Journal of Turgut Ozal Medical Center 2016;23(1):62-9
ORİJİNAL MAKALE/ORIGINAL ARTICLE DOI: 10.5455/jtomc.2015.3224

Side-based Activation of Sympathetic Skin Responses Recorded from the Frontal Region in Idiopathic Parkinson's Disease

İdyopatik Parkinson Hastalığı'nda Frontal Bölgeden Kaydedilen Sempatik Deri Yanıtlarının Tutulum Tarafına Göre Etkilenimi

Sule Aydın Turkoglu, Serpil Yıldız, Nebil Yıldız, Elif Sultan Bolaç

Abant İzzet Baysal University, Faculty of Medicine, Department of Neurology, Bolu, Turkey

Abstract

Objective: In a unilateral onset Idiopathic Parkinson disease, sympathetic skin responses elicited from previously and markedly affected and also from unaffected palm and forehead were recorded before and after the treatment. The difference (if any) in sympathetic skin responses recordings obtained from patients and control cases and the impact of Idiopathic Parkinson disease treatments on response sympathetic skin responses were investigated.

Materials and Methods: A total of 23 patients and 22 healthy volunteers were included in the study. The patients were examined for autonomic nervous system involvement and the patients with facial hyperhidrosis were determined. Sympathetic skin responses of the patients were recorded twice (before and after initiation of therapy) from both sides of the forehead and both hands and compared with healthy volunteers.

Results: A statistically significant difference was not detected between sympathetic skin responses amplitudes of left and right hands in Tests 1 and 2. Significantly lower sympathetic skin responses amplitudes were observed in Test 2. Correlations among amplitudes of hand sympathetic skin responses, Hoehn and Yahr Staging and Unified Parkinson's Disease Rating Scale scores demonstrated significant decreases in amplitudes of sympathetic skin responses in parallel with disease progression. Left side dominancy in patients with hyperhidrosis is statistically significant.

Conclusion: Detection of lower amplitudes in hand sympathetic skin responses after therapy may be due to habituation or used drugs. Significant decreases in amplitudes of sympathetic skin responses in parallel with disease progression were observed. No data concerning left side dominancy in the patient group with hyperhidrosis have been detected so far.

Keywords: Parkinson Disease; Sympathetic Skin Responses; Autonomic Dysfunction.

Öz

Amaç: Bu çalışmada, unilateral başlangıçlı İdyopatik Parkinson Hastalığı'nda, daha fazla tutulan tarafta sempatik deri yanıtlarında diğer tarafa göre fark olup olmadığı ve sempatik deri yanıtları üzerinde kullanılan tedavilerin etkisi araştırılmış ve sağlıklı gönüllüler ile karşılaştırılmıştır.

Gereç ve Yöntemler: Çalışmaya 23 hasta ve 22 sağlıklı gönüllü alınmıştır. Hastalar otonom sinir sistemi bulguları ve yüzde hiperhidrozis varlığı açısından sorgulanmıştır. Tedavi öncesi (test 1) ve tedavi sonrası (test 2) sempatik deri yanıtları iki yanlı frontal ve el bölgesinden kayıtlanarak kontrol grubuyla karşılaştırılmıştır.

Bulgular: El yanıtlarında Test 1, Test 2 ve kontrol grubunda sağ ve sol taraf arasında, aynı zamanda hasta-sağlam taraf arasında istatistiksel olarak anlamlı bir farklılık göstermemiştir. İlaç tedavisi sonrasında yanıt amplitüdlerinin istatistiksel olarak anlamlı olarak düştüğü kaydedilmiştir. El yanıt amplitüdleri ile Hoehn and Yahr Staging (H&Y) skorları ve Unified Parkinson's Disease Rating Scale (UPDRS) puanları arasında hastalık ilerledikçe negatif korelasyon gözlenmiştir. Sol taraf başlangıçlı olan hastalarda hiperhidroz varlığı sağ taraf başlangıç olanlara göre istatistiksel olarak anlamlı bulunmuştur.

Sonuç: Tedavi sonrasında tedavi öncesine göre el yanıtlarında amplitüdlerin düşmesi, habituasyona veya kullanılan ilaçlara bağlı olabileceği düşünülmüştür. Hastalık ilerledikçe amplitüdlerinin istatistiksel olarak anlamlı düştüğü gözlenmiştir. Hiperhidrozlu grupta sol taraf başlangıçlı hastalık olma olasılığının yüksek olması ile ilgili bu güne kadar literatürde herhangi bir bilgiye rastlanmamıştır. Bu konuda daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Parkinson Hastalığı; Sempatik Deri Yanıtları; Otonomik Disfonksiyon.

