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Prevalence and Incidence of Infectious Neuropathies in a Population with Neuropathic Pain and Presenting With Complex Regional Pain Syndrome

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Abstract

Purpose: The purpose of this study was to investigate the prevalence and incidence of antecedent and current infections with neurotropic viruses in a patient population with chronic neuropathic pain and presenting with Complex Regional Pain Syndrome (CRPS). The diagnosis was based on the International Association for the Study of Pain criteria.

Methods: This study investigated a pool of 409 patients who presented over a 10 year period with neuropathic pain and a history of one of the following diagnoses: Carpal tunnel syndrome, cubital tunnel syndrome, brachial plexopathy, or radiculopathy, or had received a nerve block, chemodenervation, or a brachial plexus block for relief of neuropathic symptoms and presented with acute symptoms suggestive of CRPS. Evaluations included physical assessments, antibody titer screening, inflammatory markers, skin biopsy results, and electro diagnostic studies when indicated.

Results: A total of 74 patients out of 409 neuropathic pain patients (prevalence 18.1%) had at least one positive titer of the following: Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Herpes simplex virus 1 and 2 (HSV), Parvovirus, Varicella-Zoster (VZV), or COVID-19. The most commonly associated pathogen found in this study was HSV-1 (n=22, 5.37%), followed by HSV-2, EBV, CMV, and Parvo (all n=8, 1.95%), VZV (n=7, 1.71%), and COVID (n=6, 1.47%). A total of 8 out of 74 patients (incidence 10.8%) met criteria for acute infectious neuropathy and required antiviral therapy with successful resolution of symptoms for over one year. The median nerve was most frequently involved.

Conclusions: If infectious neuropathies are not considered, there is the risk of using CRPS as the only diagnosis, thereby increasing morbidity, chronicity, and in some cases ongoing nerve damage. Patient screening for infectious neuropathies should include neurotropic viral screening as part of the routine workup. In our series, a prevalence of 18.1% was a significant frequency that triggered a more comprehensive workup. These conditions are treatable and a satisfactory response is highly probable.

Keywords: Complex regional pain syndrome; Neuralgia; Neuropathic pain; Immune system; Nerve compression syndromes; Virus disease

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Background

In a small percentage of patients with neuropathic pain and exacerbation of symptoms suggestive of Complex Regional Pain Syndrome (CRPS), the lead author noted decades ago that an infectious neuropathy was occasionally present in these situations. Specific treatment of the infectious neuropathy resulted in improvement or remission in a short time period. This

prompted an investigation into a larger population of patients with neuropathic pain who developed CRPS signs and symptoms to determine the prevalence of infectious neuropathies in this population. Diagnosis of CRPS was based on the international Association for the Study of Pain accepted criteria for CRPS [1].

Introduction

The mechanisms underlying CRPS are poorly understood, but multi-modal interactions that include tissue trauma, abnormal pain processing, autonomic imbalance, and immune system alteration are hypothesized [2]. While tissue trauma resulting from nerve compressions has long been recognized as a pre-disposing factor of CRPS, immune system alterations from viral infections and decreased fiber density are less well-recognized [3]. Evidence suggests viral infections are linked to neuropathic pain syndromes, and alterations in skin innervation due to decreased fiber density may be associated with CRPS [4,5]. However, standard screening criteria for CRPS do not include viral screening or skin biopsies [6]. The purpose of this study was to investigate the prevalence and incidence of antecedent and current infections with neurotropic viruses in a patient population with chronic neuropathic pain and presenting with CRPS symptoms.

Methods

This study was a retrospective review with a prospective component of a pool of 409 patients who presented with neuropathic pain and were documented to have had one of the following criteria: Carpal tunnel syndrome, cubital tunnel syndrome, brachial plexopathy, radiculopathy, or had received a nerve block, chemodenervation, or a brachial plexus block for relief of neuropathic symptoms and presented with acute symptoms suggestive of CRPS.

This study was approved under Burrell IRB 0093_2022. The patients were evaluated using multiple diagnostic indicators. Evaluations included physical assessments, antibody titer screening, inflammatory markers, skin biopsy results, and electrodiagnostic studies when indicated. The physical assessment included findings of hyperhidrosis, allodynia, vasomotor instability, herpetiform rash, or erythematous rash with dermatomal distribution. Antibody titers (IgG & IgM) were screened for Herpes Simplex Virus 1 and 2 (HSV 1&2), Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Parvovirus, Varicella-Zoster (VZV) and COVID-19. Inflammatory markers (Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), and white blood cell count) were evaluated as evidence of acute viral activity in association with signs and symptoms of CRPS. Skin biopsy results were evaluated for decreased fiber density. Electrodiagnostic studies were used to confirm the diagnosis.

Power analysis

A total of 66 participants were needed, with 22 in each of three independent groups to adequately power the study for a large effect size. The effect size was defined as f=0.4, an alpha value of 0.05, and a beta value of 0.20. The power calculation was performed using G*Power. Frequency and percentage statistics were performed to establish measures of prevalence and incidence.

Results

A total of 74 patients out of 409 neuropathic pain patients (prevalence18.1%) had at least one positive titer of the following: Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Herpes Simplex Virus 1 and 2 (HSV), Parvovirus, Varicella-Zoster (VZV), or COVID-19. The most commonly associated pathogen found in this study was HSV-1 (n=22, 5.37%), followed by HSV-2, EBV, CMV, and Parvo (all n=8, 1.95%), VZV (n=7, 1.71%), and COVID (n=6, 1.47%). A total of 8 out of 74 patients (incidence 10.8%) met criteria for acute infectious neuropathy (positive inflammatory markers (sedimentation rate and C-reactive protein), rash, skin biopsy and positive titers IgG and IgM).

