


## CASE REPORT

# A case of post-COVID-19 myalgic encephalomyelitis/chronic fatigue syndrome characterized by post-exertional malaise and low serum acylcarnitine level

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## Abstract

COVID-19 afflicts patients with acute symptoms and longer term sequelae. One of the sequelae is myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is often difficult to diagnose, having no established tests. In this article, we synthesize information from literature reviews on patients with ME/CSF that developed after recovery from COVID-19.

## KEYWORDS

acylcarnitine, COVID-19, fatigue syndrome, malaise

## 1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative virus of coronavirus disease (COVID-19), which was discovered in China in December 2019.<sup>1</sup> To date, there is no end in sight to the disease. The recognized acute phase symptoms of COVID-19 are fever, dyspnea, cough, dysgeusia, and anosmia. Recent attention has focused on COVID-19 sequelae referred to as “long COVID” or post-COVID-19 syndrome.<sup>2</sup> After recovery from COVID-19, approximately 50% of patients reportedly experience sleep disturbance and chronic fatigue,<sup>3</sup> and approximately, 25% meet the diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome

(ME/CFS).<sup>4</sup> ME/CFS causes various symptoms, such as morbid fatigue, pain, and mental disorders, that worsen after exertion; however, its pathogenesis and treatment remain unclear.<sup>5</sup> Thus, as many as 80% of patients struggle to receive a diagnosis of ME/CFS, and, in some cases, are forced to consult several specialists and medical facilities for a diagnosis.<sup>6</sup>

Currently, no blood tests or imaging studies provide a definitive diagnosis of ME/CFS, although such procedures may serve to rule out alternative competing diagnoses. However, of the clinical symptoms and laboratory test findings commonly regarded as suggestive of ME/CFS, two are especially noteworthy and therefore warrant additional attention: post-exertional malaise (PEM)<sup>7</sup>

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and serum acylcarnitine level.<sup>8</sup> In this report, we present a review of the literature concerning these two features and describe the case of a patient for whom we were able to correctly diagnose ME/CFS based on accurate history-taking and clinical examination.

## 2 | CASE REPORT

A 59-year-old man was referred to our hospital for generalized myalgia. Approximately 2 years ago, he had been hospitalized for COVID-19, and 6 months after recovering from COVID-19, he began to notice generalized muscle pain and fatigue. He was subsequently referred to local clinics, where blood tests and imaging studies were performed, including magnetic resonance imaging and computed tomography. However, no abnormal findings were observed. This was the case at several medical facilities visited by the patient, with one doctor advising that he exercise. The patient's symptoms further exacerbated, prompting his visit to our hospital. Although we performed a variety of tests to identify all possible causes of myalgia, we found no obvious anomalies (Table 1). Physical examination revealed no second wind phenomenon or muscle hypertrophy or atrophy, and his score on the Medical Research Council Scale was normal, with no evidence of myopathy. After excluding all possible causes, we recalled the history-taking interview in which the patient expressed a concern about PEM, a symptom that has been suggested in the literature as consistent with ME/CFS. Given previously published reports of atypical serum acylcarnitine profiles in ME/CFS, we sought additional bloodwork and found the patient to have decreased levels (Table 2). Subsequently, we found that all of the criteria were met for a diagnosis of ME/CFS (Table 3),<sup>7</sup> leading to a confirmed diagnosis, at which point the patient was referred to a specialized facility to pursue epipharyngeal abrasive therapy for its anti-inflammatory effects.

