Original Article

Vitamin D serum level in subjects with critical illness polyneuropathy and myopathy

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Abstract

Background: Critical illness polyneuropathy and myopathy (CIPNM) is a disabling neuropathy that occurs in intensive care unit (ICU) subjects. It was hypothesized that a low serum level or deficiency of 25(OH)D might be associated with CIPNM. The aim of the present study was to ascertain the 25(OH)D serum level in subjects with CIPNM. **Method**: Consecutive ICU patients admitted to neuro-rehabilitation were prospectively enrolled. At admission, vitamin D serum levels were measured and EMG examination was performed to ascertain those with CIPNM. 25(OH)D was stratified as sufficient (≥30 ng/mL) insufficient (20-29.9 ng/mL), and deficient (<20 ng/mL). **Results**: Eighty-four patients (31 F, 53 M; mean age 51.7±12.6) were identified and 63 (21 F, 42 M) enrolled. CIPNM was detected in 38 (9 F, 29 M) patients. A deficient mean serum level of vitamin D was observed in the whole population: 18.1 ± 9.2 ng/mL. No difference of vitamin D serum levels was detected in subjects with and without CIPNM: 17.5 ± 8.4 and 19.0 ± 10.5 ng/mL (p=0.58), respectively. **Conclusion**: Almost all subjects showed Vitamin D deficiency. No difference was detected between those with and without CIPNM. The condition might represent a secondary phenomenon resulting from the inflammatory process as well as from conditions that could interfere with vitamin D metabolism.

Keywords: Critical Illness Polyneuropathy, Vitamin D, Deficiency, Inflammation

Introduction

Critical illness polyneuropathy (CIP) is a disabling neuropathy that occurs in intensive care unit (ICU) subjects. The incidence has been variably reported with a wide range spreading from 45 to 80%[1-3] and higher values in those suffering from systemic inflammatory response syndrome (SIRS), sepsis and multi-organ failure (MOF)[4-5]. CIP is defined as a sensory and motor axonal neuropathy characterised by symmetrical upper and lower limb weakness that compromises predominantly distal legs with reduced or absent deep tendon reflexes[6]. The electrophysiological examinations (electroneurography: ENG, and electromyography: EMG) are generally characterized by normal or mildly reduced nerve conduction velocities with reduction in the amplitudes of compound muscle action potentials (CMAPs) and sensory-nerve action potentials (SNAPs)[7-8]. This disorder is frequently associated with an acute, primary myopathy called critical illness myopathy (CIM)[9]. The clinical pictures are not sufficient to make a differential diagnosis between the different forms. CIM diagnosis needs of muscular biopsy and histological examination. ENG and EMG can contribute to differentiating CIM, CIP or CIP/CIM[10], but the discrimination between the myopathic and neuropathic type remains difficult and often unclear. ICU patients have neurophysiological and morphological evidence of both forms[11], making their differential diagnosis difficult or even impossible. Hence,

the terms critical illness polyneuropathy and myopathy[6] and polyneuromyopathy (CIPNM)[8,12] have been proposed. Several risk factors have been reported to favour the development of CIPNM including sepsis, multiple organ failure and longer ICU stay[13-14], but the origin of CIPNM remains unknown, and no pharmacological or non-pharmacological treatment has resulted in efficacious prevention of CIPNM occurrence[15-16].

The role of vitamin D [25-hydroxyvitamin D (25(OH)] in Ca/P balance and pathophysiological mechanisms underlying skeletal system disorders is well-known, but 25(OH)D has a multi-faceted and widespread action in human multi-organ systems. In recent decades, increased attention has been paid to non-skeletal targets such as diabetes[17], cardiovascular[18-19], muscular[20], and nervous system. Studies have suggested that 25(OH)D may be important for the development of the nervous system, and it may also play a role in neuroimmunology and neuroprotection. Low 25(OH)D serum levels have been associated with risk of multiple sclerosis (MS)[21-23], Alzheimer's disease[24-25], Parkinson's disease[26-27], stroke[28-29] and epilepsy[30]. Furthermore, the relationship between 25(OH)D and other neurological disturbances such as cerebral small vessel disease[31] and spinal cord injury have recently been investigated[32]. The role of 25(OH)D in acquired peripheral nervous system disorders is unclear. Interestingly, studies have suggested that 25(OH)D deficiency can promote polyneuropathy in diabetic patients[33-34] and can be associated with immune mediate polyneuropathy[35].

