Diagnosis of Carpal Tunnel Syndrome: The Role of RANTES

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Abstract

Carpal tunnel syndrome (CTS) is regarded as most frequent entrapment neuropathy in upper extremities with high prevalence in females. It is a multi-factorial disease that had signs and symptoms due to compression of median nerve at the carpal tunnel in wrist, although may be asymptomatic. Immune system has been recognized as the main factor of neuropathic pain. Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) is among the cytokines that revealed a dysregulated pattern of neuropathy specific cytokine profile in CTS and, in human, it is encoded by CCL5 gene. Sixty-four patients suffering from CTS were enrolled in this controlled cross sectional study. For all, nerve conduction study was performed to prove the diagnosis of CTS and to classify its severity. The mean age of all patients was 44.9±7.8 years, 89.1 % were female, 40.7% had mild type CTS and 40.7 % had right side CTS. 5 ml blood was obtained from each participant to measure the level of serum RANTES using specific ELISA kit. There was significant high RANTES levels in CTS patients when compared with its reference value. We conclude that RANTES level increases in patients with carpal tunnel syndrome and can be used as a predictor for its diagnosis despite its proposed neuroprotective role.

Key Words: Carpal Tunnel Syndrome, CCL5, RANTES.

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Introduction

Carpal tunnel syndrome (CTS) is the disease that had signs and symptoms arise from compression of median nerve at level of carpal tunnel in wrist. The roof of carpal tunnel is the transverse carpal ligament and the base is carpal bones. The median nerve and nine flexor tendons of forearm pass through this tunnel (kozaka et al. 2015). CTS is considered to be the most frequent entrapment neuropathy in upper extremities. It has constant characters over time and across countries and its prevalence is about 3% of general population (kozaka et al. 2015). Females have three times chance of get the disease than males. Furthermore, its severity and incidence increase with age (pourmemari MH et al. 2018, farioli A. et al. 2018) and some studies showed a peak age incidence in female to be 40 - 60 years (lopez E. et. al. 2017, Adamson et. al. 2015) It is known that CTS is a multi-factorial disease. Still, any increment in pressure of carpal tunnel might increase compression on median nerve and, sometimes, end with nerve damage and ischemia. Furthermore, significant compression of a nerve may results in demyelination and ultimately axonal loss (Alsharif A. et. al. 2017). Any of these might be the source of the signs and symptoms, although CTS could be asymptomatic and be discovered only through the nerve conduction studies (Alsharif A. et. al. 2017).

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The most common manifestations are tingling with numbness distributed in thumb, index, middle finger and radial half of ring finger. These could be intermittent and it is not uncommon for patients to complain of pain in anterior part of their forearm and wrist with hand weakness (kozaka et al. 2015). Work-related professions that need a high degree of replication and force or the use of hand operated vibratory apparatuses expressively rise the risk of getting CTS. Furthermore, any anatomical changes in the wrist region like fractures or surgery might be a causative factor (Mondelli et al. 2016). On the other hand, positive family history and genetic predisposing, obesity and pregnancy along with a wide list of systemic diseases like diabetes, thyroid dysfunction, rheumatoid arthritis; space-occupying lesions at this tunnel might all increases the disease prevalence (kozaka et al. 2015, farioli A. et al. 2018, Mondelli et al. 2016, Kadhim M. et al. 2019). Considering these factors, many authors study the carpal tunnel that trend within families supposing that biochemical and anatomical changes like aplasia of median nerve or thickened transverse carpal ligament could inheritable. And they proposes that disturbance in function of the median nerve can outgrowth through time, especially when performing repetitive hand activities (Puchalski P. et al. 2019). CTS can be diagnosed in patients with familial amyloidosis polyneuropathy (FAP). FAP results from transthyretin variations in different point mutation and is characterize by systemic sedimentation of amyloidogenic subtypes of transthyretin. This deposition particularly takes place at theperipheral nervous system causing a progressive sensory and motor polyneuropathy and, similarly, this deposition can takes place at the carpal tunnel leading to signs and symptoms (Puchalski P. et al. 2019). Other systemic disorder like familial hypercholesterolemia and inheritable myopathies are also reported of structural changes leading to CTS (Padua l. et al. 2016). Immune system has been recognized by many of studies as the main factor of neuropathic pain in peripheral and central nervous system disorder. The cellular immunity contains the manufacture of cytokine and chemokine in responding to antigen and mediated by T types of cells (Taylor G et al. 2017). Families of cytokine play an important function in signaling the connection between cells and in controlling the immune system and nervous system. Both cytokine and chemokine had been concerned in controlling neuronal excitability and contributing to neuropathic pain (Russo L. et al. 2014). Chemokine (C-C motif) Ligand 5(CCL5) is also referred as Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) is among the cytokines and chemokines that revealed a dysregulated pattern of neuropathy specific cytokine profile in CTS and, in human, it is encoded by CCL5 gene in human (white A. et al. 2007, lechner J et al. 2015). RANTES level in normal people is370.9-631.9pg/ml (Tokami et al. H. el al 2013, Albert V. et al. 2017). Aim of study to evaluate the role of RANTES in diagnosing carpal tunnel syndrome.

