RESEARCH ARTICLE / *Araştırma Makalesi*

Thin Fiber Neuropathy Associated With Vitiligo

Vitiligo Hastalarında İnce Lif Nöropatisinin Değerlendirilmesi

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Abstract

Objective	This study is designed to evaluate thin fiber neuropathy, if any with patients who had vitiligo and had normal standard nerve conduction studies. **(Sakarya Med J 2019, 9(1):148-153)**
Materials and Methods	This case - control study was conducted between March 2016-June 2016 in ENMG laboratory of our neurology clinic. Amoung 123 vitiligo patients, 40 vitiligo patients between ages 18-60 without evident neuropathy by standard nerve conduction studies were included in this study. Furthermore 40 healthy individuals without vitiligo or any neuropathy with matching age and gender were included in this study. All participants divided into two groups (vitiligo and control groups). Demographic data were recorded with weight, height, body mass index (BMI) data of participants. Cutaneous silent period conduction study was performed in median and sural nerves to evaluate small fiber conduction.
Results	CSP duration and distal latency measurements abductor pollicis braves muscle on the upper extremity and tibialis anterior muscle on the lower extremity were similar in both CTS and control groups. Our findings show no association with vitiligo and small fiber neuropathy,
Conclusion	In our study, thin fiber neuropathy was not detected in vitiligo patients. We believe that this study may contribute to the literature in terms of the effect of vitiligo on myelinated A delta fibers and demyelinated thin C fibers.
Keywords	cutaneous silent period; vitiligo; thin fiber neuropathy

Öz

Amaç	*Bu çalışma, normal standart sinir iletim çalışmaları olan vitiligo hastalarında ince lif nöropatisini değerlendirmek için tasarlanmıştır.* ***(Sakarya Tıp Dergisi 2019, 9(1):148-153).***
Gereç ve Yöntemler	*Bu vaka- kontrol çalışması Mart 2016-Haziran 2016 tarihleri arasında XX Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi Nöroloji Anabilim Dalı'nda ENMG laboratuvarında gerçekleştirildi. Çalışmaya 123 vitiligo hastasından dışlama kriterlerine göre seçilmiş 18-60 yaş arasında 40 vitiligo hastası ile kontrol amaçlı yaşları ve cinsiyetleri eşleştirilmiş 40 sağlıklı birey dahil edildi. Katılımcılar vitiligo grubu ve kontrol grubu olarak iki gruba ayrıldı. Katılımcıların demografik verileri kaydedildi. İnce lif iletimini değerlendirmek için kutanöz sessiz periyot (KSP) iletim çalışması yapıldı. Vitiligo şiddeti vitiligo alan skorlama indeksi ile değerlendirildi.*
Bulgular	*Üst ve alt ekstremitelerin KSP distal latans ve süre değerleri iki grupta benzerdi (vitiligo grubu ve kontrol grubu). Vitiligo hastalarında hastalığın şiddeti ve süresi ile üst ve alt ekstremitelerin KSP değerleri arasında ilişki saptanmadı.*
Sonuç	*Çalışmamızda vitiligo hastalarında ince lif nöropatisi saptanmamıştır. Bu çalışmanın, vitiligonun miyelinli A delta lifleri ve demiyelinize ince C lifleri üzerindeki etkisi bakımından, literatüre katkı sağlayabileceği kanaatindeyiz.*
Anahtar Kelimeler	*kutanöz sessiz periyot; vitiligo; ince lif nöropatisi*

INTRODUCTION

Cutaneous silent period (CSP) is a spinal inhibitor reflex. Strongly stimulation of a cutaneous nerve electrically inhibits the voluntary muscle contraction temporarily for a definite period of time after voluntary contraction of the muscle.[1-3] The physiology of CPS is not yet clearly explained. The clinical convenience of CSP appears in evaluating the continuity of nerve fibers which cannot be determined by standard electrophysiologic studies.[4]

Vitiligo is a pigmentation disorder presenting with hypopigmented macules; with a prevalence of nearly 1%. The exact etiology of vitiligo is unknown, but autoimmune, neurological and auto-toxic mechanisms are focused on studies.[5,6] It is widely accepted that vitiligo is an autoimmune reaction in genetically predisposed individuals.[7] Previously, vitiligo was implied just as a skin disease, but some recent studies showed increased frequency of insulin resistance, metabolic syndrome and atherosclerosis in patients with vitiligo.[8-9] The neural hypothesis is based on some clinical aspects, particularly the distribution of segmental, dermatomal vitiligo.[10]

This study is designed to detect thin fiber neuropathy, if any with patients who had vitiligo and had normal standard nerve conduction studies.

MATERIALS AND METHODS

Participants population

This case - control study was conducted between March 2016-June 2016 in ENMG laboratory of our neurology clinic.