It has been suggested that CIPNM occurrence might be promote by derangement of hormonal and metabolic alterations such as hyperglycemia, hormone imbalance, hypoalbuminemia, amino acid deficiency and activation of proteolytic pathways that might be related to Vitamin D[36]. On this basis, it was hypothesized that a low serum level or deficiency of 25(OH)D might be associated with CIPNM favouring occurrence, particularly in patients experiencing an ICU stay and suffering from severe critical illness conditions. The aim of the present study was to ascertain the 25(OH)D serum level in subjects coming from ICU with and without CIPNM and if patients with CIPNM showed lower vitamin D serum level than patients without CIPNM.

Methods and participants

With approval from the local Ethics Committee (Comitato etico presso IRCCS Casa Sollievo della Sofferenza on 9-18-2016, ICF V.10_18 ago 16), consecutive subjects admitted to neuro-rehabilitation from the ICU during the period from December 2017 to December 2018 were prospectively enrolled. Patients with a history of polyneuropathy (diabetic polyneuropathy, Guillain Barrè syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP)) or neuro-muscular diseases (myasthenia gravis, polymyositis and amyotrophic lateral sclerosis) were excluded as well as patients with malignancy, impaired renal function (estimated glomerular filtration rate: 30 ml/min) and liver failure.

Patients gave informed consent in cases in which they had the capacity. In cases in which the patient lacked the capacity, the patient's nearest relative or legal representative gave consent for inclusion. All research was performed in accordance with relevant guidelines/regulations. Clinical and neurological evaluations were performed in all subjects at admission. Previous or current 25(OH)D supplementation was recorded as well as supplementation before assessment. All patients underwent an EMG examination to assess the presence of neuromuscular disorders, at admission. All enrolled subjects were divided into two groups, patients with and without CIPNM. To reflect the difficulty in discriminating between myopathic and neuropathic causes of muscle weakness, we decided to use the term critical illness polyneuropathy and myopathy (CIPNM), and differentiation between neuromuscular types was not performed. Furthermore, body mass index (BMI) was calculated in all subjects.

Vitamin D dosage and blood parameter assessment

Serum levels of 25(OH)D were analysed using 25-hydroxy chemiluminescent immunoassay (DiaSorin Liaison; Stillwater, MN), which has a 100% cross-reactivity with both metabolites within a week from admission. The serum level of 25(OH)D was stratified as sufficient (≥30 ng/mL [75 nmol/L]), insufficient (20-29.9 ng/mL [50-75 nmol/L]), and deficient (<20 ng/mL [50 nmol/L]) according to the Endocrine Society criteria[37].