Patients and Method

This is a controlled cross sectional study conducted at the Unit of Neurophysiology\ Middle Euphrates Neuroscience Center\ Al-Najaf Health directorate, between January 2019 through February 2020. The exclusion criteria were pregnancy, obesity, diabetes mellitus, thyroid dysfunction, joint problems or acromegaly. Furthermore, the patient will be excluded if had a history of local wrist, hand or upper limb trauma. Considering these exclusion criteria, 78 patients with a complaint of hand pain and paresthesia were primarily included in this study. From them, only 64 patients who had positive findings on nerve conduction study (NCS) were enrolled from whom an informed consent were obtain ahead. For all participants, demographic data were collected, medical history was asked about and the Visual Analog Scale (VAS - a scale use for pain assessment in patients) were calculated. Specific clinical examination (Phalens test, Tinels test, Pin-Prick sensation), NCS and some other tests were also done. The diagnosis of CTS was based on clinical and electrophysiological grounds and its severity was graded into three groups, mild, moderate and severe according to modified Padua Criteria (Albert V. et al. 2017):

- Mild CTS: increased distal sensory latency of median nerve > 3.5 ms.
- Moderate CTS: in addition to point (1), decrease SNAP of median nerve amplitude (< 50% in comparison with non affected side or < 10 μV are regarded as abnormal) or increased motor distal latency of median nerve > 4.4ms.
- Severe CTS: in addition to points (1) and (2), decrease median CMAP amplitude (< 50% comparison with non affected side or < 4 mV) and denervation of muscles supplied by median nerve on EMG.

A blood sample of 3 mL was collected from each participant (in to gel tube) to measure the level of

serum RANTES. Sera were thawed and analyzed undiluted using ELISA kit was used from Elabscience (human RANTES). Statistical analysis had been done using SPSS version 20 and a *P*-value less than 0.05 was considered significant. Continuous variables provided in mean and standard deviation, discrete variables provided in number and percentage. T-test was used to account the difference between genders. Chi-square was to assess the association between severity and the hands effected. Regression line was used to test if the age of patients affect RANTES level. ANOVA test was applied to determine the difference between groups of severity in regarding to RANTES level. In addition 95% Confidence Interval for Mean of RANTES.

Result

The mean age of the 64 patients with CTS was 44.9±7.8 and they were divided into 3 age groups. Also, the patients are divided according to the severity into another 3 groups. The educational level and which side is affected were also listed (Table 1). The majority of patients who belong to the mild group presented with right side CTS whereas the majority of patients who belong to the moderate and severe groups presented with bilateral CTS (Table 2).

Table 1. Demographic and baseline information of the patients

Variant	Groups	No.	Percentage
Age group	20-34 years	33	51.5%
	35-49 years	21	32.8%
	50-65 years	10	15.6%
	Total	64	100%
Gender	Male	7	10.9%
	Female	57	89.1%
	Total	64	100%
Affected limb	Left hand	13	20.3%
	Right hand	26	40.7%
	Bilateral	25	39%
	Total	64	100%
Severity of CTS	Mild	24	37.5%
	Moderate	18	28.1%
	Severe	22	34.4%
	Total	64	100%

Table 2. The severity of CTS according to the affected side

Severity	Left	Right	Bilateral	Total	*P*-value
Mild	5	12	7	24	0.5
Moderate	3	6	9	18	
Severe	5	8	9	22	
Total	13	26	25	64	

As the difference of RANTES levels between the males and females was insignificant (Table 3), they were considered as one group and the mean of RANTES level was 834.62±539.1pg/mL.