Received/Başvuru: 13.07.2015
Accepted/Kabul: 07.10.2015

Correspondence/İletişim
Şule AYDIN TURKOGLU
Abant İzzet Baysal Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, BOLU, TÜRKİYE
E-mail:suleaydinturkoglu@hotmail.com

For citing/Atıf için
Turkoglu SA, Yildiz S, Yildiz N, Bolac ES. Side-based activation of sympathetic skin responses recorded from the frontal region in idiopathic parkinson's disease. J Turgut Ozal Med Cent 2016;23(1):62-9

DOI: 10.5455/jtomc.2015.3224

2016;23(1):62-9
DOI:10.5455/jtomc.2015.3224

INTRODUCTION

Idiopathic Parkinson disease (IPD) is a neurodegenerative disease related to age. It has an asymmetrical involvement pattern on the onset of the disease. Autonomic symptoms, which are considered to be non-motor symptoms, include constipation, frequent urination and urgency, impotence, sweating disorders, sialorrhea and orthostatic hypotension (1, 2). Motor symptoms demonstrate relatively asymmetrical involvement even in the advanced stages of the disease, however, asymmetrical involvement is not expected for such as symptoms as seborrhea, sialorrhea and thermoregulatory dysfunction. Numerous neurophysiological and neuropathological studies have analyzed autonomic nerve function in IPD (3-8). Recording sympathetic skin responses (SSRs) used in the evaluation of nervous system is an easily applicable method, which can be implemented by means of a standard electromyography device. During classical electrocardiographic examination, SSR are recorded from palms and soles where the skin resistance is at its lowest level. The most frequently used stimulation method is electrical stimulation of sympathetic and parasympathetic nerves of arms or legs (9). Previously, changes indicating asymmetry (if any) in SSR recorded from palms and in other autonomic tests in IPD have been investigated. Schestatsky *et al.* found SSR recorded from lower and upper extremities had significantly lower amplitudes in IPD patients when compared with the control group (7). Fusina *et al* made SSR recordings from both hands in cases with early stage IPD and detected decreased amplitudes consistent with the side with motor involvement (6). Giza *et al.* made recordings from both hands and could not detect any significant difference between IPD and the control group (10). SSR recordings obtained from the frontal region or forehand have not been analyzed before. In this study in a unilateral onset IPD, SSRs elicited from previously and markedly affected and also from unaffected palm and forehead were recorded before and after the treatment. The difference (if any) in SSR recordings obtained from patients and age-matched normal control cases and the impact of IPD treatments on SSRs were investigated. Besides, the presence of asymmetry, which is observed in motor symptoms, has been also investigated in SSR recordings obtained from hand and forehead.

MATERIALS and METHODS

The study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Ethical Committee (2007/100–41). Informed consent was taken from each individual. Changes in SSRs which are recorded from bilateral forehead and hand in pre-treatment and after treatment and according to the affected side were investigated in this study.

A total of newly diagnosed treatment-naive IPD patients or patients on drug break (vacation) at least for two days [women (n=11) and men (n=12)] were included in the study. Diagnosis of IPD made according to the United Kingdom Parkinson' s Disease Society Brain Bank (UKPDSBB) citeria (11) differentiation of IPD patients from other Parkinson plus syndromes by National Institute of Neurological Diseases and Stroke (NINDS) guidelines (12).

In routine biochemical analyses and cranial images, we did not meet any pathology that might cause IPD-like symptoms. The patients were examined for autonomic nervous system involvement and the patients with facial hyperhidrosis were determined. SSRs of the all the patients enrolled in the study were recorded twice (at a median interval of 9.3 days (range, 24 hours to 21 days). First recording was made before the treatment (Test 1); the second recording was made after initiation of therapy (Test 2). In Test 2, the tests were performed at least one hour after the treatment of the patients was completed. SSRs of the patients were recorded from both sides of the forehead and both hands. These patients were started on L-Dopa, dopamine agonists and rasagiline therapy. For Test 2, we could contact with 20 [women (n=11) and men (n=9)] out of 23 patients.

Control group consisted of 22 healthy volunteers [women (n=7) and men (n=15)] selected among patients who applied to the outpatient clinic for any other reason or from patient's relatives. Bilateral frontal and hand SSRs of the control subjects were also recorded.

SSRs were recorded between 09.00 and 17.00 h. The subjects lay in a comfortable supine position in a quiet, well-lit air-conditioned room maintained at 24±1 degrees Celsius (°C). The skin temperature of each subject was > 32°C. The subjects were instructed to keep their eyes open, not to breathe deeply, cough, talk or move their head during the procedure. The experiment was performed with a Nicolet Viking IV channel electromyography. SSR recordings were made with standard surface electrodes made from Ag-AgCl (10 millimeter (mm) diameter, Nihon Kohden, NM-312S). Recording method was similar to the method mentioned by Yildiz *et al.* (13).

