Abstract

Background and purpose: Among post-COVID-19 symptoms, fatigue is reported as one of the most common, even after mild acute infection, and as the cause of fatigue, myopathy diagnosed by electromyography has been proposed in previous reports. This study aimed to explore the histopathological changes in patients with post-COVID-19 fatigue.

Methods: Sixteen patients (mean age = 46 years) with post-COVID-19 complaints of fatigue, myalgia, or weakness persisting for up to 14 months were included. In all patients, quantitative electromyography and muscle biopsies analyzed with light and electron microscopy were taken.

Results: Muscle weakness was present in 50% and myopathic electromyography in 75%, and in all patients there were histological changes. Muscle fiber atrophy was found in 38%, and 56% showed indications of fiber regeneration. Mitochondrial changes, comprising loss of cytochrome c oxidase activity, subsarcolemmal accumulation, and/or abnormal cristae, were present in 62%. Inflammation was found in 62%, seen as T lymphocytes and/or muscle fiber human leukocyte antigen ABC expression. In 75%, capillaries were affected, involving basal lamina and cells. In two patients, uncommon amounts of basal lamina were found, not only surrounding muscle fibers but also around nerves and capillaries.

Conclusions: The wide variety of histological changes in this study suggests that skeletal muscles may be a major target of SARS-CoV-2, causing muscular post-COVID-19 symptoms. The mitochondrial changes, inflammation, and capillary injury in muscle biopsies can cause fatigue in part due to reduced energy supply. Because most patients had mild–moderate acute affection, the new variants that might cause less severe acute disease could still have the ability to cause long-term myopathy.

Keywords: electromyography, fatigue, long-term COVID, muscle biopsy, myopathy, post-COVID syndrome
INTRODUCTION

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in Wuhan, China, in December 2019, the coronavirus disease 2019 (COVID-19) pandemic has caused up to 312 million confirmed cases and 5 million deaths. The clinical manifestations of COVID-19 range from asymptomatic or minor, influenza-like symptoms to acute respiratory distress syndrome and death [1], and neurological symptoms are often seen [2–7]. Fortunately, vaccination tends to cause less severe COVID-19 symptoms [8]; however, it appears reasonable to suspect that society will face COVID-19 challenges for several years to come.

Myalgia has been reported in up to 60% of the patients during acute infection [9–11], and critical illness myopathy [12, 13] and rhabdomyolysis [14] are widely reported in critically ill patients. Muscle biopsies are rarely performed, but in a few case reports of acute COVID-19 [15–17] and in two recent large postmortem studies following acute infection [18, 19], myositis has been shown in muscle biopsies.

We can expect long-term complications in patients with severe acute disease and intensive care unit treatment [5, 6, 20]. However, several studies demonstrate long-term disease after COVID-19 (post-COVID-19) also in patients who had minor symptoms, indicating that post-COVID-19-induced symptoms may be an important health care issue [21, 22]. Among post-COVID-19 symptoms, fatigue is reported as one of the most common (up to 50%–70%) [5, 10, 23–25], even several months after an infection with SARS-CoV-2.

In a recent study of patients with long-term muscular complaints or fatigue, we showed that up to 8 months after mild or moderate COVID-19, myopathy was frequently observed based on quantitative electromyography (EMG) [26]. This finding provided a completely novel explanation for the very frequent long-term muscular complaints following COVID-19. Furthermore, it raised concerns as to whether the worst consequences of COVID-19 are yet to come, appearing as chronic morbidity in millions of people.

The aim of the present study was to explore the histopathological changes in post-COVID-19 patients with long-term fatigue and to correlate these with clinical and electrophysiological findings.

METHODS

Patients

Sixteen patients were included from January to June 2021. The inclusion criteria were (i) a prior infection with SARS-CoV-2 demonstrated with typical symptoms and a positive polymerase chain reaction test or the presence of antibodies in nonvaccinated patients; and (ii) complaints of muscle fatigue, myalgia, or weakness on clinical examination persisting for at least 3 months after the infection. Patients were referred from post-COVID-19 outpatient department. Clinical, electrophysiological examinations and the muscle biopsies were performed as a part of diagnostic workup. Medical history and symptoms were registered, and a comprehensive blood panel was performed. Patient data were registered in a secure REDCap database hosted at the Clinical Trial Unit, Aarhus University. Data collection and interview study were approved by the Central Denmark Region (references: 1-45-70-5-20 and 1-16-02-4-21). The registry- and questionnaire-based design did not require ethics approval, which was confirmed by the Regional Ethics Committee (reference: 1-10-72-181-20).

