Electrodiagnostic Signs of Carpal Tunnel Syndrome in Ocular Pseudoexfoliation Syndrome: A Case-Control Study

Mansoor Shahriari
Imam Hossein Medical Center: Imam Hossein Hospital
Afshin Karimzadeh (Karimzadeh@sbmu.ac.ir)
Imam Hossein Medical Center: Imam Hossein Hospital
Hadi Esmaily
Imam Hossein Medical Center: Imam Hossein Hospital https://orcid.org/0000-0001-6915-6028
Saman Rezanejad
Imam Hossein Medical Center: Imam Hossein Hospital
Homayoun Nikkhah
Imam Hossein Medical Center: Imam Hossein Hospital
Maryam Yadgari
Imam Hossein Medical Center: Imam Hossein Hospital
Asma Pourhoseingholi
Imam Hossein Medical Center: Imam Hossein Hospital

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Abstract

Purpose To assess the occurrence and severity of electrodiagnostic signs of carpal tunnel syndrome (ED-CTS) in patients with ocular pseudoexfoliation (PEX) and compare them with normal subjects.

Method A 1:1 case-control study was designed and 60 patients with PEX were recruited from May 2019 to February 2021, and the findings were compared with 59 age- and gender-matched healthy controls. All patients underwent complete ophthalmologic examination and nerve conduction velocity test at the median nerve was used to assess the occurrence and severity of ED-CTS in both hands.

Results The mean age of participants was 59.8 ± 4.5 years. Occurrence of ED-CTS was 38.3% in PEX patients and 20.3% in control subjects ($P = 0.025$). There was also a significant difference in the severity, and presence of asymptomatic CTS ($P < 0.05$). Adjusting other variables, including; age, sex and job difficulty, having severe ED-CTS showed a 3.49-fold higher chance in the PEX group ($P = 0.002$).

Conclusion There is a direct relation between PEX and the occurrence, as well as severity of ED-CTS.

Introduction

Ocular pseudoexfoliation syndrome (PEX) is a relatively common systemic disorder first described by Lindberg in 1917 [1]. It mainly affects ocular tissues through the gradual deposition of fibrogranular material at the anterior segment of the eye and elsewhere. Although the chemical composition is not fully understood, overproduction and abnormal metabolism of glycosaminoglycans have been shown to play a key role [2, 3]. PEX is more common in men over 60 years of age. Incidence rates vary greatly by race and geographic region. Studies showed that the incidence of PEX is about 0.3% in the Netherlands, 3% in France, 16% in Russia, 28.7% in Spain, and 42% in Sweden [4, 5].

This syndrome manifests as flakes on the pupil margin and anterior lens capsule, increased pigmentation of the trabecular meshwork, and open-angle glaucoma. Deposits of extracellular matrix, exfoliative materials and amyloid in PEX have also been found in other organs [3, 6]. Associations between PEX and various systemic diseases such as diabetes, ischemic heart disease, systemic hypertension, and cerebrovascular disease have been discussed in the literature [7, 8]. It has also been shown that this syndrome can affect peripheral nerves [9, 10].

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy resulting from the median nerve compression in the carpal tunnel [11]. Certain conditions, such as diabetes mellitus, amyloidosis, hypothyroidism, and rheumatoid arthritis, may predispose one to CTS [12]. Obesity, pregnancy, use of birth control pills, menstrual irregularities, aging, and smoking are also risk factors for CTS [13]. Regardless of the risk factors, the prevalence of the condition in the general population is approximately 15% [14].

Indeed, the diagnosis of CTS is based on both clinical findings and the results of electrodiagnostic tests [15, 16]. Regarding the pathophysiology of CTS, protein deposits have been found in some patients [17]. Nerve conduction studies (NCV) and electromyography (EMG) can determine the occurrence and severity of median neuropathy at the wrist [18]. Needle EMG studies are less sensitive than NCV studies in diagnosing CTS. Sensitivities of electrodiagnostic methods range from 49–84% with specificities of 95% or higher [19].