The frequency bandpass was 0.2– 100 Hertz (Hz). The time window for recording was 5 second (s) and the gain was 500 microvolt (μV) per division. The electrical stimulation (square pulse with 0.2 milisecond (ms) duration and 10-100 milliamps (mA) intensity) was applied over the right tibial nerve at the ankle. In subjects without any recordable response, we increased the intensity level by 10 mA (maximum 100 mA) until the responses occurred and reached a stable form. Subjects who showed no response on either side after receiving five consecutive electrical stimuli of an intensity of 100 mA were considered unresponsive. The recording location is shown in Figure 1.

In each subject, the right and left sides of the frontal region and hand were studied and bilateral F-SSRs were recorded. The stimuli were delivered at irregular intervals at least 20 s apart. Ten to twenty stimuli were delivered to each subject in every single examination

2016;23(1):62-9
DOI:10.5455/jtomc.2015.3224

(examinations 1, 2 and 3). SSRs were considered to be present when their amplitude was > 50 μV and its latency was similar for at least two of the subsequent stimuli. The peak-to-peak amplitude was measured for each response. Responses with maximum amplitude were calculated for each session in each subject. To avoid habituation, interval between impulses set on approximately 45-60 seconds. We observed that the responses appeared whenever the subjects laughed or were startled by a sudden noise. However, responses were distorted slightly because of movement artefact while laughing. Such responses were excluded from the analyses.

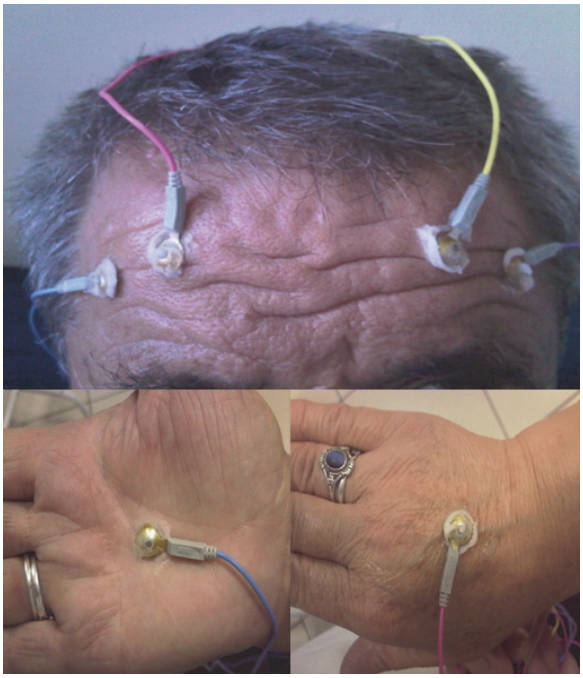

Figure 1. Sites of recording: A) Recording from the both sides of the forehead; B) Recording form hands (active electrode); C) Recording from hands (reference electrode)

In statistical analyses, maximum amplitudes of the right and left sides evoked by electrical stimulation in test 1 and test 2 evoked by electrical responses in patient groups, were compared using a two related sample test (Wilcoxon signed ranks test). Data from the control subjects and iPH patients were compared using the Mann–Whitney test. Latency responses were not use in statistical analyses. $P < 0.05$ was considered to be statistically significant.

RESULTS

Test 1 group consisted of a total of 23 patients with probable diagnosis of IPD. Their symptoms originated from the right and the left side whom symptoms begun from right in 12 and and from left in 11 of the patients. Test 2 could be applied on only 20 patients with symptoms originated from the right (n=11) and left (n=9) sides.
Median duration of the disease was 12 months (1-56 months), laterality of involvement was as follows; right in 12 and left in 11subjects. Median H&Y and UPDRS scores were 1,5 (0,5-2,5) and 30,74±11,28, respectively.

Control group consisted of 15 male and 7 female healthy individuals. Mean ages of the patients and the control subjects were 67.7±7.7 (Test 1, n=23) and 66.18±8.1 (n=22) years, respectively. A statistically significant difference was not found between ages of either group (p>0.05).

The characteristics of the patient group and diagnostic IPD criteria were based on UKPDSBB citeria. All 23 patients with IPD had bradykinesia while 15 of them had been asymmetrical onset. 20 of these patients had resting tremor and 16 had rigidity. Flexion posture was seen in 17 patients and 15 had postural instability. In terms of autonomic involvement; sweating, orthostasis, seborrhoea and urinary incontinence has been described by 7, 12, 5 and 12 subjects, respectively. One patient denied any autonomic symptoms, while constipation, sialorrhea have been described by 10 patients.

