, diamond- GS Post, squares) and controls (triangle).*

Table 1 Demographic and neurological features of the 11 patients with parkinson's disease.

Patient	Sex	Age	Affected Side	Duration (months)	H/Y Stage	Motor UPDRS	Tremor	Brady kinesia	Rigidity	NINDS
1SB	W	50	L>R	180	3	39	+	+	+	PrbiPH*
2FA	W	74	L	12	1	19	+	+	-	PrbiPH
3KU	W	76	R	12	1	26	+	+	-	PrbiPH
4 IY	M	58	L>R	30	2	32	+	+	+	PrbiPH
5 ID	M	62	R>L	54	2	29	+	+	+	PrbiPH
6 HG	M	66	R	12	1	22	-	+	+	PrbiPH
7 BO	M	53	L>R	56	2	33	+	+	+	PrbiPH
8 IP	M	52	R>L	54	2	24	+	+	+	PrbiPH
9 RS	M	69	R	12	1	14	+	+	-	PrbiPH
10 DS	M	63	R	12	1	21	+	+	-	PrbiPH
11 FY	M	70	L>R	108	3	38	+	+	+	PrbiPH

*PrbiPH : *Probable Idiopatic Parkinson's Disease.*

When the changes with the treatment were analysed, there was not any significant difference between the values of the good or less affected side of the patients for both periods. However, there were significant differences in the comparison of the pre and under treatment values of the affected side of patients for the 20, 10, 5, 3 and 2 ms as the conditioning test interval (paired student t test, 0.031, 0.027, 0.014, 0.026, 0.037) (see Table 2).

There was a weak correlation between the motor UPDRS (pearson correlation coefficients: 0.33; 0.4) or H/Y staging values (0.4; 0.4) and the presynaptic (20-10 ms) / disynaptic inhibition ratios (3-2 ms) in the pretreatment period of the affected side, but both of them were not statistically significant (p : 0.32-0.26; 0.26-0.25) .

Table 2 Mean soleus H reflex percentage values (*mean ± SD, SE, range*) that shows presynaptic and disynaptic inhibition levels of the controls and patients with the parkinson's disease (in the periods with and without the effects of an antiparkinson treatment)

Groups	Inter Stimulus Intervals				
	Presynaptic inhibition			Disynaptic inhibition	
	20 ms	10 ms	5 ms	3 ms	2 ms
Control (C)	83.7±5.2	87.2±8.2	90.9±6.2	86.6±7.9	84.4±9.5
	(1.6) (75-90)	(2.5) (75-98)	(1.9) (80-100)	(2.4) (70-95)	(2.9) (70-95)
	p¥: 0.00	p: 0.026	p: 0.046	p: 0.015	p: 0.019
Goodside*	87.8±7	86.2±8.2	90.5±6.8	86.9±6.2	86.4±8
Pretreatment (GSP)	(2.1) (78-100)	(2.5) (81-91)	(2) (80-100)	(1.9) (83-91)	(2.4) (81-91)
	p: 0.02	p: 0.025	p: 0.16	p: 0.01	p: 0.012
Goodside **	88.2±7.3	84.5±9.7	92.2±6.4	89.4±5.9	85.5±8.3
Under-treatment	(2.2) (77-96)	(2.9) (70-95)	(1.9) (80-100)	(1.8) (77-95)	(2.5) (70-95)
(GSU)	p: 0.012	p: 0.016	p: 0.062	p: 0.003	p: 0.014
Affected side	89.4±7.4	87.4±8.1	92.1±7.3	90.3±7.8	86.4±7
Pretreatment (ASP)	(2.2) (75-100)	(2.4) (72-95)	(2.2) (80-100)	(2.4) (75-96)	(2.1) (68-95)
	p: 0.051	p: 0.028	p: 0.32	p: 0.14	p: 0.005
Affected side	86.2±6.7	82.7±8.5	87±8.6	81.7±8	81.4±7.6
Under-treatment	(2.1) (70-95)	(2.6) (70-95)	(2.6) (75-100)	(2.4) (70-95)	(2.3) (70-90)
(ASU)	p: 0.003	p: 0.003	p: 0.035	p: 0.001	p: 0.001
Statistic	p§ (ASP-C): 0.046				
	p†(ASP-ASU):0.04	p(ASP-ASU):0.04	p(ASP-ASU):0.03	p(ASP-ASU):0.015	p(ASP-ASU):0.036