The severity of CTS is usually rated based on the results of the NCV test, which reflects the degree of demyelination and axonal loss in the median nerve [20]. Asymptomatic individuals with electrodiagnostic evidence of CTS appear more prone to develop CTS later in life than others with a normal NCV [21]. Therefore, it is important to determine the prevalence of electrodiagnostic CTS, especially in asymptomatic individuals who do not have any of the known risk factors. It bears noting that early and accurate diagnosis of CTS is essential for effective non-surgical management and valid identification of surgical candidates [22].

The study was designed to investigate an association between PEX and electrodiagnostic signs of CTS (ED-CTS). This may guide future research in identifying new risk factors for CTS.

Patients And Methods

Design and Setting

From May 2019 to February 2021, we conducted a case-control study in the ophthalmology department of Imam Hossein Hospital, a teaching hospital affiliated with Shahid Beheshti University of medical sciences (SBMU), Tehran, Iran. The department is well-equipped, and the hospital is a large referral hospital with a high patient turnover.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine affiliated with SBMU under reference number IR.SBMU.MSP.REC.1398.232.

Eligibility

Men and women aged 55–70 years were included. Diagnosis of PEX was based on an ophthalmic examination by slit-lamp biomicroscopy. Subjects with hypothyroidism and hyperthyroidism alike, diabetes mellitus, amyloidosis, rheumatic diseases, and a positive family history of neuropathy, previous wrist fracture, pregnancy, lactation, and carpal tunnel surgery were excluded. The control group consisted of normal subjects in the same age range who were referred to the clinic for ophthalmological examination.

Recruitment

PEX patients and normal subjects were recruited. Initially, patients were invited to attend a screening visit. At the screening visit, the rationale of the study was explained to all potential participants. If any patient declined to participate, another was invited in the same manner until the required sample was recruited. We reviewed the patients' medical records and performed ophthalmologic examinations. Participants who gave written informed consent were enrolled in the study. Those subjects who worked heavily with their hands were excluded. A nurse, who had experience in performing work tasks, determined the level of employment hardship. The use of fingers and wrists during daily activities was used to decide whether a subject's employment was difficult or not.

Outcome Measures

All subjects were evaluated by history taking and physical examinations, including pain, paresthesia, weakness, Tinel's sign, and Phalen's maneuver. Physical examinations categorized patients into symptomatic and asymptomatic. The NCV testing at the median nerve of both hands was evaluated using the Nicolet EDX® EMG/NCS/ EP /IOM system (Natus machine, U.S.A). According to the American Association of the Electrodiagnostic Medicine criteria, neurophysiological tests rated CTS as mild, moderate, and severe [21]. All examinations were performed by a well-trained, physiatrist, who were blinded to patients’ group.

Sample Size

CTS has a prevalence of approximately 3.4% in women and 0.6% in men and the incidence increases with age to such an extent that it reaches 22.2% in those over 55 years of age [13, 14]. To the best of our knowledge, no reports were presenting an association between PEX and CTS. Based on the documented medical records from our hospital information system, our research team estimated that the occurrence of CTS in PEX patients was approximately 50%. Considering this rate, we needed 52 samples in each group for a 1:1 independent case-control study to detect a significant discrepancy in the presence of CTS between PEX patients and the control group, with a power of 80% and a two-sided confidence level of 95%, using Kelsey's formula. We added eight samples to each group to ensure that the study was adequately powered for a 10% loss to follow-up.

Statistical Analyses

Results are presented as mean (SD) for continuous variables and absolute numbers (%) for categorical data. Means of continuous variables were compared using paired and independent t-tests. Normality of outcome variables was examined with the Shapiro-Wilk test, and homogeneity of variances was examined with Levene's test. To test the differences between study groups for categorical variables, either a $\chi 2$ test or Fisher's exact test was used. Also generalized estimating equations (GEEs) were used to analyze the effect of PEX on ED-CTS with adjusting the effect of other variables including: sex, age and job difficulty. An exchangeable working correlation matrix was considered as structure of correlation matrix for two hands. The significance level was set at two-tailed $\alpha < 0.05$. All data analyses were

performed using SPSS Statistics, version 25 for Windows. The data analysts were masked to the patients' group.

