

good ILD profile in patients with RA, it would be of great interest to collect more data with all DMARDs and bDMARDs in these patients.

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Long COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome: Similarities and differences of two peas in a pod



COVID-19 persistente y encefalomiélitis miálgica/síndrome de fatiga crónica: similitudes y diferencias

Dear Editor,

Coronavirus disease 2019 (COVID-19) is a highly contagious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Prolonged recovery of COVID-19 symptoms, so-called Long COVID-19, has been described even in patients who have mild symptoms and did not require hospitalisation. Various studies showed that at least one out of ten COVID-19 symptomatic patients develop Long COVID-19.¹

Although there is an absence of evidence-based clinical practice guidelines neither a clear aetiopathogenesis, a clinical case definition of post-COVID-19 condition was proposed across the International Severe Respiratory and Emerging Infection Consortium (ISARIC) and the World Health Organization (WHO). Long COVID-19 occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.²

Patients may present with a multifaceted and marked variability of non-specific symptoms that might fluctuate or relapse over time. Common symptoms include fatigue, pain, dyspnoea, sleep disturbances, physical sequelae, psychological distress, and cognitive impairment but also others which generally have an impact on quality of life. Symptoms may persist from the initial illness or new onset, following initial recovery from an acute COVID-19 episode.² These clinical manifestations can lead to symptoms commonly presented in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

ME/CFS is a long-term complicated, heterogeneous, multisystemic and disabling disorder, that was first proposed in 1988 by

Holmes et al. to redefine the chronic mononucleosis syndrome as a post-viral fatigue syndrome (PVFS). It is diagnosed according to the 1994 Fukuda criteria, the Canadian consensus document published in 2003 or, more recently, the international consensus criteria of 2011; that offers a review on its physiopathology, symptoms and treatment.³

It is characterised by prolonged generalised and abnormal fatigue after exercise and non-remitting significantly with rest, recurrent headache and problems of concentration and memory, which are of recent appearance and that have lasted for at least 6 months. It is accompanied by such other symptoms as tender lymph nodes, musculoskeletal pain, sleep disruption and psychiatric problems.⁴

Although the cause is unclear, research into the aetiopathogenesis is ongoing. Female sex, type A personality, and family aggregation are established as predisposing factors. Infectious agents (human herpesvirus family), toxicity exposure, and psychological and social experience are associated as precipitating and trigger factors. Other conditions such as advanced age, delay in diagnosis, severe initial involvement, comorbidity, and adaptive disorder are those that maintain the illness once it has become established. Accumulating data indicates a relationship between redox imbalance, mitochondrial dysfunction and oxidative stress pathways in patients with ME/CFS. These abnormalities were also found in patients with Long COVID-19 and suggests that the two disorders may share common pathophysiological features.

However, any potential relationship between ME/CFS and Long COVID-19 is complicated, due to the great heterogeneity of both in its clinical expression and the lack of sensitive screening and standardised instruments to order its different symptoms or agreement regarding the diagnostic criteria. Based on the hypothesis that post-COVID-19 patients can develop a PVFS that is very strikingly similar to ME/CFS, we suggest subgrouping patients with Long COVID-19 into two clinical clustering phenotypes (Table 1).

Table 1
similarities and differences between Long COVID-19 and ME/CFS.

