

## Patients with Sensory Symptoms of Acral Paresthesia: Routine Laboratory Findings in Neuromuscular Consultation

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### Abstract

**Introduction:** Laboratory studies to uncover the underlying etiology for patients with neuropathy are essential in practice. To address if there is an increased frequency of abnormal routine laboratory finding in patients with acral paresthesia, we performed a retrospective clinical observational study.

**Methods:** Charts of patients with acral paresthesia with or without numbness were retrospectively reviewed. They all had neurologically either normal examinations or only mildly distal sensory abnormalities. Their clinical data and routine laboratory findings were collected and analyzed.

**Results:** Two hundred and two patients (mean age:  $56.3 \pm 13.7$  years, male/female = 88/114) were studied. Significantly increased frequencies of abnormal findings, such as elevated values of HbA1c ( $p < 0.002$ ), body mass index ( $p < 0.003$ ) and decreased vitamin D levels ( $p < 0.0001$ ), were noted.

**Discussion:** Our study suggests that, in addition to diabetes mellitus, vitamin D deficiency and obesity may frequently be seen in patients with acral paresthesia.

### Highlights

- Patients with acral paresthesia are frequently seen in clinic for neuromuscular consultation.
- Laboratory studies to uncover the underlying etiologies for patients with acral paresthesia is critical.
- Abnormal HbA1c, vitamin D<sub>-25OH</sub> and BMI are most commonly seen with acral paresthesia.
- Diabetes, vitamin D deficiency and obesity may potentially serve as a biomarker for acral paresthesia.

### Keywords

Acral paresthesia, Body mass index, Diabetes mellitus, HbA1c, Paresthesia, Peripheral neuropathy, Vitamin D deficiency

### Introduction

Acral paresthesia (AP) can be the early symptoms of neuropathy which are frequently seen in clinic and in neuromuscular consultation. The term of paresthesia is collectively used in this article for abnormal sensations of tingling, crawling, pins, and needles with or without numbness, alone or in combination. Peripheral, particularly sensory, neuropathy at the early stage may manifest as AP,

without weakness. It is well known that diabetes mellitus (DM) is an independent risk factor for the development of peripheral neuropathy and causes AP [1]. However, a medical condition with or without concomitant peripheral neuropathy (PN) may cause paresthesia. For example, liver or kidney dysfunction can cause truncal and acral paresthesia due to the toxic metabolites directly stimulating the sensory nerve endings [2]. Laboratory studies to uncover the underlying etiology responsible for development of paresthesia are critical in practice. Treating patients with paresthesia symptomatically may temporarily be helpful but targeting the underlying etiologies should be essential. The present study was undertaken to elucidate the frequency of abnormal routine laboratory findings in patients with AP.

## Methods

Charts of patients seen in the Neuromuscular Clinic for consultation with chief complaints of AP such as tingling, crawling, pins and/or needles with or without numbness, alone or in combination, from January 1, 2015 to December 31, 2017 were retrospectively reviewed. Patients with a history of a CNS disorder, or established neuropathy such as Guillain-Barre syndrome or chronic inflammatory demyelinating polyneuropathy, traumatic neuropathy, neoplasms and status post of chemotherapy or radiotherapy were excluded. Clinical data and routine laboratory findings were collected, including chief complaints, past medical history, age, gender, body mass index (BMI), thyroid stimulating hormone (TSH), mean corpuscular volume, vitamin B12, vitamin D-25-hydroxyl ( $D_{-25OH}$ ), folic acid, methylmalonic acid, homocysteine, glycosylated hemoglobin (HbA1c), creatinine, lipids including triglycerides, low- (LDL) and high- (HDL) density lipoprotein and total cholesterol, HIV, hepatitis, Lyme disease, metals, serum protein electrophoresis and immunofixation. The references of normal versus abnormal cutoffs were adopted from the laboratory's recommendations and some were arbitrarily determined based on the clinically practical convenience (i.e., when HbA1c value greater than 6.1 is considered as abnormal instead of 5.7 suggested by the Laboratory). The variables were obtained and their ratios of abnormal to normal calculated. When a ratio of abnormal versus normal was greater than 1, the pairs of the variables underwent further statistical analyses using the Chi-squared test for proportional comparisons; a p-value less than 0.05 was considered statistically significant. Some risk factors were not analyzed due to small sample numbers such as hepatitis, HIV, Lyme disease, heavy metals, serum protein electrophoresis and immunofixation. The study was approved by the Institutional Review Board of Temple University.