Table 3. RANTES levels (pg/mL) according to gender

Gender	N	RANTES (Mean± SD)	95% Confidence Interval for Mean	*P*-value
Male	7	732.8±381.2	380.27-1085.30	0.66
Female	57	843.7±649.6	671.35 - 1016.05	

There was no significant difference on comparing RANTES levels in CTS patients with its control level (Table 4).

Table 4. RANTES levels between patients and healthy

Patient/Control	N	RANTES (Mean± SD)	95% Confidence Interval for Mean	*P*-value
patients	64	834.62±539.1	380.27-1085.30	0.01
Reference value\ other study[16]	15	471.2±90.3	370.9 - 631.9	

The relationship between patients' age and RANTES level was shown in Figure1.

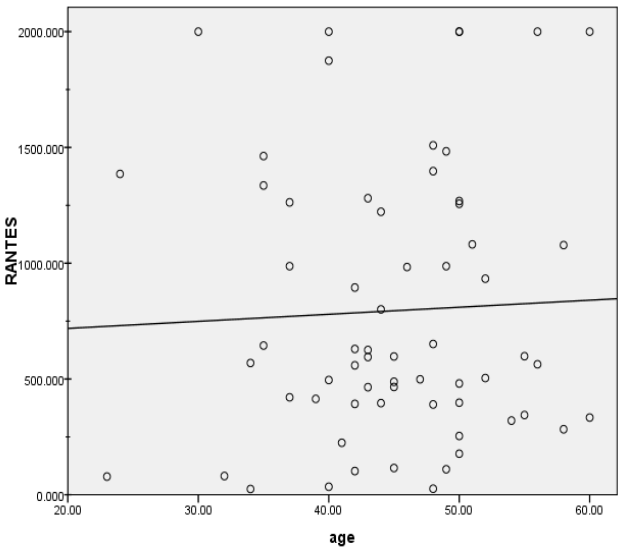

Figure 1. Relation between patients' age and RANTES level

RANTES showed highest level in patients with moderate severity and lowest level in patients with severe disease, although the difference was insignificant (Table 5) (Figure 2).

Table 5. RANTES levels according to the severity of CTS

Severity	Number	Rantes (Mean± SD)	95% Confidence Interval for Mean	p-value
Mild	24	830.4±603.3	575.78-1085.27	0.71
Moderate	18	1001.3±628.5	723.17-1280.56	
Severe	22	624.91±528.4	317.37 - 932.46	