Bilateral hand SSRs were obtained from all patients in Test 2. Bilateral frontal SSRs could be recorded from 5 patients and from 2 out of 15 patients bilateral responses could not be elicited. In 13 patients, only right- sided responses could be obtained. In the control group, in 22 healthy volunteers, bilateral hand responses could be recorded. Bilateral frontal SSRs could be obtained from 6 persons, while in 6 healthy controls only unilateral SSRs could be elicited. Bilateral frontal SSRs could be recorded in 6 individuals, while in 6 individuals bilateral responses could not be acquired. In the remaining 10 individuals only right-sided SSRs could be elicited, while left –sided responses could not be obtained. Hand and frontal response patterns in Test 1, Test 2 and the control groups are shown in Table 1.

Table 1. Sympathetic skin response patterns elicited from hands and forehead in Test 1 and 2 and the control groups.

		Test 1 (n=23)	Test 2 (n=20)	Control (n=22)
Hand SSR	Bilateral responsive	23 (100%)	20 (100%)	22 (100%)
	Unilateral responsive*	0	0	0
	Bilateral non-responsive	0	0	0
Frontal SSR	Bilateral responsive	8 (35%)	5 (25%)	6 (27%)
	Unilateral responsive*	10 (44%)	13 (65%)	10 (46%)
	Bilateral non-responsive	5 (22%)	2 (10%)	6 (27%)

* In all cases with unilateral responses, any response could not be obtained from the left side.
SSR= Sympathetic skin response

2016;23(1):62-9
DOI:10.5455/jtomc.2015.3224

Two out of 4 patients with bilateral frontal SSRs were not examined in Test 2, while 2 patients with unilateral responses were observed in Test 2. Bilateral frontal responses could be recorded in one patient without frontal response in Test 1.

In Test 1, SSRs of both hands of all patients were recorded. Bilateral frontal SSRs could be elicited from 8 patients and from 5 out of remaining 15 patients bilateral frontal SSRs could not be obtained In 10 patients only right-sided SSRs could be elicited.

Descriptive data of hand SSRs elicited from Test 1, Test 2 and the control groups and comparisons between right and left sides and also affected and unaffected sides are shown in Table 2.

No statistically significant difference was detected between SSRs amplitudes of left and right hands in Test 1. (n=23, p>0.05). In the comparison between previously and more severely affected hand and the other (unaffected) hand (comparison between affected and unaffected side) a statistically significant difference could not be obtained. (n= 23, p> 0.05).

No statistically significant difference was detected between the right and left hand SSRs in Test 2 (n=20, p>0.05). No statistically significantly difference was detected between affected and unaffected hand SSRs (n= 20, p> 0.05). In the control group, no statistically significant difference was found between right and left SSRs amplitudes (n=22, p>0.05).

Amplitudes of hand SSRs in Test 1 and Test 2 were compared and statistically significantly lower SSRs amplitudes were observed in Test 2 (n=40, p=0.003; See Table 2).

Table 2. Comparison between involved and compact side sympathetic skin responses of hand recorded in Test 1, Test 2 and control groups.

Hand	Patient group				Control group	
Amplitüd (μV)	**Right**	**Left**	**involved side**	**compact side**	**Right**	**Left**
Test 1	n=23	n=23	n=23	n=23	n=22	n=22
Median	607	596	607	596	523	435
min-max	163-2012	136-1854	163-1854	122-2012	169-2536	140-2301
	p=0.083		p=0.394		p= 0.559	
Test 2	n=20	n=20	n=20	n=20		
Median	378	464.5	360	487.5		
min-max	147-1409	99-1384	147-1384	99-1409		
	p=0.161		p=0.641			
	Test 1- Test 2 n=40					
	* p=0.003					

SSR= Sympathetic skin response
*Amplitudes of hand SSRs obtained in Test 2 were significantly lower relative to Test 1.

No statistically significant difference was detected when amplitudes of hand SSRs in Test 1 and the control group were compared (n=90, p>0.05). Significant differences were not detected between hand SRRs of the right hands of the control group (n=22) and affected right hands of the patients (n=12) and also between the left hand SSRs of the control group (n=22) and affected left hands of the patient group (n=11) (n=34 and n=33, for both p>0.05; See Table 4).

Descriptive data of frontal SSRs obtained in Test 1, Test 2 and control groups and also comparisons between right and left and also affected and unaffected sides are shown in Table 3.

When data of only patients with bilateral responses in Test 1 were compared, we did not observe any statistically significant difference between amplitudes of the right and the left frontal SRRs (n= 8, p=0.017, amplitudes of the left frontal SRRs were lower when compared with those of the left SRRs). No statistically significant difference was detected between previously and much more affected side and the other side (affected and unaffected sides) (patients with bilateral responses, n=8, p>0.05).