## Results

A total of 202 patients (mean age:  $56.3 \pm 13.7$  years, range: 20-86; male/female: 88/114) were studied (Table 1). Their neurological examinations were either normal or had mildly distal sensory deficits with pinprick and temperature in toes or fingers, without other abnormal findings, such as motor,

coordination and gait. Significantly increased frequency of abnormal and ratio of abnormal/normal findings were seen including elevated levels of HbA1c ( $p < 0.002$ ), decreased levels of vitamin  $D_{-25OH}$  ( $p < 0.0001$ ), and increased BMI values of greater than  $30 \text{ kg/m}^2$  ( $p < 0.0003$ ), but no significant changes of other paired variables (Table 1).

## Discussion

Paresthesia can be caused by neurologic or non-neurologic conditions. AP may be an early symptom of PN. According to the 2005 US Congress report, there are twenty million Americans suffering from PN [3]. Etiologies causing PN are broadly diverse, including metabolic, infectious, inflammatory, toxic (including adverse effects of certain drugs and radiation), malnutritional, inherited, traumatic, or autoimmune-mediated mechanisms. To effectively treat patients with PN and AP, not only their symptoms but more importantly the underlying etiologies, it is an acceptable practice manner to order laboratory studies to investigate whether a risk factor(s) exists, such as DM, dysfunction of thyroid, liver or kidney, and vitamin deficiency(ies). In the present study, we also investigated additional factors such as methylmalonic acid, homocysteine, vitamin D and lipids.

It has been well established that DM is an independent risk factor for the development of PN, which causes AP [1]. Measurement of fasting plasma glucose and HbA1c levels has been proposed to be a useful tool for diagnosing, and monitoring the responses to treatment of DM. While the plasma level of fasting glucose may vary significantly over days, HbA1c reflects a "true" DM status for the past 2-3 months. Our study showed a significantly increased frequency of elevated levels of HbA1c in patients with AP (Table 1), consistent with, and supporting, the previous proposition that DM is a risk factor for PN responsible for paresthesia.

Thyroid dysfunction may cause sensory symptoms such as paresthesia [4]. A small percentage (10.8%) of patients with AP in our patient population had an abnormal TSH level, which is in agreement with previous observations. Similarly, chronic renal failure, which is also an established risk factor for PN [2], is not the most frequently encountered etiology for patients with AP in our office setting. In other words, patients with chronic kidney dysfunction causing PN with paresthesia may be seen in an advanced kidney dysfunction status.

It is well known that vitamin B12 deficiency causes AP due to PN or neuromyelopathy [5]. Recent studies suggested that methylmalonic acid and homocysteine also contribute to the development of PN. Isolated elevated plasma levels of homocysteine with normal levels of vitamin B12 and folic acid have been suggested as an independent risk factor for PN [6], in which their clinical manifestations are predominately sensory deficits [7]. Increased levels of methylmalonic acid may play neurotoxic effect on the dorsal root ganglionic neurons in culture [8] and cause neuropathic pain in Parkinson patients [9]. Notably both methylmalonic acid and homocysteine are intermediary metabolites during methylation mediated by vitamin B12 and folate. Elevated levels of homocysteine can

**Table 1:** Demographic and Laboratory data.

Age	56.3 ± 13.7 (years)	n = 202	Male = 88	Female = 114	
	(Range: 20-86)		M/F = 1:1.3		
	BMI (kg/m <sup>2</sup> )	Mean ± SD	n = 202 (%)	Ratio (abnl/nl)	P<
Normal	20 - 25	22.6 ± 1.6	36 (17.8%)		
Abnormal	<19.9	18.2 ± 1.1	12 (5.9%)	0.3	
	25.1 - 30.0		48 (23.8%)	1.3	0.51
	>30.1	34.3 ± 7.7	106 (52.5%)	2.9	0.0003
	TSH (mU/L)		n = 158		
Normal	0.2 - 4.0	1.6 ± 0.9	141 (89.2%)		
Abnormal		8.1 ± 12.0	7 (10.8%)	0.1	
	B12 (pg/mL)		n = 125		
Normal	>250	602.1 ± 362.3	114 (66.7%)		
Abnormal	<249	209.8 ± 41.2	11 (33.3%)	0.1	
	HbA <sub>1c</sub> (%)		n = 119		
Normal	<6.0	5.5 ± 0.2	42 (35.3%)		
Abnormal	>6.1	7.9 ± 2.1	77 (64.7%)	1.8	0.002
	CR (mg/dL)		n = 123		
Normal	<1.5	0.9 ± 0.2	112 (91.1%)		
Abnormal	>1.6	4.6 ± 3.5	11 (8.9%)	0.1	
	HDL (mg/dL)	M ± SD	n = 32		
Normal	>41	64.7 ± 23.6	21 (65.6%)		
Abnormal	<40	31.5 ± 7.0	11.0 (34.4%)	0.5	
	HDL/LDL ratio				
	<0.5	0.3 ± 0.1	13 (41.9%)		
	>0.5	0.8 ± 0.2	18 (58.1%)	1.4	0.4
	Vit D (ng/mL)		n = 78		
Normal	>30	42.0 ± 13.0	16 (20.5%)		
Abnormal	<29	18.4 ± 6.3	62 (79.5%)	3.9	0.0001
	MMA (nmol/L)		n = 58		
Normal	0-378	145.3 ± 71.2	54 (93.1%)		
Abnormal		1000 ± 394.9	4 (6.9%)	0.1	
	Hcy (µmol/L)		n = 81		
Normal	<12.0	9.4 ± 1.8	42 (51.9%)		
Abnormal	>12.1	17.3 ± 4.7	39 (48.1%)	0.9	
	Folate (ng/mL)	<b>0.0001</b>	n = 106		
Normal	>5.0	16.1 ± 6.3	103 (97.2%)		
Abnormal	<5.1	3.9 ± 0.6	3 (2.8%)	0	

