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Original Article

Delayed habituation in Behcet's disease

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Background: The autonomic nervous system in Behcet's patients may be affected due to various reasons. This entity may be detected with the measurement of the electrodermal activities, heart rate variability and pupillometric methods. Habituation is one of the implicit forms of learning and memory and the loss of habituation can reveal pathological changes in the synaptic regions. **Aim:** To determine whether there is a functional decrease in the synaptic effectiveness (habituation) of the pathways to sympathetic neurons that had been repeatedly activated in Behcet's. **Materials and Methods:** Twelve patients with Behcet's disease and 12 healthy controls were included in the study. Sympathetic skin potential (SSP) records were taken at normal room temperature in a quiet place within a Faraday cage. Sixteen square wave single shock impulses (duration: 1200 μs, strength: 5 mA) were applied on each case. **Results:** After the 1st stimulus, the SSP amplitudes were lower in the patients compared to the controls (P<0.001, t value = 7.69). There was no significant differences among the SSP amplitudes after the 13th impulse in the patients (P>0.05). Whereas there was no significant differences among the SSP amplitudes after the 9th impulse in the controls (P>0.05). The habituation rate of the SSP after consecutive impulses was slowest in the patients compared to controls (P<0.001, t value = 12.39). **Conclusions:** There is a delayed habituation in Behcet's disease and that may due to pathologic changes with vasculitis through their peripheral nerves.

Key words: Autonomic nervous system, Behcet's disease, habituation, sympathetic skin potentials

Neuro-Behcet's disease (BD) is a motor-mental disorder usually affecting the brainstem and basal ganglions.[1] In some cases without neurological manifestations, there is a possibility of subclinic involvement which can be detected by various methods, including single photon emission computed tomography (SPECT), brain stem auditory evoked potentials (BAEP), visual evoked potentials (VEP), motor evoked potentials (MEP), and P300.[2] The autonomic nervous system (ANS) in Behcet's disease had been evaluated with the measurement of the electrodermal activities, the hearth rate variability, and pupillometric studies.[3,4] Cognitive, emotional, and physical behaviors involve changes in peripheral autonomic activity. The phenomenon of electrodermal activity (EDA) is accepted as an indirect indicator of the sympathetic nervous system.[5] The sympathetic skin response (SSR) is a polysynaptic reflex associated with the activation of sweat glands. The SSR is most evident when recorded from the palmar and plantar sites, where there is a larger concentration of eccrine glands. The afferent component may be activated by nonspecific sensory stimuli. The central processing circuitry is predominantly represented by cerebral structures, under strong influence of consciousness, emotions and cognitive activity.[6] The efferent component of the reflex consists of sympathetic-cholinergic fibers from the paravertebral sympathetic chain of the central nervous system (CNS) to sweat glands. In human lesion deficit models with post-ganglionic sympathetic denervation (pure aunotomic failure) the SSR cannot be elicited.[7]

Habituation is the simplest form of implicit learning.[8] Depression of the connections made by sensory or interneurons or both, seems to be a fairly common mechanism of habituation.[8] The loss of habituation can be shown in some neurological disorders, including migraine and may reveal pathologic changes in the synaptic regions of peripheral nerves. In this study, the loss of habituation in Behcet's patients has been investigated with the measurement of the sympathetic skin potentials (SSPs) against consecutive nerve stimulation.

Materials and Methods

We compared measures of electrodermal activity in 12 subjects with Behcet's disease with those of 12 healthy controls. Twelve patients with Behcet's disease admitted to our Dermatology service were accepted for the study. All patients met criteria established by the International Study Group for Behcet's disease.[9] Control subjects, age-sex-matched, were healthy and without history of

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neurological, psychiatric diseases or sweating disorders. Exclusion criteria for the patients included neurological or psychiatric disorders orthostatic hypotension, eccrine sweating defects, sphincter disorders, presence of any lesion in magnetic resonance of brain and use of any drugs at least in the last two weeks.