Results

This study involved 119 subjects (238 hands), 60 in the PEX group and 59 in the control group. Results of one subjects of control group excluded at the final steps of the study, finding a random fasting plasma glucose of more than 200 mg/dL in her laboratory findings. The mean age was 59.83 ± 4.52 years, and 56 (47%) cases were male. **Table 1** shows the baseline characteristics of the participants.

All 119 subjects underwent both a clinical examination and NCV testing for CTS. ED-CTS were detected in 23 (38.3%) cases in the PEX group and in 12 (20.3%) subjects in the control group (P = 0.025). The chance of having ED-CTS in subjects of the PEX group is 2.71 times that of the control group (OR = 2.71, CI 95% = 1.17–6.26). Regarding the clinical symptoms, out of 23 patients with ED-CTS in PEX group, 11 patients (47.8%) had symptoms, and 12 patients (52.2%) had no symptoms, while out of 12 patients with ED-CTS in the control group, 10 patients (83.3%) had symptoms and 2 patients (16.7%) had no symptoms. The difference in frequency of asymptomatic patients were significant (P = 0.045).

Analysis of the data on the hands showed that the frequency of ED-CTS was 21 (17.7%) in 118 hands in normal subjects (control group) and 41 (34.1%) in 120 hands in the PEX group (P = 0.003), The chance of having ED-CTS in each hands of subjects in the PEX group is 2.39 times that of the hands of control group (OR = 2.39, CI 95% = 1.31–4.39).

Table 2 shows the severity of ED-CTS per hand of the participants. Adjusting other variables including age, sex and job difficulty in multivariate GEE analysis, showed the chance of having higher severity of ED-CTS in the PEX group is 3.49 (P = 0.002) times more than control group. **Table 3** shows these associations in both univariate and multivariate models, with more details.

Discussion

PEX is considered an age-related disease that can lead to ocular complications such as cataracts or open-angle glaucoma. Numerous studies of PEX patients have shown that fibrogranular material is secreted from multiple sites, including the iris pigment epithelium, ciliary epithelium, and anterior lens capsule epithelium. However, the chemical nature of this substance is still unknown despite extensive research [8].

On the other hand, this syndrome is considered a systemic process with a possible increased risk of cardiovascular and cerebrovascular morbidities. Extracellular matrix and exfoliative materials found in other organs such as heart, lung, aorta, liver, kidneys, and peripheral arteries can confirm this idea [3, 6].

An association between PEX and systemic diseases such as diabetes, ischemic heart disease, systemic hypertension, asthma, and rheumatoid arthritis has been discussed [7, 8]. Manaviat et al. investigated the

association between PEX and diabetes. They found that the prevalence of PEX was higher in diabetics [23]. An alteration in collagen metabolism, which is more common in diabetics, may be related to the higher rates of PEX [2].

In addition, Djordjevic et al. reported that PEX is one of the most important clinical parameters associated with abdominal aortic aneurysm, along with diabetes and hypertension [24]. Kovac et al. found a significant association between PEX and cardiac ischemia but no association with hypertension, diabetes, and cerebrovascular disease [25]. This discrepancy may be due to geographic differences that contribute to the development of PEX in different communities.

Researchers have noted the association between PEX and some neurological diseases. Singham et al. suggested that the accumulation of pseudoexfoliation material in sensorineural cells could explain the association between PEX and hearing loss [26]. Zojaji et al. also showed a strong association between PEX and sensorineural hearing loss [27]. Turgut Coban et al. showed an association between PEX and polyneuropathy in a case-control study of 31 PEX patients. They suggested, progressive infiltration of amyloid and proteins in the retinaculum flexor and synovial tissue was thought to cause neuropathy [10].

To our knowledge, this is the first study to examine the relationship between PEX and CTS. It seems that the secretion and deposition of protein substances in PEX could cause the compression of the median nerve, and it may have a role in the pathophysiology of CTS. In view of this, this study aimed to investigate the relationship between PEX and ED-CTS.

The results of the current 1:1 case-control study showed an increased risk of developing ED-CTS in PEX patients vis-a-vis the normal group. The severity of ED-CTS was also higher in PEX patients.