Pathological entities	ME/CFS	Long COVID-19	
		PCFS	PACS
Prevalence	0.5–2.5% of general population	10–12.2% of COVID-19 patients after acute episode	79% were hospitalised during acute episode (inpatient)
Gender F/M	4:1	1:1	Male gender is slightly prevalent (56%)
Age	Bimodal incidence 15–20 years 33–45 years	40–55 years Mean age 54.4 years	
Aetiology related to infectious agents	HHV (Human Herpesvirus family) SARS-CoV-1 MERS-CoV	SARS-CoV-2	
Patogenesis	Redox imbalance Mitochondrial dysfunction Oxidative stress pathways Abnormal gut microbiota Indirect consequence on mental health due to posttraumatic stress, social isolation, and economic factors, such as loss of employment	Direct consequence of viral injury involvement, resulting in ME/CFS-like patogenesis, host cell-mediated immune response mechanism, and neurotropism using a transsynaptic spread mechanism (hypoxic driven neuronal apoptosis)	Indirect consequence on mental health PICS-like patogenesis: adverse therapy effects prolonged immobilisation immunologic alterations Vasculitis involvement
Prolonged symptoms	>6 months	>3 months	
Functional mobility impairment	+/++	+/++	++/+++
General and constitutional symptoms: fatigue or muscle weakness, joint and muscle pain, flu-like symptoms, ...	++	++	++/+++
Pulmonary abnormalities	-/+	-/+	+++
Cardiovascular disorders	-/+	-/+	++/+++
Neurologic symptoms and dysautonomia	+ / ++	+ / ++	++ / +++
Gastrointestinal disorders	++	++	++
Mental health disorders	++	++	++/+++
Treatment	Follow-up multidisciplinary treatment programme: Pharmacological treatment based on symptomatology Education Physical exercise Cognitive behavioural therapy		

First cluster, those patients who had mild symptoms and did not required hospitalisation (outpatient care), and develop persistent symptoms after the acute episode, so-called post-COVID-19 fatigue syndrome (PCFS). Many clinical similarities and common pathophysiological features may exist between ME/CFS and PCFS patients (ME/CFS-like).

Second cluster, those patients who required admission to hospital for severe COVID-19 (ICU or non-ICU ward hospitalisation), and develop persistent symptoms after discharge, so-called post-acute COVID-19 syndrome (PACS). Thus, ICU-PACS patients should be differentiated and ICD-10 identified from post-intensive care syndrome (PICS) defining as “new or worsening impairment of cognition, mental health or physical function after critical illness, persisting beyond the acute care hospitalisation”.⁵ Although some differences between ICU-PACS and PICS exist that may likely reflect the variable impact, the symptoms of both entities may be related, *ex aqua*, to immunology alterations, vasculitis involvement, adverse therapy effects, prolonged immobilisation, and mitochondrial dysfunction.

Taking into account the high grade of evidence of the multidisciplinary treatment programme, composed by the combination of pharmacological treatment based on symptomatology, education, physical exercise and cognitive behavioural therapy, in ME/CFS patients, we believe that the implementation of this follow-up programme might be an effective in Long COVID-19 patients.

In summary, Long COVID-19 should be considered a public Health emergency. Well-conducted studies are needed to identify the real prevalence, phenotypes, risk predictors, future treatments,

and the potential differences with ME/CFS and other overlapping pathological entities (PICS).

Significance

Clinical manifestations and pathophysiological features of Long COVID-19 can lead to symptoms commonly presented in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. We present similarities and differences of both entities. Management of both entities may be similar.

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Disease impact in axial spondyloarthritis: Divergent roles between family history of disease and HLA-B27?



Impacto de la enfermedad en la espondiloartritis axial: ¿papel divergente entre los antecedentes familiares de la enfermedad y el HLA-B27?

Dear Editor,

Spondyloarthritis (SpA) is a group of interrelated processes with a strong genetic component.^{1,2} A positive family history of SpA has been reported in up to 40% of axial SpA (axSpA) patients and the

risk to develop SpA in HLA-B27-positive first-degree relatives of HLA-B27-positive SpA patients has been estimated to be 16-times higher than that of HLA-B27-positive individuals in the general population.³ This has led to assume that both family history and HLA-B27 positivity are factors whose weight in the genesis and evolution of these diseases is interchangeable.⁴ Herein, we explore the relationships between HLA-B27, family history, and disease impact, in axSpA.