Records were taken from the right arm in a supine position at normal room temperature (20 ± 2°C) in a quiet place under dim light within a Faraday cage with sound insulation. Minimally unpolarized Ag/AgCl electrodes were attached to the hypothenar blister of the hand and two-thirds upper portion of the inside of the forearm.[4] The electrodes were fixed after the inside of the forearm was cleaned with a piece of cotton, dipped in alcohol and then the skin resistance was decreased by removing the stratum corneum by the use of a fine sandpaper. In this manner, the connection part of the inactive reference electrode was determined. For the amplification, Nihon Kohden's AA-600 H model was used and the records were kept in DC mode. For the electrical stimulation of the left ulnar nerve, silver EEG electrodes (inner caliber: 9 nm) were used. Sixteen consecutive square wave shock impulses (duration: 1200 μs, strength: 5 mA) were applied on each volunteer. Nihon Kohden Ag/AgCl electrodes with inner caliber of 7 mm were used as the skin potential recording electrodes.

After connecting the electrodes to the subjects, they were informed about the experimental conditions and 10 min were allowed for their adaptation to these conditions as well as their skins' adaptation to the mean of records which occurred after three electrical stimuli in each session. Moving ranges of two stimuli (delta SSP 1-15) were calculated by subtractions of SSP at the S2-S16 from those at S1-S15, respectively.

Age, sex, duration of disease and SSPs at the S1-S16 of Behcet's patients and controls were analyzed with *t*-test. The amplitudes of SSP at the S1-S16, delta SSPs at the S1-S15 and the latencies of SSP at the S1-S16 were analyzed with repeated-measures ANOVA test followed by post hoc Tukey test.

Results

We compared measures of electrodermal activity in 12 subjects (48.8 ± 8.5 years) with Behcet's disease with those of 12 healthy controls (six women and six men, mean age 29.7 ± 4.2 years) following the first and 16th stimuli. In controls, the mean amplitude of the SSPs decreased from 4.9 ± 0.3 mV at the first stimulus to 0.8 ± 0.1 mV at the 16th stimulus ($P<0.001$, *t*-value: 27.37). In Behcet's patients, the mean amplitude of the SSPs decreased from 4.1 ± 0.2 mV at the first stimulus to 0.8 ± 0.1 mV at the 16th stimulus ($P<0.001$, *t*-value: 44.52) [Figure 1]. There was a significant difference in mean amplitudes of SSP especially after the first stimulus between patients and controls (respectively; mean: 4.1, SD: 0.2; mean: 4.9, SD: 0.3; $P<0.001$, *t*-value = 7.69). In controls, at the first, second, and third stimuli, the mean amplitudes of SSP were higher than those of Behcet's patients ($P<0.001$, *t*-value = 7.69; $P<0.001$, *t*-value = 5.80; $P=0.04$, *t*-value = 2.16; respectively) [Figure 2]. The difference in habituation rate of the SSP after the 13th stimulus was not significant in the patients' group ($P>0.05$) [Figure 3]. However, in controls, the difference in habituation rate of the SSP after the ninth stimulus was not significant ($P>0.05$)