In Test 2, right and left frontal SRR amplitudes were compared and amplitudes of the left side were found to be significantly lower than those of the right side (patients with bilateral responses (n= 5) (p=0.043); amplitudes of the left frontal SRRs were lower than those of the right side). No statistically significant difference was detected between amplitudes of the affected and the unaffected side SRRs (patients with bilateral responses n=5, p>0.05).

In the control group, amplitudes of the left frontal RSSs were significantly lower than those of the right side (patients with bilateral responses, n= 6, p=0.028, amplitudes of the left frontal SRRs were lower than those of the right side).

Since a statistically significant difference was detected between left and right frontal SRRs recorded in Test 1,

2016;23(1):62-9
DOI:10.5455/jtomc.2015.3224

Test 2 and the control groups (left side SSRs amplitudes were relatively lower or absent), data related to the right and the left sides were compared individually (see Table 3).

We failed to record right frontal SSRs in one patient and left frontal SRRs in two patients in Test 1. However, in Test 2, these responses could not be obtained. Contrarily, patients with undetectable right (n=4) and left (n=4) frontal SSRs demonstrated recordable responses in Test 2.

In the comparisons between frontal SSRs elicited in Tests 1 and 2, the patients who responded on the side to be examined were included in the analysis. In both tests on a total of 18 patients, right and left frontal SSRs could be recorded. No statistically significant difference was recorded between Test 1 and Test 2 as for frontal SSRs (n=18, p>0.05). When we investigated whether only right frontal or solely left frontal SSRs changed significantly between Test 1 and 2 and we still did not observe any statistically significant difference for either side (right frontal SSRs, n=14, left frontal SSRs, n=5, for both p>0.05; See Table 3).

In the comparison between amplitudes of frontal SSRs in Test 1 and the control group, right and/or left frontal SSRs could be obtained in a total of 26 patients. When these data were compared with 22 right and/or left frontal SSRs elicited in the control group, no statistically significant intergroup difference was detected (n= 48, p>0.05). When amplitudes of the right frontal SSRs recorded in Test 1 (n=18) were compared with the amplitudes of the left frontal SSRs of the control group (n=16 a statistically no significant difference could be detected (n=34 and n=14, respectively; for both p>0.05; See Table 3).

Right frontal SSRs amplitudes in patients whose right side was more severely affected (in only 9 out of a total of 12 patients right frontal SSRs could be recorded) recorded in Test 1 and those of the control group (right frontal SSRs could be obtained in 16 out of 22 control subjects) were compared and any statistically significant intergroup difference was not detected (n=25, p>0.05; See Table 3).

Table 3. Comparison between involved and compact side of frontal sympathetic skin responses recorded in Test 1, Test 2 and control groups.

Frontal	**Patient group**				**Control group**	
Amplitude (μV)	Right	Left	involved side	compact side	Right	Left
Test 1	n=18	n=8	n=14	n=12	n=16	n=6
Median min-max	166,5 56-1393	98 67-267	148,5 56-517	137 57-1393	219.5 50-1835	124 78-629
	n=23, p=0.000 *n=18, p=0.000 **n= 8, p=0.017		n=23, p=0.862 *n=18, p=0.862 **n= 8, p=0.889		n=22, p=0.000 *n=16, p=0.000 **n= 6, p=0.028	
Test 2	n=18	n=5	n=13	n=10		
Median min-max	193 53-818	73 58-111	111 53-818	180.5 58-768		
	n=20, p=0.000 *n=18, p=0.000 **n= 5, p=0.043		n=20, p=0.913 *n=18, p=0.913 **n= 5, p=0.225			
	Test 1- Test 2					
Responsives in both tests	p=0.420 (n=18)					
Right frontal SSR	p=0.826 (n=14)					
Left frontal SSR	p=0.080 (n=5)					

SSR= Sympathetic skin response
* Bilaterally unresponsive patients were not included in the analysis
** Only bilaterally responsive patients were included in the study

In patients with more severely affected left side (in only 5 out of a total of 11 patients frontal SSRs could be recorded) in Test 1, amplitudes of the left frontal SSRs and the data of the control group in Test 1 were compared without a statistically significant difference between groups (left frontal SSRs could be elicited in 6 out of 22 control subjects) (n=11, p>0.05; See Table 4).

2016;23(1):62-9
DOI:10.5455/jtomc.2015.3224

Table 4. Comparison of hand and frontal SSRs in Test 1 and the control groups.