The majority of those who met the criteria were given antiviral therapy for 4-6 weeks with successful resolution of symptoms for over one year. A small number of patients required longer courses of therapy (up to one year). Median nerve involvement was the highest prevalence at 44.1%. Of note, the median nerve is the most frequently involved nerve in CRPS. Following the median nerve prevalence were the ulnar nerve (16.0%), cervical radiculopathy (7.7%), brachial plexopathy (4.0%), radial neuropathy (3.0%), lumbar radiculopathy (1.8%), tibial neuropathy (1.5%), common peroneal neuropathy (0.8%), sural neuropathy (0.5%). The order of prevalence of nerve involvement in this study replicates that reported in the literature **(Tables 1-3)** [7].

Table 1: Cognitive domains in relation with benzodiazepines treatment.

Infectious agent	HSV-1	HSV-2	EBV	CMV	PARVO	VZV	COVID
IgG	22	8	8	8	8	7	6
IgM	3	1	1				2

Table 2: Virus association with other findings.

	Physical findings		Inflammatory marker		Decreased fiber density	
	IgG	IgM	IgG	IgM	IgG	IgM
HSV-1	5	1	5	1	1	
HSV-2			2		1	
EBV					1	1

CMV	3	3				
PARVO	1		1		1	
VZV	2		1		1	
COVID-19	1		1			
Totals	12	4	10	1	5	1
Section totals	16		11		6	

Table 3: Prevalence of infectious agents.

Infectious agent	HSV-1	HSV-2	EBV	CMV	Parvo	VZV	COVID
Combined IgG & IgM	4.20%	1.50%	1.50%	1.30%	1.30%	1.20%	1.30%

Discussion

While knowledge about the evaluation and management of chronic neuropathic pain has greatly improved in the last decade, multiple knowledge gaps exist and a subset of patients do not respond to conventional therapies. Considering an infectious neuropathy opens up additional treatment options. For example, some of the conditions are responsive to specific antiviral antibiotic therapy. Some patients may require long-term suppressive therapy (up to a year) to prevent recurrences. Effective medications in this study were acyclovir, valacyclovir, and valganciclovir. In this patient population, the more pronounced rashes were associated with HSV-2. When this population is compared with available prevalence percentages for HSV-1 and HSV-2 in the general population, this population has lower rates of both **(Figures 1 and 2)** [8].

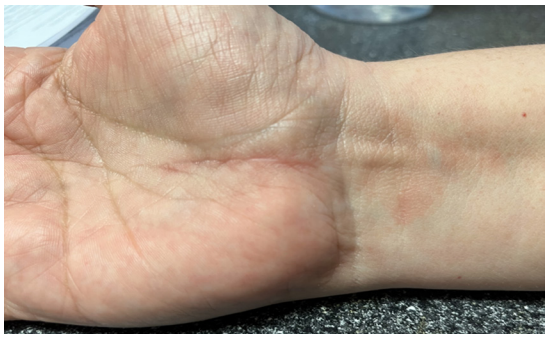

Figure 1: Subtle presentation of maculopapular rash.

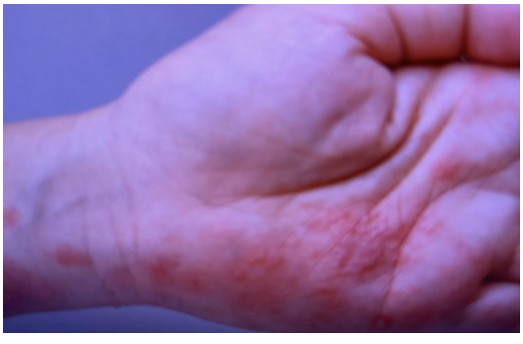

Figure 2: Pronounced presentation of maculopapular rash.

The patient presented at one month post-op from open carpal tunnel release with an acute episode of pain after an uneventful post-op course. She had positive viral titers and elevated inflammatory markers (ESR and CRP) and was treated with a six-week course of acyclovir until the viral titers and inflammatory markers were negative.

There was no recurrence after two years. The patient presented with an exacerbation of pain during non-operative treatment for ulnar nerve entrapment at the elbow. The diagnosis was supported by clinical and electrodiagnostic studies. She had positive viral titers and was treated with an eight-week course of acyclovir until viral titers and inflammatory markers (ESR and CRP) were negative. There was no recurrence after one year, and the neuropathy has remained stable.

Erythrocyte sedimentation rate, C-reactive protein, white count, elevated IgM and presence of a rash were used to determine the acuity of the infectious process and confirmation of the process with a positive skin biopsy.

Conclusion

The importance of considering the diagnosis of infectious neuropathy in patients who present with CRPS and who do not respond to conventional therapies opens the possibility of offering other pathways of intervention. If infectious neuropathies are not considered, there is the risk of using CRPS as the only diagnosis, thereby increasing morbidity, chronicity, and perhaps ongoing nerve damage based on the findings by skin biopsy of decreased fiber density.

Patient screening for infectious neuropathies should include neurotropic viral screening as part of the routine workup. In our series, a prevalence of 18.1% and incidence of 10.8% was a significant frequency that triggered a more comprehensive workup. These conditions are treatable and a satisfactory response is highly probable. In patients with neuropathic pain who present with exacerbation of pain and symptoms suggestive of CRPS, infectious neuropathy must be considered. Some of the conditions are responsive to specific antiviral antibiotic therapy. If infectious neuropathies are not considered, there is the risk of missing the opportunity to provide definitive treatment for infectious neuropathies and perhaps prevent ongoing fiber damage.

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