**Abbreviations:** BMI: body mass index; TSH: thyroid stimulating hormone; HbA<sub>1c</sub>: glycosylated hemoglobin; CR: Creatinine; HDL: high density lipoprotein; LDL: low density lipoprotein; MMA: methylmalonic acid; Hcy: homocysteine

be caused by deficiency of either B12 or folate alone or in combination, while elevated methylmalonic acid is only caused by B12 deficiency [10]. Genetic predisposition may cause an

elevated homocysteine level without vitamin deficiency, such as C677T polymorphism of the methylenetetrahydrofolate reductase gene. Our observations suggest that deficiency of B12 and folate or increased levels of homocysteine and methylmalonic acid, either alone or in combination, may cause AP but not the most commonly encountered.

Recent clinical observations showed that vitamin D deficiency may worsen PN symptoms in diabetic patients [11] and administration of vitamin D improved the quality of life of those patients with DM-PN [12]. Whether or not vitamin D deficiency is an independent risk factor for PN remains to be elucidated [13]. Our study showed a significantly increased proportion of vitamin D deficiency in patients with AP (p < 0.0001). In a separate ongoing study, we have observed that a group of 14 patients with AP were found to exhibit “isolated” vitamin D deficiency without any other identifiable risk factors for PN. Supplementation of vitamin D to those patients with AP ameliorated their symptoms (personal observation). Our findings suggest that a possible causal relationship may exist between the vitamin D deficiency and AP, which warrants further investigation.

Our previous clinical observations [6] showed inconsistent findings relative to the frequency of occurrence of lipids in patients with PN, such as increased levels of HDL with decreased ratio of LDL/HDL due to statin administration, which were interpreted as an apparent therapeutic effect of statins on lipids. In the present study we failed to observe a positive correlation between the lipids or increased levels of HDL and the frequency of AP, concerning the previous report of the potential interference of statin-induced PN [14].

Finally, we noticed that increased BMI could be correlated to the occurrence of AP (Table 1). The BMI in calculation of body weight versus height is considered as normal (20-25 kg/m<sup>2</sup>), overweight (25.1-30 kg/m<sup>2</sup>) and obese (>30.1 kg/m<sup>2</sup>). A significant increase of the frequency of BMI great than 30 kg/m<sup>2</sup> (p < 0.003) in patients with AP was observed, which suggests an additional and previously unrecognized risk factor for paresthesia.

Our study has limitations. Firstly, it is a retrospective study with a small number of participants; secondly, the selection of laboratory tests was not uniform to the clinical evaluation in all cases; thirdly, because AP is a sensory symptom, which may be caused by small fiber neuropathy, electrophysiology and tissue biopsy had not been performed. Our study was designed simply to address the question: how frequently would the common risk factors for PN be encountered in patients with paresthesia in the routine laboratory evaluations in a clinical setting. Understandably, determination of an underlying etiology is more imperative than merely treating symptoms of paresthesia.

Summary, our study suggests that abnormal findings such as elevated HbA<sub>1c</sub> value, decreased vitamin D<sub>-25OH</sub> and increased BMI are the most commonly encountered laboratory abnormalities in the patients with AP and neurologically normal examinations or only mildly distal sensory findings in our neuromuscular clinic for consultation. Those abnormal

variables may potentially serve as a biomarker contributing to the underlying etiologies for AP. A larger scale clinical study is warranted to validate this observation.

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## Disclosure

Dr. Luo, Mr. Bumanlag and Dr. Dun declared no conflict of interest.

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