Clinical examination

All patients underwent a detailed clinical evaluation and neurological examination including bilateral manual muscle strength testing of all major muscle groups (shoulder abduction, elbow and wrist extension and flexion, hip flexion, knee extension and flexion, and ankle dorsal flexion), activities of the deep tendon reflexes, and sensory testing.

Electrophysiological examination

Sensory and motor nerve conduction studies in the upper and lower limbs were performed in all patients to exclude entrapment neuropathy and polyneuropathy. Quantitative EMG was performed using a 35-mm concentric needle electrode and the department’s standard filter settings of 20Hz–10 kHz, gain of 100mV/division, and sweep speed of 10 ms/division. In all patients, biceps brachii, vastus medialis, and anterior tibial muscles were examined. Examination of other muscles was included to the diagnostic workup when necessary. The presence of spontaneous activity was assessed at 10 separate sites. Quantitative motor unit potential (MUP) analysis was done by sampling at least 20 MUPs during weak voluntary contraction. Mean duration, amplitude, and percentage of polyphasic potentials were evaluated. The mean MUP duration was calculated for the simple potentials. The results were compared with laboratory reference material.

Laboratory tests

In all patients, routine blood tests including vitamin B12, hemoglobin A1c (HbA1c), and thyroid-stimulating hormone (TSH) levels, erythrocyte sedimentation rate (ESR), and creatinine kinase (CK), myoglobin, and lactic dehydrogenase (LDH) levels in the long-term COVID-19 period were performed. Vitamin D levels were examined in all but one patient.

Myositis autoantibodies were examined in a panel including Mi-2 alpha, Mi-2 beta, TIF1 gamma, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, and Ro-52.

Muscle biopsy and histopathological tests

In all adult patients, a percutaneous conchotome skeletal muscle biopsy was taken from biceps brachii muscle, whereas in a 15-year-old girl the biopsy was taken with a Bergstrom 2-mm needle.
biopsy needle from quadriceps femoris muscle. Specimens were processed for paraffin embedding, frozen sectioning, and epoxy embedding for electron microscopy. Immunohistochemistry was performed on a Ventana Benchmark Ultra platform. Paraffin sections of 2 μm were used for CD3 (Ventana, 2GV6, RTU), CD8 (Dako, Agilent, C8/144B, 1:200), CD68 (Ventana, KP-1, RTU), myosin heavy chain slow (Novocastra, WB-MHCs, 1:50), and myosin heavy chain fast (Sigma-Aldrich, MY32, 1:8000), whereas 5-μm cryosections were used for human leukocyte antigen ABC (HLA-ABC; Dako, Agilent, W6/32, 1:100). In enzyme histochemistry for cryosections were used for human leukocyte antigen ABC (HLA-ABC expression was seen in seven cases, ranging from a weak to prominent macrophage reaction was also present. Muscle fiber degeneration was found in seven biopsies. Five of these showed many nuclei with large nucleoli indicating activity, and oxygen in the acute phase: none of the other patients needed oxygen supplementation. None of the patients had comorbidity for neuromuscular disease. Neurophysiological examination and muscle biopsy were performed 5–14 months (median = 10) after initial symptoms of acute COVID-19 (Figure 1).

RESULTS

Participant demographics

Patients had a median age of 48 years (range = 15–68), 13 (81%) were female, and the median body mass index was 24.4 (range = 18.3–46.2). During the acute COVID-19 infection, no patients had been critically ill or had received treatment in an intensive care unit. Only six patients (37.5%) had been hospitalized, three patients for 1 day, two patients for 3 days, and one patient for 10 days. One patient who was hospitalized for 10 days was treated with remdesivir, dexamethasone, and oxygen in the acute phase: none of the other patients needed oxygen supplementation. None of the patients had comorbidity for neuromuscular disease. Neurophysiological examination and muscle biopsy were performed 5–14 months (median = 10) after initial symptoms of acute COVID-19 (Figure 1).

Clinical characteristics

All patients had muscle fatigue during the acute infection and as a long-term COVID-19 symptom. Myalgia was reported during acute infection in 13 patients, whereas no information was found in the files of the remaining three patients. Myalgia was a long-term symptom in 81% of the patients. There was symmetrical proximal muscle weakness in shoulder abduction and hip flexion in 44%. The muscle strength according to Medical Research Council (MRC) grading system was 4. In one patient (Patient 15), there was also muscle weakness in distal muscles (Figure 1), and in the muscles EMG was performed (biceps brachii, vastus medialis, and tibialis anterior; MRC = 4). None of the other patients had muscle weakness in these muscles. In addition to the myopathic complaints and findings, headache (81%), cognitive complaints (81%), dyspnea (88%), and paresthesia (69%) were common long-term symptoms. All patients had normal deep tendon reflexes and preserved vibratory sensation, including the patients with paresthesia.