The results of this study showed that 16.7% in the control group and 52.2% in the PEX group showed ED-CTS and were asymptomatic. This finding of healthy individuals is consistent with Alrawashdeh's report on CTS patients, which showed that 15% of patients with ED-CTS are asymptomatic [28]. This means that PEX patients not only have a higher chance and severity of ED-CTS, but also a higher percentage of them are asymptomatic. As discussed above, sensory fibers of the peripheral nervous system are affected by PEX, so it might explain why PEX patients with their median nerve involved at the wrist are asymptomatic.

According to the present study, the OR of ED-CTS in PEX patients is 2.71 times higher than in healthy subjects. Therefore, since another possible hypothesis for the coexistence of the two disorders is the presence of another underlying systemic disease, further studies should be done to investigate the occurrence of PEX in patients with ED-CTS. In addition, studying the occurrence of PEX in patients with ED-CTS is important because of the possibility of ocular damage due to an increase in intraocular pressure in patients with PEX glaucoma; it can help prevent dangerous ocular complications. Performing in vitro studies on the deposited materials is also suggested to clarify the molecular mechanisms further.

Limitations

The limitation of this study is that the duration of PEX was unknown in the participants as all patients were primary naïve.

Conclusions

Based on the present study results, there seems to be a direct relationship between PEX and the occurrence and severity of CTS-associated electrophysiological changes. Moreover, the occurrence of asymptomatic CTS is higher in PEX patients compared to previous studies.

Declarations

Founding: None

Conflicts of interest/Competing interests: There is no conflict of interest of any of the authors with the results of this study.

Availability of data and material: All results are available and could be shared if requested.

Ethics approval: The protocol of study was approved by research ethics committee of the faculty of medicine affiliated with Shahid Beheshti University of medical sciences (IR.SBMU.MSP.REC.1398.232).

Consent to participate: Only participants who signed the written informed consent were enrolled in the study.

Consent for publication: All authors have signed the consent form for the publication of this manuscript.

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Tables

Table 1
Baseline characteristics of the participants in the groups

Variable	PEX[a]	Control	P-value
n (hands)	60 (120)	59 (118)	-
Age (Year)	60.13 ± 4.39	59.52 ± 4.67	0.46*
Gender (Male: Female)	27:33	29:30	0.65*
Smoking	14 (23.3%)	12 (20.3%)	0.66*
Alcohol Consumption	11 (18.3%)	9 (15.3%)	0.87*
Job Difficulty			
Difficult Employees	1 (1.7%)	3 (5%)	0.51*
Not Difficult Employees	20 (33.9%)	22 (36.7%)	
Housewife	18 (30%)	12 (20%)	
Retired	21 (35.5%)	22 (36.7%)	

[a] Pseudoexfoliation
* Not significant according to the significance tests $p > 0.05$

Table 2
The severity of ED-CTS per hand of participants

	PEX	Control	
Total number of hands	120	118	P-value
Without ED-CTS (%)	79 (65.8%)	97 (82.2%)	< 0.0001
Mild ED-CTS (%)	7 (5.8%)	17 (14.4%)	
Moderate ED-CTS (%)	26 (21.6%)	3 (2.5%)	
Severe ED-CTS (%)	8 (6.6%)	1 (0.8%)	

Table 3
Association of PEX with ED-CTS, in univariate and multivariable GEE analysis

Variable		Univariate		Multivariate	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Group	PEX	3.49 (1.60–7.59)	0.002**	3.50 (1.61–7.60)	0.002**
	Control*			-	-
Age		0.99 (0.91–1.08)	0.914	0.98 (0.90–1.08)	0.803
Gender	Male	0.86 (0.39–1.87)	0.706	0.89 (0.39–2.05)	0.792
	Female*			-	-
Job	Difficult	0.91 (0.21–3.97)	0.907	1.04 (0.22–4.83)	0.960
	Housewife	0.72 (0.25–2.04)	0.541	0.69 (0.23–2.07)	0.508
	Retired	0.84 (0.33–2.14)	0.717	0.88 (0.34–2.30)	0.808
	Not difficult*			-	-