		Test 1 (n=23) Control (n=22)
Hand SSR	All data	p=0.725 (n=46, n=44)
	Right hand SSR and control right hand SSR in right side diseases	p=0.466 (n=12, n=22)
	Left hand SSR and control left hand SSR in left side diseases	p=0.317 (n=11, n=22)
Frontal SSR	All data	p=0.878 (n=46, n=44) *p=0.321 (n=26, n=22)
	Right frontal SSR	p=0.784 (n=23, n=22) *p=0.384 (n=18, n=16)
	Left frontal SSR	p=0.825 (n=23, n=22) *p=0.181 (n=8, n=6)
	Right frontal SSR and control right frontal SSR in right side diseases	p=0.631 (n=12, n=22) *p=0.357 (n=9, n=16)
	Left frontal SSR and control left frontal SSR in left side diseases	p=0.510 (n=11, n=22) *p=0.537 (n=5, n=6)

*Unattainable SSRs were not included;
SSR= Sympathetic skin response

DISCUSSIONS

In some studies where sudomotor activities have been evaluated in IPD, abnormalities including prolonged latency (14), decreased amplitudes (3,15) or loss of responses have been reported, Conversely, some studies reported that SSRs had not changed in IPD (10). Still, some studies have reported abnormalities in SSRs in the involved side when compared with the intact side (18) or lack of any difference between the intact and the affected side. Surprisingly, in studies performed on groups with IPD, multiple system atrophy and the control groups and many studies cited in the literature presence of SSRs abnormalities have been reported in IPD. However, presence of normal SSRs has been also indicated in IPD and its inmeasurable value in the differential diagnosis between multiple system atrophy and IPD coursing with marked autonomic symptoms have been also emphasized (19,20). In other words, in the discrimination of clinical conditions progressing with parkinsonism from IPD, presence of symptoms of autonomic involvement and abnormal SSRs detected during electrophysiologic examinations have been considered in the exclusion criteria for IPD. In this study, amplitudes of hand SSRs did not differ between the right, and the left hand and also between the affected and the unaffected sides in Test 1, Test 2 and the control groups Insignificant differences between SSRs recorded from symmetric organs or regions (hands and feet etc) are also an expected condition which has been already supported by many studies cited in the literature (13). In a neuropathological study performed by Break *et al.* in patients with IPD inclusion bodies in the form of α-sinuclein aggregates had been demonstrated in pre- and postganglionic neurons of parasympathetic and sympathetic nervous systems (21). In none of the neuropathological studies, asymmetric involvement - excluding extrapyramidal system- has not been detected in IPD. Conversely, pathological findings are detected in a symmetrical pattern. As a prerequisite for the diagnosis of IPD, asymmetric onset of motor findings and maintenance of this asymmetry even during disease progression should be detected. From the perspective of findings suggestive of autonomic involvement this asymmetry is not an expected or previously reported condition (22). In patients with asymmetric IPD, entirely symmetrical distribution of sweating was reported. In this dissertation study, no significant difference could be found between amplitudes of SSRs recorded from the affected and unaffected sides.

Amplitudes of SSRs of Test 1 and Test 2 were compared and significantly, lower SSRs amplitudes were observed after drug therapy. This condition may be explained in two mechanisms. Habituation of SSRs is a known condition. Since surprising effects of stimulation in Test 2 will decrease relative to Test 1, lower amplitudes of the responses might be recorded in Test 2. Frontal SSRs are also exposed to habituation as have been demonstrated previously in our laboratory studies (13). In this case, decrease in amplitudes of frontal SSRs in Test 2 is anticipated. However, such a decrease in frontal SSRs was not detected. A decrease in hand SSRs secondary to the use of antiparkinson drugs constitutes the second explanation. However, lack of any effect of antiparkinson and anticholinergic drugs on SSRs and perspiration has been already indicated (3,18,23,24).

Yet, critical importance of dopamine on autonomic regulation of brainstem and diffuse population of immunoreactive fibres in these centers are also known (25). Hand and face may demonstrate different sweating patterns or they may be controlled by different centers. Indeed, sweating is realized in two different patterns as thermoregulatory and mental sweating; a third explanation is not valid for our investigation.

Progression of the disease and decrease in the amplitudes of SSRs has been thought to be unlikely because of very short interval between Test1 and Test 2 (min. 24 hrs, max 21 days). Reports released up to now have yielded controversial results on variations in SSRs in patients with IPD. In some of these reports, SSRs were analyzed while drug therapies were maintained and in some others SSRs were recorded during drug-free period. Our outcomes have suggested that some of the