*Good or less affected side
** Comparison of the GSP, GSU and C values are non significant
¥Repeated Measures, Bonferroni procedure
§Independent student t test
† Paired student t test

DISCUSSION

CPN stimulation produces a significant depression of the soleus H reflex at a conditioning test interval of 2-3 ms[8].This depression has been shown to be mediated probably by the disynaptic 1a pathway[9]. Symmetrical central connections between the antagonist flexors and extensors were assumed, and under this assumption the central delay for the inhibition, in addition to the delay for monosynaptic 1a excitation, was calculated to be about 1 ms.[8,9]. At conditioning-test intervals longer than 8-10 s, CPN stimulation evokes a second inhibition in healthy subjects. This inhibition was termed as D1[35] and it is believed to be caused by presynaptic inhibition of the terminals of 1a afferents of soleus motor neurons.

In this study, it was demonstrated that there were presynaptic inhibition and disynaptic reciprocal 1a inhibition on both sides of the patients with PD and control subjects. We observed that this inhibitions were lower and shorter (only for the 2 and 10 ms conditioning test intervals in the analyses of variance of the repeated measures) at the affected side in the pretreatment period. The ratio was significantly different for the 20 ms conditioning test interval than control subjects, and dopaminergic treatment caused significant increases in the inhibition ratios at the affected side for the 2-3-5-10-20 ms intervals.

Spinal segmental control mechanisms are important in the execution of supraspinal motor commands. Changes in transmission in various excitatory and inhibitory reflex pathways from both cutaneous[17] and muscle primary afferents have been described in PD. There is now a consensus about the long latency stretch reflexes are enhanced in PD. It was suggested that increased transmission in the transcortical and other pathways mediating them might play a role in rigidity[2,48]. Decreased transmission in various inhibitory spinal reflex pathways might also contribute, but the evidences are more conflicting. It was reported that there is a pronounced reduction in lb inhibition in parkinsonian patients[12]. Reciprocal inhibition was recently shown to be decreased in the upper limbs of patients with PD[27] but previous evidence suggested increased reciprocal inhibition[1]. On the other hand recurrent inhibition was reported as unchanged[27]. Presynaptic inhibition of Ia terminals were reported to be decreased when elicited by electrical stimulation of an antagonist nerve in the upper limb[27] and to be reduced when obtained by a brief conditioning pulse of vibration to tibialis anterior at a conditioning test interval of 60 ms is reduced in patients with PD[47]. Our findings are complementary to the suggestions about the reduction in spinal inhibitory mechanisms in patients with PD.

Katz et al. reported that in normal subjects, presynaptic inhibition increased while standing without support compared with standing with support or sitting[26]. They considered that this increase depresses excessive segmental reflexes and would be used to establish stability during standing. Morita et al[39] found marked reduction in presynaptic inhibition in patients with PD, and they suggested that instability of posture is an important factor in parkinsonism, and disturbance of the central control of presynaptic inhibition appears to be a factor responsible for bradykinesia, gait disturbance, and postural instability in that disease. Our results support the assumption that reduction in the presynaptic inhibition in PD indicates that a dopa-responsive neural mechanism controls descending tonic presynaptic inhibition on Ia terminals on soleus motoneurons[39].