Electrophysiological evaluation

Because most of the ICU patients at study entry were poorly collaborative and since CIP and CIM frequently coexist and present overlapping neurological pictures, for the purposes of this study, only conventional electrophysiological examination by an NCS-EMG evaluation (MEDELEC Synergy N2 machine) was used according to a method described elsewhere[38]. All patients underwent conventional orthodromic motor and antidromic sensory nerve conduction studies on eight motor nerves (median, ulnar, common peroneal and tibial nerves, bilaterally) and six sensory nerves (median, ulnar and sural nerves, bilaterally). Muscular activity at rest and, when possible, during contraction was assessed with concentric needle electrodes. Sensory nerve action potential (SNAP), distal motor latencies, F wave, compound muscle action potential (CMAP) and nerve conduction velocities were registered. Abnormal CMAP or SNAP amplitudes were considered significant if they were found in at least two nerves. Spontaneous activity and, when possible, recruitment and interference patterns were detected bilaterally by needle EMG from the deltoid, first dorsal inter-osseus, tibial anterior and abductor hallucis muscles. CIPNM was defined if electrophysiological results revealed very low amplitude or absent SNAPs, low amplitudes of CMAPs with normal or mildly reduced conduction velocities, or normal nerve conduction velocity and reduced CMAPs amplitude. In patients who were not collaborative or too weak to exercise,
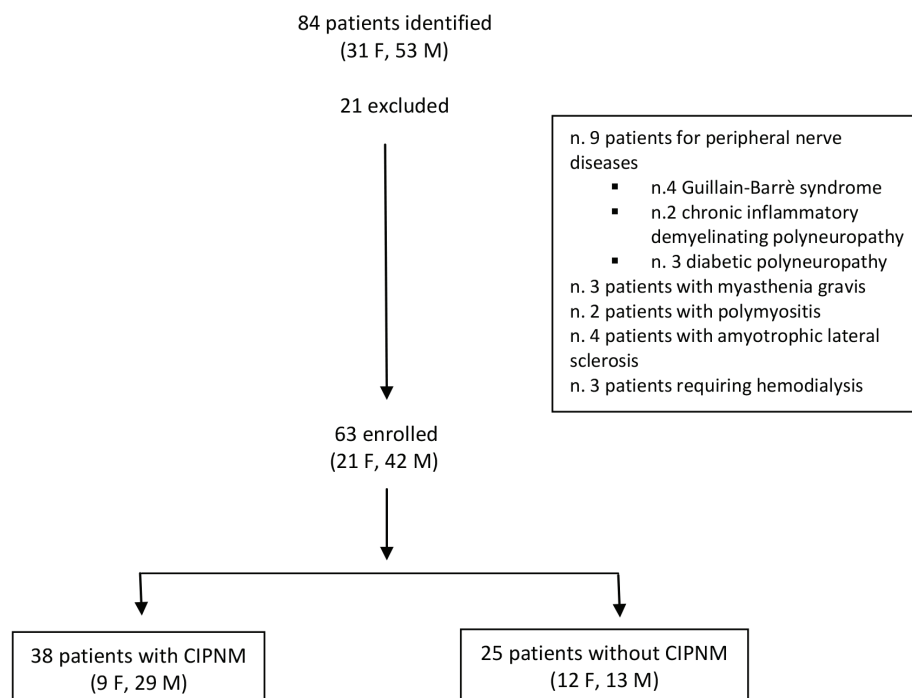
Figure 1. Flow Chart. Legend: ICU=intensive care unit; CIPNM=critical illness polyneuropathy and myopathy.

repetitive stimulation at 3 Hz was performed to exclude myasthenia gravis.

Statistical analysis

Patient characteristics were reported as the mean ± standard deviation (SD) and median along with the first-third quartiles (q_1-q_3) and as frequencies and percentages for continuous and categorical variables, respectively. Comparisons between groups were assessed using Mann-Whitney U (or Kruskal-Wallis) test and Pearson Chi-square test (or Fisher exact test as appropriate) for continuous and categorical variables, respectively. Comparisons between time variables (i.e., days spent in intensive care unit and days between admission and 25(OH)D measure) were assessed using Poisson regression models. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS Release 9.4 (SAS Institute, Cary, NC, USA).

Results

Eighty-four (31 F, 53 M; mean age 51.7±12.6 years) were identified. Of these, 21 subjects were excluded: 9 patients as a result of peripheral nerve diseases (4 subjects with Guillain-Barrè syndrome, 2 with CIDP, 3 patients with diabetic polyneuropathy); 5 patients with muscular

diseases (3 patients with myasthenia gravis, 2 patients with polymyositis), 4 patients suffering from amyotrophic lateral sclerosis, and 3 subjects as a result of renal failure requiring haemodialysis (Figure 1), and 63 (21 F, 42 M) subjects were enrolled. Clinical characteristics and primary causes of all enrolled patients are reported in table 1. CIPNM was detected in 38 (9 F, 29 M, mean age: 55.3 ± 15.8) (60.3%) patients (Table 1). No difference in body mass index was detected between groups: 24.5 ± 3.5 and 24.3 ± 4.2 (p= 0.912) in subjects with and without CIPNM, respectively.

No subjects took vitamin D preparation before hospitalization, and none received vitamin D supplementation before their serum assessment. Eighteen (28.5%) patients: 11 and 7 subjects with and without CIPNM respectively, were treated with antiepileptic agents. Only 3 patients (2 with CIPNM and one without) assumed statins. Deficient mean serum levels of vitamin D were detected in the whole population: 18.1 ± 9.2 ng/mL. Subjects with CIPNM showed lower mean serum levels of vitamin D than those without CIPNM, but the difference was not significant: 17.5 ± 8.4 and 19.0 ± 10.5 ng/mL (p=0.58), respectively (Table 2). No significant variation in seasonal vitamin D assessment was detected (Table 3).

Discussion

No difference of vitamin D serum levels was detected in subjects with and without CIPNM, even if a deficiency of

Table 1. Clinical characteristics, primary causes of ICU admission in patients with and without CIPNM.

