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Clinical Note

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Is Vitamin D Deficiency an Independent Risk Factor for Peripheral Neuropathy?

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Abstract

Objective: Study on whether the symptoms of acral paresthesia in patients with vitamin D deficiency (VDD) could be alleviated by vitamin D (VD) supplementation.

Methods: We retrospectively reviewed the charts of patients with paresthesia and *isolated* VDD (*i*VDD)for a 3-year period. Patients with identifiable etiologies for neuropathy or comorbidities in history as an established risk factor for neuropathy, or without an electrophysiology study, were excluded. Symptoms and serum 25(OH)D_3 levels prior to and post-VD supplementation were analyzed.

Results: Of 78 patients with VDD and acral paresthesia, 10 patients (age: 46.7±12.8 years) with *i*VDD [25(OH)D_3, 20.9±5.4 ng/mL] were studied. Supplementation of VD increased the serum VD level (28.6±9.1 ng/mL, p=0.03) and partially ameliorated symptoms in 6/10 (60%) of patients in 10.3±7.1 months.

Conclusions: VDD may contribute to developing, or potentiating the severity of, symptoms in patients with acral paresthesia as a potentially risk factor for peripheral neuropathy, particularly for patients with acral paresthesia.

Keywords

Neuropathy, Paresthesia, Vitamin D deficiency

Clinical Note

We recently reported an increased prevalence of vitamin D deficiency (VDD) is seen in patients with small fiber sensory neuropathy with acral paresthesia in neuromuscular consultation [1], suggesting a plausibly causal relationship between VDD and neuropathies [2]. More recent clinical observations showed that VDD is highly prevalent in patients with painful diabetic-neuropathy (DM-NP) [3, 4]. The prevalence of VDD in patients with DM-NP was estimated to be from 40% to 89% [5-7]. Indeed, VDD was an abnormal laboratory finding that was the second most often seen in patients with acral paresthesia [1]. The degree of VDD correlated well with the severity of DM-NP [8] and VDD affects both large[9] and small fibers [1, 9]. However, no study on *isolated* VDD (*i*VDD) in patients with sensory neuropathy is seen in the literature after extensive online search (PubMed and Google Scholar). Whether *i*VDD is an independent risk factor for neuropathy needs to be addressed. In this report, we studied whether the symptoms of acral paresthesia in patients with *isolated* decreased serum vitamin D (VD) level could be alleviated by VD supplementation.

Methods

We retrospectively reviewed charts of patients with paresthesia for a 3-year

period (January 1, 2015, to December 31, 2017). Their medical history, demographic, clinical, laboratory, and neuro-electrophysiology data were recorded. Patients with identifiable etiologies for neuropathy in history or comorbidities as an established risk factor for neuropathy, body mass index >30 kg/m^2, any abnormal laboratory derangements other than 25-hydroxyvitamin D_3 [25(OH)D_3], were excluded. Additionally, patients without an electrophysiology study were also further excluded. Symptoms and serum 25(OH)D_3 levels prior to and post-VD treatment were compared and analyzed. Responses to treatment of VD supplementation were recorded as improving (ameliorated symptom intensities), no change, or worsening. Temple University IRB approved this study.

Results

From the identified 217 patients with acral paresthesia, 78 who had 25(OH)D_3 laboratory tests were initially recorded. Of those, 10 with *i*VDD who met the inclusion criteria were studied. They were 46.7 ± 12.8 (mean ± SD) years old with decreased serum levels of 25(OH)D_3 (20.9 ± 5.4 ng/mL). They were supplemented with VD at either 1,000 IU daily (n=7) or 50,000 IU weekly (n = 3) (Table 1). They all were not obese (e.g. body mass index <30 kg/m^2). Neuro-electrophysiology studies showed normal (9/10, 90%) or mildly sensory demyelinating, e.g. mildly slowed conduction velocities with normal amplitude (1/10, 10%) (Table 1). The symptoms at the initial presentations were numbness and tingling (4/10, 40%), pain (3/10, 30%), or combining numbness and tingling with pain (3/10, 30%). Neurologic examinations at the initial presentation showed mildly decreased sensations of pinprick and cold temperature in distal limbs in a glove-stocking like pattern (8/10, 80%), or normal (2/10, 20%). Tendon reflexes were normal in 8/10 (80%) and decreased in 2 of 10 (20%) patients. Skin biopsy was not performed. Supplementation of VD increased serum 25(OH)D_3 levels (28.6 ± 9.1 ng/mL, p=0.03) as compared to that prior to the treatment, and partially ameliorated symptoms in 6/10 (60%) of patients in 10.3±7.1 months (Table 1 and 2).