2016;23(1):62-9
DOI:10.5455/jtomc.2015.3224

controversial reports may stem from these diverse applications. In the comparison of amplitudes of hand SSRs in Test 1 and the control groups, no statistically significant intergroup difference was detected. A considerably important proportion of patients included in this study consisted of cases with very mild IPD (H&Y < 1, n=8, 8/23, 35%). Correlations among amplitudes of hand SSRs, H&Y and UPDRS scores demonstrated significant decreases in amplitudes of SSRs in parallel with disease progression. Therefore, the group of cases with a mild IPD was excluded from the statistical evaluation and when statistical evaluation was repeated SSRs with still lower amplitudes were detected albeit lack of statistical significance (p=0.084). Decrease in the number of patients and as stated above, application of Test 1 during treatment-naive period might explain this marginally insignificant result. In the comparison of hand SSRs between Test 2 and the control group, mild and severe cases were evaluated in combination and still a significant result could not be elicited. When these 8 cases with mild IPD were excluded from analyses and the remaining cases were re-evaluated, SSRs with significantly lower amplitudes were observed in the patient group relative to the control group ($p<0.05$). This outcome revealed the presence of a significant correlation between increasing severity of the disease and decreases in the amplitudes of SSRs. Besides this outcome is in compliance with the correlation between increasing severity of the disease and decrease in SSRs amplitudes and also with electrophysiological SSRs abnormalities and abnormal findings in cases with IPD under treatment cited in the literature.

We have limited information about frontal SSRs. Very few studies have systematically studied facial SSRs. Besides, almost all of them were performed in our laboratory on young patients (13). When facial SSRs were recorded symmetrically just like hand SSRs, similar responses could be elicited. However, different from hand SSRs this symmetry is not so obvious as hand SSRs. Facial responses are exposed to habituation. However, if this habituation is technically blocked, under constant stimulation, gradually increasing amplitudes called progressive increase in amplitudes is encountered. Detection of lower amplitudes only in hand SSRs in Test 2 contrary to frontal SSRs suggested the responsibility of an independent causative factor for habituation. Besides, it was thought that some peripheral or central characteristics are different between hand and facial SSRs. Amplitudes of frontal SSRs increase in line with the duration of the disease. One of the reasons underlying facial hyperhidrosis described in IPD might be this condition.

Independent from the affected and unaffected sides, loss of frontal SSRs has been detected in both patients and the control groups. Loss of left frontal SSRs is statistically significant. Even when the residual responses were analyzed, significantly lower amplitudes were observed on the left frontal SSRs. This finding, which is thought to be independent from IPD, detected in advanced age remains to be unexplained. Further studies may try to explain how and why the left frontal SSRs are lost. Sweating occurs in mental and thermal patterns. Mental sweating occurs in hands and feet, and thermal sweating is seen all over the body. Hand SSRs measure more frequently mental sudomotor activity, while frontal SSRs will measure mental sudomotor activity. Excessive sweating in IPD usually occurs on face, head and trunk. In a study by Schestatsky *et al.* on IPD patients with hyperhidrosis, SSRs recorded from hands were of lower amplitudes and they could be elicited less frequently when compared with cases without IPD (7). These findings were interpreted as a decrease in perspiration of hands leading to development of hyperhidrosis on face, head and trunk with a compensatory mechanism. In our study, hyperhidrosis was detected at an anticipated incidence. We did not observe any statistically significant difference between hand and frontal SSRs. The reason for this finding, which was incompliant with the literature data, might be related to our patient group, which consisted of the patients with early and late onset IPD, higher percentage of early onset IPD patients and scarce number of patients in two separate subgroups, each of which was insufficient to attain any level of statistical significance. For example, the group without hyperhidrosis apparently contained higher number of patients who demonstrated bilateral SSRs or conversely, the group with hyperhidrosis consisted of unresponsive patients or those displaying only unilateral SSRs. Indeed, these groups did not reach any level of statistical significance. Further investigation on this issue in a larger-scale study with more numerous patient populations will help resolve this problem.

Evaluating the patients complaining from hyperhidrosis, we observed motor symptoms with left side dominancy. Left side dominancy in the group of patients with hyperhidrosis is statistically significant. However, we have not come across any relevant data in the literature on this issue. With further studies, association between left-side dominant motor findings and hyperhidrosis can be easily enlightened. However, highly comprehensive studies in the field of neuropathology should be conducted in order to elucidate pathophysiology underlying different behavioural patterns between hand and facial SSRs can be also explained by heterogenous distribution of sympathetic denervation among various organs in IPD (26) and different degrees of involvement of sympathetic fibres (27). When all the reports presented so far are reviewed, controversial outcomes have been reported as for changes in SSRs in IPD. These incompliant results may result from diverse study designs, maintenance of treatments for antiparkinsonism, disregarding disease duration and severity and inability to construct subgroups based on the presence of symptoms related to autonomic involvement.

This study was presented in 10. National Congress of Parkinson's and Movement Disorders (Ela Quality Resort, Antalya) in 1-5 May 2013 as Poster 29 with the name of 'Sympathetic Skin Responses Obtained from the Affected Hand in İdiopathic Parkinson's Disease'.