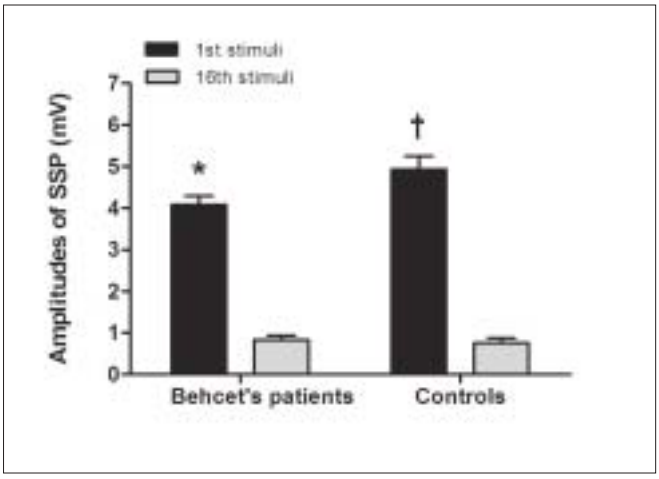

Figure 1: Mean amplitudes of sympathetic skin potential (Mean SSP) at the 1st and 16th stimuli in Behcet's patients (*n*=12) and controls (*n*=12). In controls, the mean amplitude of the SSPs decreased from 4.9 ± 0.3 mV at the first stimulus to 0.8 ± 0.1 mV at the 16th stimulus (*P*<0.001, *t*-value: 27.37). In Behcet's patients, the mean amplitude of the SSPs decreased from 4.1 ± 0.2 mV at the first stimulus to 0.8 ± 0.1 mV at the 16th stimulus (*P*<0.001, *t*-value: 44.52) **P*<0.001 vs. at the 16th stimuli of the Behcet's patients. †*P*<0.001 vs. at the 16th stimuli of controls

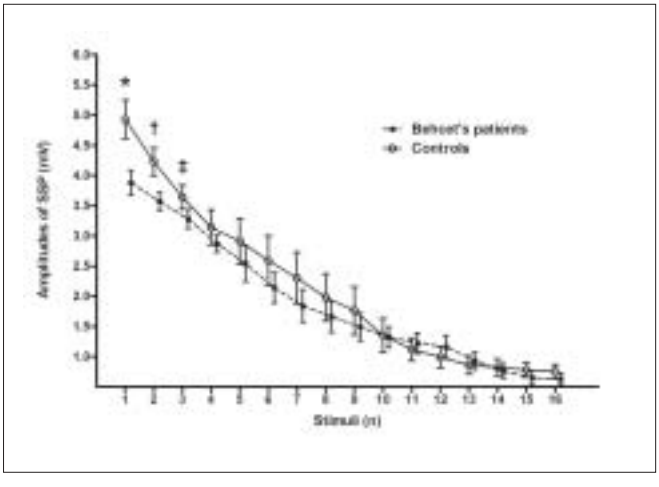

Figure 2. Amplitudes of sympathetic skin potential (SSP) from a series of 16 stimuli to the left ulnar nerve in Behcet's patients (n=12) and controls (n=12). In controls, at the 1st, 2nd, and 3rd stimuli, the mean amplitudes of SSP were higher than those of Behcet's patients (respectively; *P*<0.001, *t*- value=-7.69, *P*<0.001, *t*- value=-5.80, *P*=0.04, *t*- value=-2.16). Statistical evaluation was analyzed with t-test. Data were presented as means ± S.D. **P*< 0.001, †*P*<0.001, ‡*P*=0.04 vs. Behcet's patients

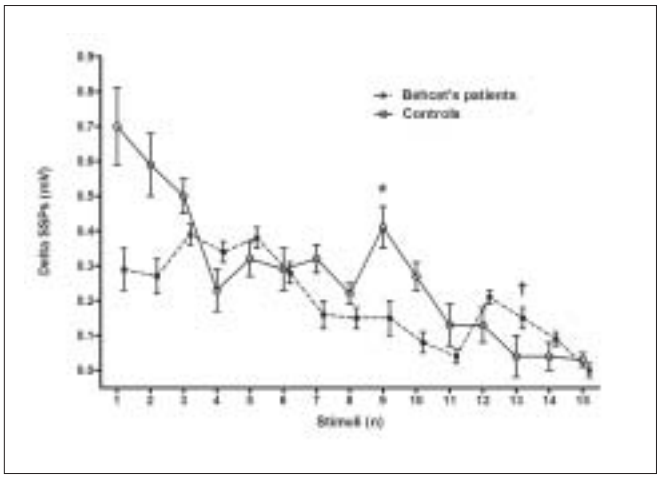

Figure 3: Delta SSPs of two consecutive stimuli for Behcet's patients (*n*=12) and controls (*n*=12). **P*>0.05 for controls, no significant difference between the sympathetic skin potentials after the 9th stimuli. †*P*>0.05 for patient group, no significant difference between the sympathetic skin potentials after the 13th stimuli