Patients	ICU subjects with CIPNM (N = 38)	ICU subjects without CIPNM (N=25)
Sex	9 F, 29 M	12 F, 13 M
Mean age ± SD	55.34 ± 15.89	45.96 ± 19.57
Diagnoses (%)	CH: n.15 (39.4) Cerebral ischemia: n. 1 (2.6) Brain injuries: n. 12 (31.5) Intracranial meningiomas: n. 3 (7.8) Cardiac surgery: n. 3 (7.8) - mitral and aortic valve graft; Respiratory failure: n. 2 (5.2) Sepsis: 2 (5.2)	CH: n.8 (32) Cerebral ischemia: n. 2 (8) Brain injuries: n.13 (52) Intracranial meningiomas: n. 1 (4) Cardiac surgery: n. 1 (4.1)
SAPS II	42.5±7.6	41.8±8.3
ICU stay Mean ± SD	35.4 ± 18.8 days	39.9 ± 17.7 days

Legend: CIPNM = critical illness polyneuromyopathy; ICU= intensive care unit; CH= cerebral hemorrhage; SAPS II = Simplified Acute Physiology Score; percentage is reported in brackets.

Table 2. Clinical characteristics, days spent in ICU, vitamin D serum levels, and seasonal variation of patients with and without CIPNM admitted in neuro-rehabilitation.

Variable	Category	ICU patients (N=63)	ICU patients without CIPNM (N=25)	ICU patients with CIPNM (N=38)	p-value*
Gender - N(%)	Females	21 (33.3)	12 (48.0)	9 (23.7)	0.045
	Males	42 (66.7)	13 (52.0)	29 (76.3)	
Age (years)	N obs	63	25	38	0.041
	Mean±SD	51.7 ± 17.9	46.2 ± 19.8	55.3 ± 15.8	
	Median (q_1-q_3)	54 (40-65)	47 (25-59)	57.5 (47-68)	
	Range (min-max)	18 - 95	18 - 95	20 - 80	
BMI (kg/m²)	N obs	61	24	37	0.912
	Mean±SD	24.4 ± 3.8	24.3 ± 4.2	24.5 ± 3.5	
	Median (q_1-q_3)	24.4 (22-26.5)	24.4 (21.2-26.7)	24.4 (22.6-25.9)	
	Range (min-max)	17.2 - 38.6	17.4 - 34.2	17.2 - 38.6	
Days spent in intensive care unit	N obs	60	23	37	0.006°
	Mean±SD	37.2 ± 18.4	39.9 ± 17.7	35.4 ± 18.8	
	Median (q_1-q_3)	35 (25-44)	36 (27-57)	30 (25-41)	
	Range (min-max)	9 - 93	17 - 88	9 - 93	
Days between admission and 25(OH)D assessment	N obs	63	25	38	0.886°
	Mean±SD	2.6 ± 3.1	2.5 ± 2.3	2.6 ± 3.6	
	Median (q_1-q_3)	2 (1-3)	2 (1-3)	1 (1-3)	
	Range (min-max)	0 - 19	0 - 8	0 - 19	
25(OH)D level (ng/mL) - N(%)	N obs	63	25	38	0.581
	Mean±SD	18.1 ± 9.2	19.0 ± 10.5	17.5 ± 8.4	
	Median (q_1-q_3)	17.4 (12.1-21.3)	18.8 (12.1-20.8)	15.7 (12.3-21.3)	
	Range (min-max)	4 - 53.6	6.5 - 53.6	4 - 42.5	
	Sufficient (≥30 ng/mL)	6 (9.5)	3 (12.0)	3 (7.9)	0.843#
	Insufficient (20 - 29.9 ng/mL)	12 (19.0)	5 (20.0)	7 (18.4)	
	Deficient (< 20 ng/mL)	45 (71.4)	17 (68.0)	28 (73.7)	
Season at which 25(OH)D was assessed - N(%)	Spring	15 (23.8)	5 (20.0)	10 (26.3)	0.793
	Summer	19 (30.2)	9 (36.0)	10 (26.3)	
	Autumn	14 (22.2)	6 (24.0)	8 (21.1)	
	Winter	15 (23.8)	5 (20.0)	10 (26.3)	

Legend: ICU= intensive care unit; CIPNM= critical illness polyneuromyopathy; SD=standard deviation; *p-values from Mann-Whitney U test or Chi-square test for continuous and categorical variables, respectively; #p-values from Fisher's exact test; °p-values from Poisson model.