2016;23(1):62-9
DOI:10.5455/jtomc.2015.3224

REFERENCES

1. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease. Mov Disord 2004;19(11):1306-12.
2. Tolosa E, Gaig C, Santamaria J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. Neurology 2009;72(7):12-20.
3. Hirashima F, Yokota T, Hayashi M. Sympathetic skin response in Parkinson's disease. Acta Neurol Scand 1996;93(2-3):127-32.
4. Schestatsky P, Ehlers JA, Rieder CR, Gomes I. Evaluation of sympathetic skin response in Parkinson's disease. Parkinsonism Relat Disord 2006;12(8):486-91.
5. Meigal AI, Rissanen S, Tarvainen MP, Karjalainen PA, Iudina-Vassel IA, Airaksinen O, et al. Novel parameters of surface EMG in patients with Parkinson's disease and healthy young and old controls. J Electromyogr Kinesiol 2009;19(3):206-13.
6. Fusina S, Conte S, Bertolasi L, Fincati E, Nardelli E, Bongiovanni LG. Sympathetic skin response asymmetry in early stage idiopathic Parkinson's disease. Clin Neurophysiol 1999;110(2):358-66.
7. Schestatsky P, Valls-Sole J, Ehlers JA, Rieder CR, Gomes I. Hyperhidrosis in Parkinson's disease. Mov Disord 2006;21(10):1744-8.
8. Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;66(7):968-75.
9. Ertekin C, Santral ve Periferik EMG. Ertekin C, editör. Otonomik Sinir Sistemi (OSS). İzmir. META Basımevi; 2006: p.884-909.
10. Giza E, Katsarou Z, Georgiadis G, Bostantjopoulou S. Sympathetic skin response in Parkinson's disease before and after mental stress. Neurophysiol Clin 2012;42:125-31.
11. Jankovic J, Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurgy Psychiatry 2008;79(4):368-76.
12. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol 1999;56(1):33-9.
13. Yildiz SK, Turkoglu SA., Yildiz N, Ozturk A, Tore F, Sympathetic skin responses of the face and neck evoked by electrical stimulation. Auton Neurosci 2007;134:85-91.
14. Taly AB, Muthane UB, Involvement of peripheral nervous system in juvenile Parkinson's disease. Acta Neurol Scand 1992;85(4):272-5.
15. Mano Y, Nakamuro T, Takayanagi T, Mayer RF, Sweat function in Parkinson's disease. J Neurol 1994;241(10):573-6.
16. Korczyn AD, Autonomic nervous system disturbances in Parkinson's disease. Adv Neurol 1990;53:463-8.
17. Wang SJ, Fuh JL, Shan DE, Liao KK, Lin KP, Tsai CP, Wu ZA. Sympathetic skin response and R-R interval variation in Parkinson's disease. Mov Disord 1993;8(2):151-7.
18. Braune HJ, Korchounov AM, Schipper HI, Schipper, Autonomic dysfunction in Parkinson's disease assessed by sympathetic skin response: a prospective clinical and neurophysiological trial on 50 patients. Acta Neurol Scand 1997;95(5):293-7.
19. Bordet R, Benhadjali J, Destee A, Hurtevent JF, Bourriez JL, Guieu JD, Et al. Sympathetic skin response and R-R interval variability in multiple system atrophy and idiopathic Parkinson's disease. Mov Disord 1996;11(3):268-72.
20. De Marinis M, Stocchi F, Gregori B, Accornero N, Sympathetic skin response and cardiovascular autonomic function tests in Parkinson's disease and multiple system atrophy with autonomic failure. Mov Disord 2000;15(6):1215-20.
21. Braak H, Sastre M, Bohl JR, de Vos RA, Del Tredici K, Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. Acta Neuropathol 2007;113(4):421-9.
22. Goetz CG, Lutge W, Tanner CM, Autonomic dysfunction in Parkinson's disease. Neurology 1986;36(1):73-5.
23. Saito H, Kogure K, Thermal sudomotor deficits in Parkinson's disease. Rinsho Shinkeigaku 1989;29(6):734-40.
24. Haapaniemi TH, Korpelainen JT, Tolonen U, Suominen K, Sotaniemi KA, Myllylä VV. Suppressed sympathetic skin response in Parkinson disease. Clin Auton Res 2000;10(6):337-42.
25. Kitahama K, Nagatsu I, Geffard M, Maeda T, Distribution of dopamine-immunoreactive fibers in the rat brainstem. J Chem Neuroanat 2000;18(1-2):1-9.
26. Goldstein DS, Robertson D, Esler M, Straus SE, Eisenhofer G, Dysautonomias: clinical disorders of the autonomic nervous system. Ann Intern Med 2002;137(9):753-63.
27. Sharabi Y, Imrich R, Holmes C, Pechnik S, Goldstein DS, Generalized and neurotransmitter-selective noradrenergic denervation in Parkinson's disease with orthostatic hypotension. Mov Disord 2008;23(12):1725-32.