[Figure 3]. The mean habituation rate of the SSP increased in the patients' group compared to controls ($P<0.001$, t- value = 12.39) [Figure 3]. We found no significant difference between the patients and controls with regard to the latency values of SSP (in controls, mean: 2.1, SD:0.2; in patients, mean: 2.2, SD:0.1, $P>0.05$).

Discussion

Since CNS involvement was first described, it is well known to occur in BD. Areas of focal inflammation can occur at different levels of the CNS. The brainstem, cerebral hemispheres, cerebellum, spinal cord and meninges are the common sites of CNS involvement.[10] The CNS changes in three cases of neuro-Behcet's disease were observed by computed tomography (CT), magnetic resonance (MR) and single photon emission computed tomography (SPECT).[11] Unlike other vasculitides, the involvement of the peripheral nervous system is a rare condition.[12] Although silent neurological involvement may occur in BD, the most common neurological symptoms or signs are related to pyramidal tract involvement.[13] Behcet's disease may have asymptomatic ANS dysfunction, which is in the form of increased sympathetic and decreased parasympathetic modulation.[3] In patients with nervous system diseases, motor and sensory defects may be the more pronounced complaints. The ANS might also be involved as autonomic system disorders may be accompanied by motor and sensory dysfunctions in peripheral diseases or CNS disorders.

The SSPs reflect the integrity of the small unmyelinated autonomic fibers, pathways not tested by routine nerve conduction studies of motor and sensory nerves. Skin potential level has two mechanisms of generation: that due to sweat gland activity (sudorific) and that due to other causes (nonsudorific).[14] The ANS may be assessed by measuring electrodermal activities.[3] Because there may be vasculitic changes in multiple brain regions in Behcet's disease, it may be speculated that decreased sympathetic activity in our patients may due to the fact a possible subclinic abnormality of the ANS.

Habituation is the simplest form of implicit learning. It was due to a functional decrease in the synaptic effectiveness of the pathways to the motor neurons that had been repeatedly activated. The decrease in synaptic transmission in the sensory neurons results from a decrease in the amount of the chemical transmitter (glutamate) released from the presynaptic terminal.[8] The biochemical base of habituation is still not known. However, the decrease of protein kinases due to the repetitive stimuli may exist in habituation. The role of adrenergic and serotonergic systems may be important and some transmitters, including acetil colin, noradrenalin, dopamin, nitric oxide, abituation of skin responses is more probably related to the activity of peripheral sweat glands activated by the efferent sympathetic fibers. The process might be influenced by adaptation at the level of the sweat glands as well as ANS.[5] This is associated with decreased release of neurotransmitter from the presynaptic terminal because of decreased intracellular Ca^{2+}.[16] The decrease in intracellular Ca^{2+} is owing to a gradual inactivation of Ca^{2+} channels. It can be short-term or it can be prolonged if exposure to the benign stimulus is repeated many times.

In conclusion, the finding that the skin potential habituation rate of Behcet's patients was lower than the controls has a consistency with similar research. We emphasize that symptoms of autonomic disturbance must be evaluated carefully for a possible involvement of ANS, even in patients with no orthostatic hypotension, eccrine sweating defects, sphincter disorders, pyramidal signs, deep tendon reflex abnormalities or sensory disturbances. It may be speculated that the delayed habituation in Behcet's disease results from the pathologic changes in the synaptic regions of peripheral nerves. The decreased SSP and delayed habituation may be a sign of the involvement of the peripheral nerves in Behcet's disease.

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