Discussion

In this pilot report, we studied the effects of VD supplementation on sensory symptoms of acral paresthesia in patients with *i*VDD, namely without any identifiable etiologies for neuropathy. Oral administration of VD produced therapeutic benefits in more than half of patients (6/10, 60%) (Table 1) with symptomatic improvement. However, not all the symptoms were completely abolished, which may be due to the suboptimal conditions of the treatment regimen and evaluation time points. Notably, the serum level of 25(OH)D_3 had yet to reach normal limits (normal ref: >30 ng/mL) in majority of the patients although the increase was statistically significant. Likely, more favorable effects may be expected if the regimen is intensified (e.g. the dosage should be given at more than 1,000 IU daily) and appropriate evaluation intervals are chosen. Unfortunately, there is no consensus on the regimen of administrating VD in treating *i*VDD patients with paresthesia. Anecdotal experience suggested supplementation of VD at a large dose is beneficial to patients with VDD and DM-NP [5, 9]. A study of larger doses of VD on paresthesia in patients with *i*VDD is underway.

Because VDD is often undiagnosed and untreated, it is not uncommon that patients with symptoms of acral paresthesia related to VDD may not respond well to conventional medical care for symptomatic control. Notably, normal findings of neuro-physiology studies in 9/10 (90%) of our patients may suggest the involvement of small fiber dysfunction while it is notorious that small fiber neuropathy are frequently refractory to conventional medical management. As a result, qualities of lives of those patients are prone to be compromised if the underlying etiology of VDD is not addressed. Therefore, an investigation of VDD by measuring serum 25(OH)D_3 in patients with acral paresthesia should be routinely considered and performed. Once the presence of VDD is identified, treatment with VD supplementation should be initiated which would produce the best cost-effective outcomes and benefit the patients. Understandably, VD is usually safe and inexpensive. Indeed, the effect of VD on improving painful sensation in patients with DM-NP has been well documented [8].

Table 1: Demographic data and vitamin D levels in patients with paresthesia.

Case	Age	Sex	BMI (kg/m2)	Vit D* (ng/ml)	Vit D Tx* (ng/ml)	Tx (months)	Tx Regimen (IU)
1	36	F	22.5	24	51	12	50.000/wk
2	72	F	25.42	28	26	20	1000/d
3	46	F	27.77	15	23	13	1000/d
4	52	F	27.9	16	24	1	50.000/wk
5	58	M	21.4	24.8	31.5	1	50.000/wk
6	31	M	23.53	22.9	35	5	1000/d
7	55	M	25.97	24.2	18.9	18	1000/d
8	38	M	25.8	11	27.5	18	1000/d
9	34	M	28.37	24	26	10	1000/d
10	45	M	29.91	19	23	5	1000/d
n = 10	46.7±12.8	F=5/M=6	25.9±2.7	20.9±5.4	28.6±9.1	10.3±7.1	
					*p=0.03		

BMI: body mass index; Vit D: Vitamin D; Tx: treated; IU: international units; d: daily; wk: weekly; Statistics: two tails of unpaired *Student t* test.

Table 2: Clinical data and responses to vitamin D supplementation in patients with paresthesia.

Case	Initial symptoms	Initial signs	Initial DTR	NCS	Response to Tx	After Tx: symptoms	After Tx: signs	After Tx: DTR
1	numb, tingling	↓glo - ↓sto	normal	normal	Improving	better, still numb in finger-tips	↓glo - ↓sto	normal
2	numb, tingling	↓glo - ↓sto	normal	normal	Improving	better, still numb in finger-tips	normal	normal
3	numb, tingling	↓glo - ↓sto	normal	↓sensory NCV	changed to pain	improved numb but still pain	normal	normal
4	pain	↓glo - ↓sto	normal	normal	No change	still pain in legs	↓glo - ↓sto	normal
5	numb, tingling	↓glo - ↓sto	↓	normal	Improving	better, still numb in finger-tips	↓glo - ↓sto	↓
6	pain, numb, tingling	normal	normal	normal	No change	worse, pain	normal	normal
7	pain, cramps	↓glo - ↓sto	normal	normal	No change	still pain, cramps	↓glo - ↓sto	normal
8	pain, numb, tingling	↓glo - ↓sto	normal	normal	Improving	better, still pain, numb, tingling in legs	↓glo - ↓sto	normal
9	pain (burning)	↓glo - ↓sto	normal	normal	improved	better, still burning	↓glo - ↓sto	↓
10	pain	normal	↓	normal	improving	Better	normal	↓
n = 10					Improving = 6/10 (60%)			

↓: mildly decreased; ↓glo-sto: glove-stocking pattern.

Conclusions

Observation from our study showing improvement of acral paresthesia in patients with *i*VDD by VD supplementation suggested that *i*VDD might contribute to developing small fiber neuropathy or potentiating the severity of symptoms in patients with acral paresthesia. Therefore, our findings are of importance in clinical implementation, given the fact that many patients with paresthesia responded poorly to the conventional medical care. Additionally, our findings also support the notation that VDD may be a potentially independent risk factor for peripheral neuropathy, particularly for those with acral paresthesia. Furthermore, VDD may serve as a biomarker, paralleling others such as hemoglobin A1c, for painful DM-NP. To validate our conclusion, a large-scale study is warranted and further study is underway.

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