Neurophysiological examinations

Sensory and motor nerve conduction studies were normal. None of the patients showed spontaneous activity in any of the examined muscles. In 12 patients, MUP analysis showed definite myopathic changes with shortened MUP duration with or without decreased amplitude or increased number of polyphasic potentials in two or more muscles, and the findings were interpreted to be consistent with myopathy. In the remaining four patients, there was shortened MUP duration in only one muscle in two patients, and in two patients EMG examination was either normal or there were only unspecific changes such as increased number of polyphasic potentials (Figure 1). In all patients with myopathic MUP analysis, interference pattern was also myopathic, with full pattern and low amplitude.

Laboratory tests

One patient (Patient 10) had a CK value just above the upper limit of normal. All other patients had normal routine blood tests results, including vitamin B12, HbA1c, ESR, CK, LDH, and TSH levels. Myositis autoantibodies were normal in all except one patient (Patient 2), who expressed TIF1 gamma autoantibody.

Muscle histopathology

All biopsies displayed some types of change (summarized in Figure 1). None of the biopsies showed necrotic fibers, but degenerative changes were common. In six, we found atrophic fibers seen as small fibers with fragmented fibrils (Figure 2a,i), and excess of basal lamina material (Figure 2b). Immunohistochemistry showed three with type 2 atrophy, one with predominantly type 1, and two with mixed type atrophy. Nuclear aggregates as a sign of atrophy were also present (Figure 2f). In nine cases, there were signs of fiber/sarcosomal damage seen as basal lamina duplications (Figure 2c–f). In two cases (Patients 6 and 14), this finding was very pronounced, with many sites having multiple basal lamina layers.

In 10 biopsies, we found ultrastructural indication of fibrillar disorganization (Figure 2g–i), most frequently foci with Z-band streaming, and 10 biopsies presented signs of mitochondrial involvement as COX-negative fibers (Figure 2j), abnormal mitochondrial structure (Figure 2k), or larger subsarcolemmal mitochondria accumulations (Figure 2l).

Regenerative signs were discrete. In all biopsies, the muscle fibers showed many nuclei with large nucleoli indicating activity, and basophilic regenerating fibers were found in seven biopsies. Five displayed central nuclei.

In five cases, small T-lymphocyte infiltrates were present (Figure 3a–f). However, only few CD8-positive, cytotoxic T lymphocytes were present. In one of these, Patient 14 (Figure 3d–f), a prominent macrophage reaction was also present. Muscle fiber HLA-ABC expression was seen in seven cases, ranging from a weak
staining of the muscle fiber membrane to a more intense expression including the cytoplasm (Figure 3h,i). Eight cases were negative for muscle fiber HLA-ABC presentation. Coinciding with inflammation, we found hyperplastic fibroadipogenic progenitor cells (FAPs; Figure 4d,f,g).

In 12 biopsies, we observed increased amounts of capillary basal lamina material as increased thickness of the membrane (Figure 4a), as multiple layers (Figure 4a,d), or as disruption of the membranes (Figure 4f). Particularly, multiple layers were found in the cases where multiple layers were also seen in relation to muscle fibers (Figure 4d). Empty capillary basal membranes were found in three cases, indicating capillary loss. Degeneration of pericytes was found in two cases (Figure 4e). Thrombocyte adhesion (Figure 4b) was seen in three biopsies, and also in three biopsies, endothelial cells with prominent presence of Weibel–Palade bodies were seen (Figure 4c). In 10 biopsies, the endomysium contained increased amounts of collagen (Figure 4h,i).

In two biopsies, small nerves were present. In one, Patient 14 (Figure 4j), Schwann cells and perineurial cells showed basal lamina multiplication, as in the adjacent muscle fibers. Moreover, we found loss of unmyelinated axons in Patient 10.