Table 3. Vitamin D serum level and seasonal assessment in all patients admitted to neuro-rehabilitation.

Variable	Category	Spring (N=15)	Summer (N=19)	Autumn (N=14)	Winter (N=15)	p-value*
25(OH)D level (ng/mL) - N(%)	N obs	15	19	14	15	0.582
	Mean±SD	20.1 ± 10.8	18.6 ± 9.2	17.9 ± 10.7	15.8 ± 5.9	
	Median (q_1-q_3)	19.4 (12.6-23.8)	18.8 (10.9-21.8)	16.2 (9.1-19.9)	13.9 (12.3-19.7)	
	Range (min-max)	8.5 - 53.6	4 - 42.5	6.5 - 41.3	6.7 - 31	
	Sufficient (≥30 ng/mL)	1 (6.7)	2 (10.5)	2 (14.3)	1 (6.7)	0.427
	Insufficient (20 - 29.9 ng/mL)	4 (26.7)	6 (31.6)	1 (7.1)	1 (6.7)	
	Deficient (< 20 ng/mL)	10 (66.7)	11 (57.9)	11 (78.6)	13 (86.7)	

Legend: SD=standard deviation; *p-values from Kruskal-Wallis test or Fisher exact test for continuous and categorical variables, respectively.

vitamin D was observed in both groups. Low or deficient levels of vitamin D have been detected in critically ill patients, and it was suggested that this condition increases the susceptibility for severe infections, longer ICU stays and mortality[39-41]. In this respect, there are biologically plausible mechanisms by which deficiency might contribute to adverse outcomes, such as immune dysfunction, cardiovascular disease, dysglycaemia, and endothelial and mucosal barrier disruption[42]. However, no relationship was reported with CIPNM, and to the best of our knowledge, this is the first study about a potential relationship between vitamin D deficiency and CIPNM. Our finding supports the fact that a deficient serum level of 25(OH)D can be detected in patients with CIPNM, but given that also patients without CIPNM had vitamin D deficiency, a causal relationship with onset of the disease cannot be supported.

A growing body of evidence suggests that vitamin D plays a pleiotropic effect in the nervous system by regulating brain development, neuroplasticity and function. Its role has been demonstrated in a wide spectrum of neurological disorders that also encompasses degenerative and inflammatory processes[43]. Deficiency or a genetically lowered 25(OH)D level has been strongly associated with increased susceptibility to multiple sclerosis (MS)[22] with a higher risk of disability in the relapsing-remitting MS form[44] and a greater decrease in brain volume and white matter abnormalities in old people[45]. Furthermore, deficiency of the 25(OH)D level has been demonstrated to represent a risk factor of ischaemic stroke[46] as well as a useful prognostic marker that could predict infarct volume, mortality[47] and poor functional outcome in stroke patients[48-49]. Despite the knowledge that the vitamin D role in CNS is progressively growing, its effect in the peripheral nervous system is still scanty and unclear. The effect of vitamin D in glycemic metabolism and its role as a risk factor in developing type 2 diabetes mellitus have been investigated[50-52]. It is well-known that diabetes mellitus is one of the main causes of polyneuropathy, and studies have reported that vitamin D deficiency could promote polyneuropathy in diabetic patients[33]. Skalli et al. reported an association between polyneuropathy and vitamin D deficiency in a sample of 111 patients with type 2 diabetes

who had a clinically diagnosed polyneuropathy[53]. The finding was confirmed by a recent meta-analysis in which vitamin D deficiency was significantly associated with an increased risk of polyneuropathy in patients with type 2 diabetes[34]. Furthermore, vitamin D deficiency has been detected in subjects with immune-mediate polyneuropathy[35]. In the present study, vitamin D deficiency was detected in both subjects with and without CIPNM. Several reasons could be carried out to explain the finding. This condition might be a consequence of systemic inflammation underlying any pathological process. This hypothesis has been suggested to explain the low level of vitamin D that has been detected in several pathological conditions such as critical illness, obesity, diabetes, cardiovascular diseases, and rheumatic and autoimmune disturbances, in which a common factor is the inflammatory process. On the other hand, normal vitamin D level was detected in non-inflammatory diseases including cognitive dysfunction, muscular disease, non infectious pulmonary disease (chronic obstructive pulmonary disease) and endocrine disorders[54]. Thus, low vitamin D might be considered a secondary phenomenon resulting from the inflammation.