Amoung 123 vitiligo patients 40 vitiligo patients between ages 18-60 without evident neuropathy by standard nerve conduction studies were included in this study. Furthermore 40 healthy individuals without vitiligo or any neuropathy with matching age and gender were included in this study. All participants divided into two groups (vitiligo group and control group).The exclusion criteria were: participants, with evident neuropathy which was confirmed by nerve conduction studies, history of neurologic or psychiatric diseases as hereditary or acquired polyneuropathy, radiculopathy, stroke and alcohol consumption, diabetes mellitus, thyroid disease, broken elbow, collagen tissue disease, osteoporosis, kidney or liver failure, and diseases causing chronic pain like fibromyalgia. Local ethics committee approval was obtained. (050.01.04.88)

The aim of this study was explained to all participants, and written informed consent was obtained from the participants.

Demographic data were recorded with weight, height, body mass index (BMI) data of participants. Vitiligo severity and period was assessed by vitiligo area scoring index (VASI) for the vitiligo group. Cutaneous silent period conduction study was performed in median and sural nerves to evaluate small fiber conduction.

Nerve conduction studies

Median and ulnar nerve conduction studies were performed on each arm of every patient (n=120) under room temperature with electromyography (EMG) device (Nihon Cohden, Tokyo, Japan). Standard protocol was applied by using standard nerve conduction techniques with superficial electrodes. [11]

F responds of both median and ulnar nerves were evaluated. To eliminate any cervical radiculopathy, upper extremity needle EMG was performed also. Bilateral lower extremity sural nerve and unilateral peroneal and tibial nerve conduction studies were done to eliminate polyneuropathy. F responds of both nerves were obtained. Motor nerve conduction of median and ulnar nerves were evaluated according to the records of abductor pollicis brevis and adductor digiti mini muscles after supra maximum stimulation considering amplitude and latency. Sensorial conduction was determined through 2. and 5. digits. Distal motor latency (DML)>4.2ms, amplitude <6, 3, nerve

conduction velocity <45m/sn, sensorial distal latency >3, 5 ms, sensorial action potential (DAP) <15 were all defined as abnormal conduction findings. [11]

Cutaneous silent period

CSP was measured in the right upper and lower extremity. Filters were 50 Hz–5 kHz, sweep speed was 200 ms, and sensitivity was 100 mV. The median sensory nerve was stimulated with a standard painful stimulus (25mA intensity, 1ms duration) through a bar electrode fixed on the second digit of the right hand and the response was recorded with an electrode fixed on the belly of the contracting abductor pollicis brevis muscle.

The sural nerve was stimulated superficially lateral to the external malleolus in the right lower extremity and recordings were obtained from the anterior tibial muscle through bar electrode.[12] Four separate responses were superposed after maximum contraction of tibialis anterior muscle in the upper extremity and abductor pollicis brevis muscle which was induced by superficial electrical stimulus. The responses obtained were defined as L1; latency between the start of the stimulus to the suppression of muscle activity, L2; latency of a new muscle activity and, d; the distance between these two.[4]

Vitiligo Area Scoring Index

The Vitiligo Area Scoring Index (VASI) was used for vitiligo patients to state the condition of the disease. VASI in a simple measure that compares disease activity by matching the degree of repigmentation in the patient. The body is divided into 5 separate parts: hands, upper extremities, trunk, lower extremities, and feet. The face and neck areas are not included in the overall evaluation. One hand unit, which is approximately 1% of the total body surface area, is used as a guide to estimate the percentage of vitiligo involvement of each body region. Depigmentation on each area was estimated to the nearest percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%.[13]

Statistical analysis

SPSS (Statistical Package for Social Sciences for Windows 24.0) software program was used for statistical analysis. Kolmogorov-smirnov test was applied for convenience of parameters for normal distribution before comparison of continuous variables. Student t test was used to compare the descriptive statistical methods and quantitative data. Ki-square was the test used for comparison of qualitative data. Univariant analysis was applied to compare the effect of L1 and D1 values of upper and lower extremities on Boston scale. Significance level was determined as 0.05.

RESULTS

The mean age in both groups was 37 ± 8.There were 19 male and 11 female participants in all groups.

There was no significant difference between the BMI averages of vitiligo and control groups (27 ± 4, and 26.4, respectively) (p: 0.519).

CSP duration and distal latency measurements abductor pollicis braves muscle on the upper extremity and tibialis anterior muscle on the lower extremity were similar in both CTS and control groups Table 1.