Concerning overall severity of pathological changes, the two cases with the prominent muscle fiber basal lamina presentation were also among those with inflammatory infiltrates (Figure 1, Patients 6 and 14).
DISCUSSION

In our population of patients with fatigue and muscular complaints such as myalgia or proximal weakness still present up to 14 months after SARS-CoV-2, we found histopathological changes in muscle biopsies in all patients. The pathological findings ranged from mild, unspecific changes, to inflammation and signs of cell damage. Most remarkable were the two patients who after 10–13 months showed extensive basal lamina production, associated not only with muscle fibers but also with capillaries and nerves. We additionally observed mitochondrial pathology and capillary changes, the latter suggesting ongoing capillary remodeling processes. The importance of the vascular mechanisms in COVID-19 pathology has been described in previous studies [27–29]. One possible reason for the capillary degeneration could be the presence of occluding thrombocyte aggregations. Microthrombi have previously been found in acute COVID-19 [30, 31]. In this context, our finding of capillary segments with unusual accumulation of Weibel–Palade bodies, known to be
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essential for platelet adhesion [32], is interesting. Another factor could be remodeling induced by fiber atrophy.

Physical fatigue has been reported as one of the most common and disabling long-term symptoms after COVID-19 [24, 33–36]. However, fatigue is a subjective and nonspecific complaint that may go unnoticed in the presence of a heterogeneous collection of post-COVID-19-induced physical and cognitive complaints. Recently, we reported myopathic changes on quantitative EMG in association with muscular symptoms as a main cause of long-term fatigue after COVID-19 even in patients who had mild COVID-19 acute disease [26]. The main limitation of our previous study was the lack of muscle biopsies. In the present study, 12 of 16 patients (75%) presented definite myopathic changes in EMG, and all patients showed histopathological findings. Among the histopathological findings, mitochondrial and capillary changes, which can result in restricted energy supply, and inflammation can cause fatigue. Mitochondrial pathology has previously been found as a result of myopathy described, for example, in some cases of inclusion body myositis and dystrophinopathy [37, 38]. The sensitivity of EMG is less than the sensitivity of histology. Our results suggest that even if EMG seems to be a cost-effective tool for myopathy in patients with long-term symptoms after COVID-19, muscle biopsy is the best method for a definite diagnosis.

Data on skeletal muscle histopathologic alterations in patients with COVID-19 are scarce [36]. To our knowledge, the present study is the first histopathology report on post-COVID-19. The existing histopathological studies on COVID-19 are limited to case reports, critically ill patients, and mostly postmortem studies in acute COVID-19 [15–19]. In a recent study [18], Aschman and colleagues found signs of inflammatory myopathy in 26 of 43 patients (60%) who had died with a diagnosis of COVID-19. The inflammation was more pronounced in skeletal muscles than in
cardiac muscles. However, they did not find necrotic myofibers and capillary complement deposition, and the authors concluded that SARS-CoV-2 was associated with an immune-mediated myopathy, but the signs of myositis observed in that study [18] were not typical for critical illness myopathy [39]. In another study, Suh and colleagues [19] investigated psoas muscle and femoral nerve sampled from 35 consecutive autopsies of patients who died with COVID-19, and showed necrotizing myopathy in 28%, myositis in 22%, and neuritis in 28% of the autopsies. These studies support our findings in late COVID-19 disease, demonstrating predominance of mild muscle fiber abnormalities in patients without critical illness during their acute infection, both in our previous study.
and in the present study. In previous postmortem studies [18, 19], immunohistochemical staining with antibodies against SARS-CoV-2 spike protein did not yield positive results, and no overt viral particles were found by electron microscopy, probably due to a postmortem interval of approximately 6 days. However, in one study that examined the diaphragm muscle obtained from 26 consecutive autopsies of critically ill COVID-19 patients, SARS-CoV-2 RNA was found in the muscle in four cases (15.4%) [40]. Further studies are needed in skeletal muscle biopsies taken during acute infection and analyzed immediately to explore whether a direct viral infection of myofibers is the cause of myopathy in acute and long-term COVID-19. Because SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) in conjunction with transmembrane serine protease 2 and/or cathepsin L to enter host cells [41–44], the sensitivity of different tissues to infection may depend on their ACE2 expression. The mRNA expression of ACE2 has been reported to be low or none in human skeletal muscle tissue, and it is mostly produced in smooth muscle cells and pericytes [44–46]. In a recent study, the expression was higher in women than in men because of differences in fat percentage and cardiorespiratory fitness, as the percentage of body fat was the main predictor of the variability in ACE2 protein expression [46]. If muscle symptoms are a direct consequence of muscle SARS-CoV-2 infection, a female predominance would be expected, just as found in our present study (13 females and three men). The female predominance in patients reporting post-COVID-19 symptoms is well established, but the reason for this has not been clear [47].

Immunohistochemistry showed muscle fiber atrophy in 38% in our patients, in both type 1 and type 2 fibers. Although immobilization might have caused the type 2 atrophy in some patients, none of our patients was critically ill or confined to bed, and type 1 atrophy cannot be explained by immobilization.