Post hoc analysis of a study in which we evaluated the construct validity of the Assessment of SpondyloArthritis international Society-Health Index (ASAS-HI) in patients with axSpA.⁵ The optimal criterion for detecting the high/very high disease activity ASDAS category was an ASAS-HI > 6, area under the ROC curve

Table 1

Univariate regression analysis of disease characteristics between patients with and without high disease impact.

Feature	ASAS HI ≤ 6 (n: 69)	ASAS HI > 6 (n: 42)	OR (95%CI)	P-Values
Age, yrs (SD)	42.7 (11.2)	44.3 (9.8)	1.01 [0.98–1.05]	.44
Disease duration, yrs (SD)	7.6 (7.5)	7.8 (5.2)	1.01 [0.94–1.08]	.88
Men, n (%)	49 (71)	25 (59.5)	0.6 [0.27–1.34]	.21
AS, n (%)	47 (68.1)	27 (64.3)	1.19 [0.53–2.67]	.67
Family history, n (%)	6 (8.7)	10 (23.8)	2.42 [0.83–7.07]	.10
HLA-B27, n (%)	62 (89.9)	26 (61.9)	0.18 [0.07–0.50]	.0008
Education level				
Primary, n (%)	25 (36.2)	18 (42.9)	Ref.	
Secondary, n (%)	20 (29)	14 (33.3)	0.97 [0.39–2.42]	.95
University, n (%)	24 (34.8)	10 (23.8)	0.58 [0.22–1.50]	.26
CVRF				
Smoking, n (%)	25 (36.2)	19 (45.2)	1.45 [0.67–3.18]	.34
Obesity, n (%)	8 (11.6)	10 (23.8)	2.38 [0.86–6.63]	.09
Diabetes, n (%)	3 (4.3)	3 (7.1)	1.69 [0.33–8.80]	.53
HBP, n (%)	9 (13)	5 (11.9)	0.90 [0.28–2.90]	.86
Dyslipidemia, n (%)	17 (24.6)	9 (21.4)	0.83 [0.33–2.09]	.69
Radiographic features				
Bilateral SI, n (%)	57 (82.6)	30 (71.4)	1.90 [0.76–4.74]	.17
Squaring, n (%)	13 (18.8)	9 (21.4)	1.17 [0.45–3.05]	.74
Syndesmophytes, n (%)	12 (17.4)	9 (21.4)	1.30 [0.49–3.40]	.59
SpA-associated features				
Enthesitis, n (%)	7 (10.1)	1 (2.4)	0.22 [0.03–1.82]	.15
Anterior uveitis, n (%)	12 (17.4)	2 (2.8)	0.24 [0.05–1.12]	.06
IBD, n (%)	2 (2.9)	4 (9.5)	3.53 [0.62–20.16]	.15
Fibromyalgia, n (%)	0 (0)	3 (7.1)	^a	.99
Depression, n (%)	2 (2.9)	6 (14.3)	5.58 [1.07–29.09]	.041
Treatments				
NSAID, n (%)	50 (72.5)	39 (92.9)	4.94 [1.36–17.90]	.015
DMARDs, n (%)	4 (5.8)	2 (4.8)	0.81 [0.14–4.64]	.81
Biologic therapy, n (%)	40 (58)	27 (64.3)	1.38 [0.63–3.05]	.41

ASAS-HI: Assessment of SpondyloArthritis international Society-Health Index, yrs: years, SD: standard deviation, AS: ankylosing spondylitis, HLA: human leukocyte antigen, CVRF: cardiovascular risk factors, HBP: high blood pressure, SI: sacroiliitis, SpA: spondyloarthritis, IBD: inflammatory bowel disease, NSAID: non-steroidal anti-inflammatory drugs, DMARDs: disease modifying antirheumatic drugs.

^a The OR for the variable referring to fibromyalgia cannot be calculated as there are no patients in the ASAS HI ≤ 6 column (the calculated ORs tend to infinite values).