Lelli et al[27] reported decreased presynaptic inhibition and disynaptic reciprocal 1a inhibition in patients with PD without dopaminergic medication by using radial – induced flexor carpi radialis H reflex inhibition. Nakashima et al[41] reported abnormality in the reciprocal

inhibition during tonic movements. On the other hand, Tsai et al[53] did not find any significant change. Menuier et al[32] found that less reciprocal inhibition occurred during wrist flexion while it was retained at rest in patients with PD. Hayashi et al[19] demonstrated decreased size of the soleus H reflex during ankle dorsiflexion, and pointed out to the decreased reciprocal inhibition as a responsible mechanism. We also observed that disynaptic reciprocal inhibition ratios were decreased in the affected side of the patients than the age matched controls, but they were not significant. On the other hand, under the dopaminergic treatment, the disynaptic reciprocal inhibition in the affected side significantly increased. It was explained that the decrease in the disynaptic reciprocal inhibition can be assummed to be supraspinal origin or to be impaired possible descending tonic inhibitory control of the reciprocal interneurons[10,32,43]. Menuier et al[32] demonstrated that movement induced reciprocal inhibition was more disturbed on the affected side than on the less affected side.They reported only a weak positive correlation with the axial signs. Bertolasi et al[3] suggested that areas of the motor cortex controlling to the antagonist muscles could be organized in a similar way to the reciprocal inhibition at the spinal level. It was reported that, in the animal and human studies, reciprocal inhibition is facilitated by the descending pathways from the brain and brainstem, cortico-rubro-vestibulo-reticulospinal tracts[24,31,49]. It was also reported that the output of the basal ganglia goes to the down through thalamus, brainstem and pedinculopontine nucleus to spinal cord[24,46]. Vidalheit et al[54] affirmed that functional changes in reticular nuclei may occur in PD. Menuier et al[32] suggested that excessive output from the globus pallidus to the pedinculopontine nucleus[34] may be responsible from the decreased reciprocal inhibition, they substantiated this claim with improved agonist-antagonist co-contraction in patients with pallidotomy[22].

Presynaptic inhibition is one of the most powerful inhibitory mechanisms in the spinal circuits, and recent human studies have shown that this inhibition is modulated centrally, dependent on the motor paradigms in voluntary movement[21,26]. Delwaide et al.[12] reported that a decrease in Ib inhibition is correlated with parkinsonian rigidity and should reflect a disturbance in supraspinal control through the reticulospinal pathway. On the other hand, Robert RC et al[47] demonstrated that the inhibition of a soleus test reflex by a brief conditioning pulse of vibration to tibialis anterior is reduced in patients with PD compared with age matched controls; they suggested that the reduction of presynaptic inhibition and the changes in other reflex pathways[2,27] showed no clear relation to the clinical features. In our study, also there were weak corellations between the motor parameters and the presynaptic/disynaptic inhibition ratios in the pretreatment period of the affected side and they did not reach to the significance level.

Significant facilitation at the early and secondary recovery and even in the secondary inhibition phases, shorter inhibition and rapid recovery has been reported in the studies about the H reflex recovery cycle (HRRC) changes in the patients with PD[30,44,50]. Increased motor neuron excitability and reduced supraspinal inhibitory mechanisms on the spinal motor neurones were found to be responsible. However, conflicting, affirmative or unfavourable results were suggested on the effect of the dopaminergic treatment on the HRRC[29,30]. Morita et al[39] studied heteronymous Ia facilitation from the quadriceps to the soleus to clarify central motor control through presynaptic inhibition (PSI) on Ia terminals of spinal motoneurons in PD. They showed that heteronymous Ia facilitation (i.e. decrease in the presynaptic

1a inhibition) in the patients with PD was significantly greater than that in the control subjects. In 2 out of 17patients who were examined twice under different clinical conditions, facilitation decreased (i.e. increase in the presynaptic 1a inhibition) with improvement in walking speed. In our study, we demonstrated an obvious increase in the disynaptic and presynaptic inhibition levels with the use of the dopaminergic drugs. So this finding also supports the role of dopa-responsive mechanisms in regulating spinal inhibitory mechanisms.

In conclusion, the decrease in the presynaptic and disynaptic reciprocal inhibition probably leads some disturbances of the agonist-antagonist co-contraction and segmental reflex regulation and stability during standing. These disturbances may explain some of the difficulties that patients with PD experience during movement.

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Received by: 18 January 2010
Revised by: 27 April 2010
Accepted: 25 May 2010

The Online Journal of Neurological Sciences (Turkish) 1984-2010
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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