## 3 | DISCUSSION

The acute symptoms of COVID-19 include headache, fever, cough, anosmia, dysgeusia, and myalgia, and, in severe cases, respiratory and multiple organ failure.<sup>2</sup> In addition to these acute symptoms, several individuals develop longer term COVID-19 sequelae, including ME/CFS. The combination of morbid fatigue, pain, and cognitive-affective symptoms associated with ME/CFS, all of which may worsen after exertion, can significantly reduce quality of life. As there is still no established treatment for ME/CFS, its impact on rehabilitation and nursing care, as well as multiple medical fields, is immeasurable.<sup>9</sup> Given the difficulty in diagnosing ME/CFS, patients who have

TABLE 1 Laboratory data

Blood biochemistry			Complete blood count		
<b>(A)</b>					
T-Bil	0.7	mg/dL	WBC	4300	/μL
AST	26	U/L	NEUT	55.4	%
ALT	31	U/L	LYM	31.1	%
γ-GTP	35	U/L	MONO	11.8	%
LDH	192	U/L	EO	1.2	%
ALP	61	U/L	BASO	0.5	%
AMY	81	U/L	Hb	14.5	g/dL
TP	6.9	g/dL	MCV	87.6	fL
Alb	4.6	g/dL	Plt	24×10 <sup>4</sup>	/μL
BUN	9.1	mg/dL	Urinalysis		
Cre	0.77	mg/dL	pH	6.5	
UA	4.7	mg/dL	PRO	–	
CK	120	U/L	GLU	–	
CRP	0.01	mg/dL	URO	–	
TC	185	mg/dL	BIL	–	
BS	127	mg/dL	KET	–	
Na	143	mmol/L	OB	–	
K	4.4	mmol/L	RBC	<1	/HPF
Cl	107	mmol/L	WBC	<1	/HPF
Ca	9.5	mg/dL	BACT	–	
P	3.2	mg/dL			
<b>Additional data</b>					
<b>(B)</b>					
Fe	62	μg/dL			
TIBC	317	μg/dL			
Ferritin	106	ng/mL			
Vit B1	69.8	ng/mL			
Vit B9	5.5	ng/mL			
Vit B12	830	pg/mL			
TSH	0.75	mIU/L			
FT3	3.89	pg/mL			
FT4	1.17	ng/dL			
TR-Ab	<0.9	IU/L			
Tg-Ab	14.7	IU/mL			
TPO-Ab	10.1	IU/mL			
IgG	974	mg/dL			
IgA	81	mg/dL			
IgE	8.2	IU/mL			
C3	128	mg/dL			
C4	18	mg/dL			
MMP-3	86.1	ng/mL			
MPO-ANCA	0.1	U/mL			
PR3-ANCA	0.2	U/mL			

TABLE 1 (Continued)

Additional data		
(B)		
AChR-Ab	<0.2	nmol/L
dsDNA-Ab	<10	IU/mL
ANA	<40	
SSA-Ab	0.4	
SSB-Ab	<0.4	
Jo 1-Ab	<0.3	
Scl 70-Ab	<0.6	
GSC-Ab	0.28	

Abbreviations: (A); Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMY, amylase; AST, aspartate aminotransferase; BACT, bacteria; BASO, basophil; BIL, bilirubin; BS, blood sugar; BUN, blood urea nitrogen; Ca, calcium; CK, creatine kinase; Cl, chlorine; Cre, creatinine; CRP, C-reactive protein; EO, eosinophil; Glu, glucose; Hb, hemoglobin; K, kalium; KET, ketone body; LDH, lactate dehydrogenase; LYM, lymphocyte; MCV, mean corpuscular volume; MONO, monocyte; Na, natrium; NEUT, neutrophil; OB, occult blood; P, phosphorus; Plt, platelet, pH, potential of hydrogen; PRO, protein; RBC, red blood cell; T-Bil, total bilirubin; TC, total cholesterol; TP, total protein; UA, uric acid; URO, urobilinogen; WBC, white blood cell;  $\gamma$ -GTP,  $\gamma$ -glutamyl transpeptidase. Abbreviations: (B); AChR-Ab, acetylcholine receptor antibody; ANA, antinuclear antibody; dsDNA-Ab, double-stranded deoxyribonucleic acid antibody; Fe, ferrum; FT3, free triiodothyronine; FT4, free thyroxine; GSC-Ab, ganglioside complex antibody; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; Jo 1-Ab, Jo-1 antibody; MMP-3, matrix metalloproteinase-3; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; Scl 70-Ab, scleroderma 70 antibody; SSA-Ab, Sjögren's syndrome A antibody; SSB-Ab, Sjögren's syndrome B antibody; Tg-Ab, thyroglobulin antibody; TIBC, total iron-binding capacity; TPO-Ab, thyroid peroxidase antibody; TR-Ab, thyrotrophin receptor antibody; TSH, thyroid-stimulating hormone; Vit, vitamin.