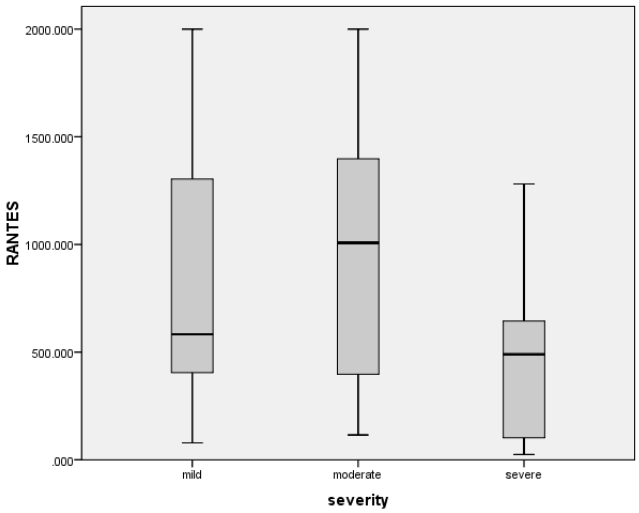

Figure 2. The difference between groups of severity in regarding to RANTES level

Discussion

Most of our patients were middle aged (Table 1) and this seems reasonable because more of consultant clinic visitor were middle age worker. The working age population have risen the chance of getting CTS than the general population and this may be due to the degenerative changes events from repetitive activity in the hand (Zyluka et al. 2011). Such finding were also recorded by many other studies (Kadhim M. et al. 2016, Puchalski P. et al. 2019, Wijdan H. et al. 2019). Females had constituted 89.1% of patients enrolled in this study and this high percentage may be due to the fact that carpal tunnel is much smaller in females than males (Lakshminarayanan et al. 2019). In addition, female's daily activity at home may aggravate the disease. Moreover, female hormonal changes like that during the menstrual cycle and pregnancy had been proven to play a role (Mohammadi A. et al. 2016). Many previous studies had recorded same results (Kadhim M. et al. 2016, Puchalski P. et al. 2019, Wijdan H. et al. 2019, Lakshminarayanan et al. 2019). Our study revealed that the majority of the patients had mild disease. This may be due to good patients' awareness to the symptoms resulting in early seeking of medical consultation (white A. et al. 2007) in addition to the availability and feasibility of the electro diagnostic tests that can detect the disease at early stages. However, other studies showed different severity prevalence and this can be due to the different sample size or due to residency issue and type of patient profession and work (Hasan Z. et al. 2013). Furthermore, what could explain such different severity prevalence is the use of Boston questionnaire by some studies to assess severity (Mohammadi A. et al. 2016). Also, the use of different electrophysiological measurements for the diagnosis and for assessing severity may play a role in such difference (Wijdan H. et al. 2019). In this study (Table 2), patients with unilateral CTS was about 61% of total patient and this can be due to the excessive use of the dominant hand by this patient. 39% of our patients had bilateral presentation which could be back to the inherited and/or congenital anomaly of carpal tunnel that leads to variation in its size or contents (Wijdan H. et al. 2019, Alford W. et al. 2004). This was consistent with many other studies like that of Al-Shami and Alford (Wijdan H. et al. 2019, Alford W. et al. 2004). However, other studies had reported much more bilateral complaint and this may be due to large sample size especially if we know that their participants were much older (Taylor G et al. 2017, Puchalski P. et al. 2019, Karadag S. et al. 2010). The insignificant difference of RANTES levels between male and female patients was accepted, as there is no actual gender variation in pathophysiology of RANTES production (Lees G. et al. 2015). Additionally, the small sample size of this study may limit catching-up the difference, if any. This study showed a significant elevation of RANTES level when compared to reference levels in normal population. This finding strengthen the belief that several specific cytokines, specially chemokines, highly increase in painful neurological diseases (Taylor G et al. 2017, Lees G. et al. 2015, Hodes E. et al. 2015). On the other hand, neuroinflammation has been suggested as a probable factor for the pathogenesis of CTS (Taylor G et al. 2017). Similarly, it had been reported that RANTES levels is elevated in CTS by many scientists like Taylor and his coworkers in 2017 and many others (Taylor G et al. 2017, Lees G. et al. 2015, Hodes E. et al. 2015). Despite that, there were insignificant

difference in RANTES levels in between patient groups according to disease severity. Knowing that RANTES level proportionally increases with disease severity (Taylor G et al. 2017) may propose that these results are unreasonable. However, it is essential to consider that in more severe disease, there could be a disturbed T-cell homeostasis and cytokine/chemokine imbalance due to the neuropathic pain and hence RANTES level may decreases (Beppu M. et al. 2015). Moreover, whether these changes has a direct effect on the pathophysiology of neuropathy or regarded as an indirect sequel of another mechanisms behind CTS remains obscure (Uceyler N. et al. 2015). In fact, there is a complicated relationship between pain on one hand and emotion, metabolic and immunity state on the other hand, and hence contributing to increasing levels of inflammatory mediators (Tripathy D. et al. 2010, Al-Imari K. et al. 2019). Such probability of an indirect effect of these variables on dysregulation of immunity cannot be excluded in carpal tunnel syndrome (Taylor G et al. 2017). RANTES and its receptors are so much expressed in the nervous system that is why some studies concluded that RANTES is related to reduced neuropathic pain despite its high levels in some neuropathic diseases including CTS. This association proposes that RANTES may be neuro-protective as well as its pro-infammatory action (Hodes E. et al. 2015, Beppu M. et al. 2015). Therefore, it is probable that RANTES plays a double role in encouraging both infammation and neuroprotection following nerve damage and thereby regulating neuropathic pain (Uceyler N. et al. 2015). There were weak positive but insignificant correlation between age and RANTES level. This is because approximately 84% of our sample below age of 50 years and 72% of them belong to mild and severe categories, in which no too much increase in RANTES level (Taylor G et al. 2017).

Conclusion

RANTES level increases in patients with carpal tunnel syndrome and can be used as a predictor for its diagnosis despite its proposed neuro-protective role.

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