Table 1: Comparison of CSP values of CTS and control groups

CSP values:	Control group (n=30)	Vitiligo group (n=30)	p
Upper extremity L1	59±7	62±8	0,250
Upper extremity d	56±8	50±9	0,100
Upper extremity L2	108±14	108±10	0,960
Lower extremity L1	86±6	88±10	0,350
Lower extremity d	54±5	51±6	0,110
Lower extremity L2	140±9	135±13	0,100

CSP: Cutaneous silent period,
CTS: Carpal tunnel syndrome,
L1: starting latency d: duration L2: ending latency

No association was detected between the severity and duration of disease in vitiligo patients and CSP values of both upper and lower extremities Table 2.

Table 2: Association between the severity and duration of vitiligo and L1 and d values of CSP on upper and lower extremities is shown with P values.

	Upper extremity L1	Upper extremity d	Lower extremity L1	Lower extremity d
VASI	0,108	0.727	0,572	0,625
Duration of vitiligo	0,655	0,144	0,599	0,831

Univariant analysis
L1: starting latency, d : duration
CSP: cutaneous silent period,
VASI: Vitiligo area scoring index

DISCUSSION

The CSP values on the upper extremity and tibialis anterior muscle on the lower extremity were similar in both CTS and control groups

There are three theories concerning the etiology of vitiligo which are autoimmune, autocytotoxic and neural hypotheses. Segmental/ dermatomal vitiligo is one of the supporting clinical finding pointing out a neural association where the other data is the common origin of central nervous system (CNS) and melanocytes: neural crest. Neural crest cells (NCC) are transient multipotent cells that detach from the neural tube end migrate in dorsolateral and ventral directions; this process is regulated by the transcription factor Foxd 3.While cells with a dorsolateral path are committed particularly to melanocyte predestination, those with a ventral path are committed to neuronal (sensorial and sympathetic), glial/melanocyte (Schwann cell precursors, SCPs) or endoneural fibroblast predestination. Neurofibromatosis, tuberosclerosis are the examples of CNS disorders presenting with hypo/ hyper pigmented skin findings. [14]

Researchers from Korea conducted a study based on cyclin-dependent kinase 5 regulatory subunit associated protein 1 (CDK5RAP1), which is expressed in neuronal tissues. Cyclin-dependent kinase 5 (CDK5) appears to take part in early post-natal period, particularly in the migration of neuroblasts. Ischemia and oxidative stress front CDK5 activation which ends with neuronal apoptosis. Monomeric CDK5 has no enzymatic activity unless it is associated with one of its regulatory proteins; p35 which is encoded by CDK5RAP1 or p39. CDK5RAP1 polymorphisms were investigated in Korean vitiligo patients, and the researchers found two polymorphisms significantly associated with vitiligo. They concluded that CDK5RAP1 might be a risk factor for vitiligo in Korean population. [15]

The "neural theory" supposed by Lerner's (1959) was based on the fact that segmental vitiligo (SV) follows the course of the dermatome with exhibiting hyperhidrosis and emotional upset. It is suggested that dysfunction of sympathetic nervous system (SNS) activity affect melanin production and lead to depigmentation. 10 subjects with facial (SV), 10 healthy individuals and 10 subjects with non-segmental vitiligo (NSV) were evaluated with iontophoresis and laser Doppler flowmetry level of microcirculation in lesions with vitiligo to assess SNS activity. It was reported that the cutaneous blood flow was higher three times on the lesions vs normal skin in SV, no difference was noted in the NSV group. [16]

Depigmented areas are reported to sweat less, have different temperature regulation.[17] Other studies concerning sympathetic skin response in vitiligo patients focusing on autonomic dysfunction report different results: one of them concluded that sympathetic skin response (SSR) was not different in vitiligo and psoriasis patient groups when compared with healthy control group.[18] The other one reported that electrodermal activity altered in vitiligo patients which in turn reversed after psoralen-UVA (PUVA) treatment.[19] Another study reported that SSR is altered significantly when autoimmune hypothyroidism and vitiligo is together. However it is noted that the exact reason of altered SSR is hard to differentiate: myxoedema,

autoimmune skin reaction or thyroxine modulation of sudomotor activity, cathecholamine level or immunological effect on autonomic system.[20]

It is inevitable to accept a neurological involvement with vitiligo based on these data upcoming from various studies.[4,19,20] Our study is the first study investigating the relation between vitiligo and small fiber neuropathy to our knowledge. Our findings show no association with vitiligo and small fiber neuropathy. It is also shown that CSP is efficient in demonstrating small fiber neuropathy.

Vitiligo is common disorder of population. We have started off the data about the common origin of melanocytes and neural cells which may act similarly under influences like autoimmunity and autotoxicity. Although our findings show no association with vitiligo and small fiber neuropathy, we suppose that this study is valuable for allowing us to observe the effects of vitiligo on each: myelinated A delta fibers and demyelinated C fibers, which are small fibers. Further larger studies may help to confirm whether vitiligo has a contribution in CSP measurements.

Declaration of conflicting interests

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Ethical Standarts

The authors declare that this article is appropriate for ethical standarts

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