TABLE 2 Serum carnitine

			Normal level	
T-carnitine	47.3	$\mu\text{mol/L}$	45~91	$\mu\text{mol/L}$
F-carnitine	43.4	$\mu\text{mol/L}$	36~74	$\mu\text{mol/L}$
Acylcarnitine	3.9	$\mu\text{mol/L}$	6~23	$\mu\text{mol/L}$

Abbreviations: F-carnitine, free carnitine; T-carnitine, total carnitine.

recovered from the acute phase of COVID-19 but who still present with symptoms often wait several years before receiving appropriate care for ME/CFS; this prolonged period without an effective diagnosis may contribute to the 30% of patients who develop depression and other psychiatric complications during long COVID.<sup>10</sup>

In an attempt to facilitate timely diagnosis, the National Academy of Medicine proposed diagnostic criteria for ME/CFS in 2015 and, in the process, suggested a new term, systemic exertion intolerance disease, to replace the combined phrase of ME/CSF.<sup>7,11</sup> Of the proposed criteria (Table 3), two factors were especially salient for our patient and, therefore,

TABLE 3 SEID/ME/CFS criteria<sup>7</sup>

All three of the following must apply		Our patient
1	A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.	○
2	Post-exertional malaise (PEM).	○
3	Unrefreshing sleep.	○
In addition, at least one of the following two symptoms must apply		
4	Cognitive impairment.	○
5	Orthostatic intolerance.	○

Abbreviations: CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis; SEID, systemic exertion intolerance disease.

were pivotal in directing our attention to the possibility of ME/CFS in the context of post-COVID recovery. The first factor is PEM, which is clearly stated in the diagnostic criteria. When a patient presents with concerns of muscle pain or weakness, the treating physician will often advise exercise, which, in turn, may exacerbate rather than ameliorate the disease and prompt further psychological distress. In ME/CFS, any form of strenuous exercise should be avoided. In contrast, graded exercise therapy and cognitive behavioral therapy have been reported to be safe and effective.<sup>12</sup> The second factor that led to an accurate diagnosis of ME/CFS for our patient was serum acylcarnitine level. A literature search for “(‘acylcarnitine’[tiab]) AND (‘fatigue syndrome, chronic’[MeSH] OR ‘chronic fatigue syndrome’[tiab] OR ‘myalgic encephalomyelitis’[tiab] OR ‘systemic exertion intolerance disease’[tiab])” on PubMed revealed 13 references, of which only four were from the last 20 years.<sup>5,13-15</sup> Despite varied opinion in these references about the precise role of l-carnitine in fatty acid oxidation, there is common agreement that ME/CFS is associated with changes in acylcarnitine and l-carnitine homeostasis.<sup>16</sup> Viral infections are known to disrupt the mitochondrial fatty acid oxidation cascade,<sup>17</sup> thus potentially contributing to a decrease in serum acylcarnitine. Consistent with this, research indicates that the rates of ME/CFS increase in conjunction with viral infections, including SARS-CoV-2 infection. As found in our case study, when ME/CFS is suspected, it may be useful to measure serum acylcarnitine level even if other laboratory tests are negative. We look forward to the development of effective laboratory tests and treatments with the accumulation of more cases in the future.

## AUTHOR CONTRIBUTIONS

**Ryuhei Jinushi:** Conceptualization; data curation; visualization; writing – original draft; writing – review and editing. **Shou Nishiguchi:** Writing – review and editing. **Sakue Masuda:** Writing – review and editing. **Akiko Sasaki:** Writing – review and editing. **K Koizumi:** Writing – review and editing. **Shomei Ryozaawa:** Writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors (RJ) upon reasonable request.

## CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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