Vitamin D serum levels could be influenced by a number of drugs that can interfere with the vitamin D metabolism including antiepileptic agents, glucocorticoids, anti-estrogens[55] and statins lowering lipids that are commonly used in patients with cardiovascular diseases[56-57]. In the present study, one third of patients was treated by antiepileptics or statins, but no difference was found between subjects with and without CIPNM in assumption of antiepileptic drugs as well as agents interfering with vitamin D metabolism. Therefore, it is important to consider that this aspect might have a role in the decreased serum levels of vitamin D found in the studied sample.

Given that the majority of ICU showed Vitamin D deficiency, it is conceivable that the finding may reflect a low vitamin D in general population. The estimation of vitamin D status in adult Italian population is lacking and few studies have been carried out in order to evaluate the prevalence of hypovitaminosis D in healthy subjects. A prevalence of circulating 25(OH)D concentration below 25 and 50 nmol/L ranging from 13

to 38.5% has been reported[58-60], while higher values up to 76% have been observed in elderly women[61]. Among factors that can influence vitamin D level, hospitalization and length of stay should be also considered. Romagnoli et al. observed that the prevalence of hypovitaminosis was 71.4% and 82.3% in subjects with medical condition and subjects engaged in long-term rehabilitation because of various neurological disorders, respectively, during the winter. The prevalence decreased to 29.8 and 57.8%, respectively, in summertime[60]. In the present study, a higher prevalence of hypovitaminosis D was detected, since 90% of all subjects had low vitamin D level. Furthermore, no seasonal variation was observed. However, in comparing the results of mentioned studies, it should be considered that Romagnoli et al. used a different cut off (serum 25(OH)D level below 30 nmol/l) in defining hypovitaminos. Since vitamin D deficiency is common in critical illness with prevalence between 40-70%[62], it is not possible exclude that our finding simply reflect this aspect, even if a higher rate was detected in the present study. Furthermore, rehabilitation setting, age and different neurological diseases requiring challenging rehabilitation might explain the finding. Indeed, the majority of enrolled ICU subjects suffered from severe acquired brain injury. This disorder embraces a number of different neurological conditions, including traumatic brain injury, hypoxic brain injury, stroke, and brain tumour that can result in cognitive, physical, emotional, or behavioural impairments[63-64]. In this respect, studies have demonstrated low vitamin D serum levels in subjects suffering from cerebral lesions such as stroke[28-29] or brain injury[65-66].

Reduced exposure to sunlight, urban habitat, urban pollution, clothing habits and seasons may influence vitamin D levels, particularly in hospitalized patients, but data were corrected for the mentioned variables and did not show any differences.

Limitations of the present study are the small sample size and the lack of CIPNM type differentiation: CIM, CIP. Indeed, it is not possible to exclude the fact that low or deficient vitamin D serum levels may be associate or contribute to the development of particular forms of CIPNM. However, almost all ICU subjects with CIPNM had a homogenously low vitamin D serum level; therefore, it is conceivable that all CIPNM subtypes may have a low vitamin D serum level.

Several questions remain unsolved when considering serum level of vitamin D in critical ill patients. Whether vitamin D deficiency is a further component of the inflammatory process or an independent factor affecting the disease course and outcome is unclear. Although there are biologically plausible mechanisms by which vitamin D deficiency produces adverse outcome, no study has demonstrated causative link. Likewise, whether the low vitamin D levels observed are merely a marker of poor general health resulting in limited exposure to sunlight, chronic illness and poor diet or merely due to laboratory techniques remain unsolved. Therefore, designed studies should redefine the values of normality of vitamin D in the critical patient population. Furthermore, well-conducted studies should be planned to investigate vitamin D measurement modalities (optimum range, what level, and assay to use), timing (single or multiple assessments), supplementation (how much, which route, how often and when) and vitamin D effects on outcome.

Conclusion

The majority of ICU patients admitted to neuro-rehabilitation showed vitamin D deficiency. No difference of vitamin D serum level was detected in subjects with and without CIPNM. The reasons of this condition remain unclear and might represent a secondary phenomenon resulting from the inflammation that underlies any pathological process as well as from conditions that could interfere with vitamin D metabolism.

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