One of the most prominent findings in our patients was basal lamina duplications. It has previously been shown that basal lamina components can be found in serum of post-COVID-19 patients with lung symptoms, indicating a long-term basal lamina involvement [48]. Smaller duplications of muscle fiber basal lamina are signs of previous membrane damage. Most remarkable were the two patients who after 10–13 months showed extensive basal lamina production, associated not only with muscle fibers but also with capillaries and nerves. The interstitial fibroadipogenic progenitor cells are major providers of basal lamina components and are widely distributed in close relation to all the structures in skeletal muscle [49]. These cells were in many cases in the present study found activated, including in these two patients. Several of our patients showed indication of inflammation, and neuritis has also been previously described as part of the acute COVID-19 infection [19]. Such chronic low-grade inflammation is accompanied by increased tumor necrosis factor β (TGFβ) levels, and it has been suggested that increased TGFβ levels induce the production of basal lamina [50]. The microenvironment in the muscle of long-term-affected COVID-19 patients thus includes several factors that could be responsible for an upregulated production of basal lamina.

Our study shows a wide range of structural myopathic changes, an observation that could be due in part to differences in duration of the post-COVID-19 condition. Although the pathology includes fiber damage, mitochondrial changes, inflammation, and capillary injury, all of which can cause fatigue, there is no unambiguous indication of whether the observed muscle damage is the result of viral infection of muscle, immune-mediated or microvascular mechanisms, toxic effect of cytokines, or another mechanism. However, we firmly believe that our findings will catalyze further initiatives and studies to identify treatments to handle these debilitating symptoms. An additional concern is the demonstration of FAP activation and the resulting collagen accumulation, because development of significant fibrosis could counteract rehabilitation [36]. The socioeconomic burden of the long-term symptoms, including excessive fatigue and inability to live normal and independent lives, is substantial. Knowledge on symptoms creates the basis for better handling and for discovering new treatments, something that is eminently needed.

Our study has limitations. First, our cohort is small, and including more patients could have led to identification of other pathologica abnormalities. Second, we only included patients with fatigue, and most of our patients had myopathic changes on EMG. Although we had patients without myopathic changes on EMG but histopathologic changes, this needs to be confirmed in more patients. Additionally, we had a wide range for the duration from acute infection. A more homogenous group might have shown more uniform findings in muscle biopsy, and a larger cohort a temporal development. Nevertheless, we could not show a common mechanism or a pattern that could suggest any relation with disease duration. Another main limitation of our study is the lack of a control group of asymptomatic patients after SARS-CoV-2 infection.

Finally, we have investigated only patients from the initial phase of the pandemic, indicating that their infection is due to the original SARS-CoV-2. Further studies are needed to explore whether the new variants cause long-term COVID-19 as frequently as the original SARS-CoV-2. Because most of our patients had a mild–moderate acute affection, the new variants that might cause less severe acute disease could still have the ability to cause long-term myopathy. As prolonged muscle symptoms and fatigue are disabling, it is important that this is addressed by further studies that relate post-COVID-19 disorders with the specific SARS-CoV-2 variants.

AUTHOR CONTRIBUTIONS

Eva K Hejbol: Data curation (equal); methodology (equal); writing – review and editing (equal). Thomas Harbo: Conceptualization (equal); data curation (equal); investigation (equal); writing – review and editing (equal). Jane Agergaard: Conceptualization (equal); data curation (equal); writing – review and editing (equal). Line B. Madsen: Data curation (equal); methodology (equal); writing – review and editing (equal). Thomas H. Pedersen: Conceptualization (equal); writing – review and editing (equal). Lars J Østergaard: Conceptualization (equal); funding acquisition (equal); writing – review and editing (equal). Henning Andersen: Conceptualization (equal); writing – review and editing (equal). Henrik Daa Schröder: Data curation (lead);
investigation (equal); methodology (lead); writing – review and editing (equal). Hatice Tankisi: Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); writing – original draft (lead).

ACKNOWLEDGMENTS
This work was supported by the Novo Nordisk Foundation (grant NNF21OC0066984) and the Independent Research Fund Denmark (grant 9039-00272B). Open access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST
None of the authors has any conflict of interest to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Hejbøl EK, Harbo T, Agergaard J, et al. Myopathy as a cause of fatigue in long-term post-COVID-19 symptoms: Evidence of skeletal muscle histopathology. *Eur J Neurol*. 2022;29:2832-2841. doi: [10.1111/ene.15435](10.1111/ene.15435)
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- Identify PD patients inadequately controlled on oral medications
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PD: Parkinson’s Disease