SARS-CoV-2 myopathy

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Since the occurrence of the first infection with SARS-CoV-2 in December 2019, increasing evidence accumulated that not only the lung but also other organs, including the central nervous system (CNS) and the peripheral nervous system (PNS), can be involved in the infection [1,2,3]. Involvement of the PNS in SARS-CoV-2-infected patients includes Guillain-Barre syndrome (GBS) [4,5], myasthenia gravis (MG) [6,7], myositis [8], myalgia [9], rhabdomyolysis [10,11,12], muscle wasting [13], and critical-ill myopathy [14,15]. Here we summarise and discuss recent findings concerning the involvement of the striated muscle in the infection.

Muscle involvement was first described in a retrospective study of 214 Chinese patients [16]. In this study, 23/214 (10.7%) of the patients were reported with “skeletal muscle injury” [16]. No specific investigations were carried out to further specify the type and pathophysiology of muscle injury, why the cause remained unclear [16]. In a study of 41 infected Chinese patients, 18 (44%) patients reported myalgia and fatigue [9]. In all these patients myalgia was present already at onset of the infection [9]. Seven patients required ICU care and 11 did not [9]. In a study of 138 infected Chinese patients, myalgia was reported by 48 (34.8%) patients [17]. Creatine-kinase (CK) was normal in most of these patients [17]. In a retrospective European study of 1420 infected patients, myalgia was found in 887 (62.5%) patients [18]. In a study of 1099 Chinese patients myalgia and fatigue were reported in 164 (14.9%) participants [19]. However, CK-elevation >200U/l was detected in only 90/657 (13.7%) tested patients [19]. In an US study on 1150 SARS-CoV-2-infected patients, 67 (26%) complained about myalgia [20]. CK-elevation was noted in some patients, without reporting the exact number [20]. Among 99 Chinese patients, 11 (11%) complained about “muscle ache” [21]. In a retrospective study of 27 pediatric patients with multisystem SARS-CoV-2
infection, four developed muscle weakness of whom three had a myogenic electromyography (EMG) [22]. All these studies did not mention how often muscle symptoms had been recognised already prior to the infection and none of these patients was prospectively investigated for primary or secondary muscle disease.

Specific myopathies have been particularly reported in single patients (table 1). Myositis has been reported in 13 patients (table 1). In a 58yo female with limb weakness and ptosis, CK-elevation, and fibrillations, myositis was diagnosed upon muscle biopsy [8]. In a 38yo Chinese male with myalgia and CK-elevation, SARS-CoV-2-associated myositis with rhabdomyolysis was diagnosed upon EMG and muscle biopsy [23]. SARS-CoV-2-associated myositis and rhabdomyolysis was also reported in another male based upon muscle MRI [24]. In a case series of 10 SARS-CoV-2-infected patients from Brazil, minimal invasive, ultrasound-guided, post-mortem studies revealed that 60% of the patients had features of myositis and 80% displayed necrotic muscle fibers on autopsy [25]. Additionally, rhabdomyolysis was reported in five other patients [10,11,12,26,27]. In one of these patients CK-elevation reached a value of >400000 (table 1) [11]. In all five patients did pulmonary manifestations occur simultaneously or preceded the onset of muscle symptoms.

The causes of muscle damage in SARS-CoV-2-infected patients are quite heterogeneous. Myopathy could be explained by infection with the virus (myositis), by immune-mechanisms (immune myositis), by electrolyte disturbances, critical ill myopathy due to treatment on the ICU, drug side effects, or hypoxia. Muscle manifestations may be particularly due to application of myotoxic drugs given for treatment of the infection, such as steroids, statins, chloroquine, lopinavir, ritonavir or atazanavir or due to interactions between drugs applied [28]. Myositis may be due to secondary T-cell mediated injury, due to generation of myositis specific antibodies, or due to generation of pro-inflammatory mediators, such as IL-6, MCP-1, or TNF-α.

Myalgia in infected patients can be due to rhabdomyolysis, edema, electrolyte imbalances, or due to immune-mediated myositis [25].
a recent review it has been concluded that myopathy in SARS-CoV-2-infected patients is rather related to damage via immune mechanisms due to massive cytokine release than direct invasion of the virus into muscle tissue [29]. Myalgia due to myositis is frequent during infections with influenza-A, influenza-B, or enterovirus. Whether the infection unMASKS previously unrecognized muscle disease or truly induces muscle disease in a previously normal muscle remains speculative but there are indications that SARS-CoV-2 truly damages the skeletal muscle in many patients.

Overall, the striated muscles are frequently affected in patients with SARS-CoV-2 infection but, in the majority of the cases, muscle involvement is non-specific, manifesting as myalgia (11-62% of cases), fatigue, weakness, or wasting. Only rarely a specific muscle disease, such as myositis, is diagnosed. Since work-up of muscle involvement in the infection is usually incomplete, the causes of muscle disease remain unsolved in the majority of the cases. Muscle damage in SARS-CoV-2-infected patients can be immune-mediated, due to electrolyte-disturbances, a complication of sepsis, bed-rest, adverse reaction to drugs, or due to hypoxia. Rhabdomyolysis requires close monitoring of muscle enzymes and renal function parameters, and treatment with fluids, diuretics, or hemodialysis in case of renal failure respectively analgesics in case of muscle pain.

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Table 1. SARS-CoV-2-infected patients with muscle involvement so far reported

| NOP | Age | Sex | Symptoms        | Signs | CK (U/l) | MG | EMG | MB |
|-----|-----|-----|-----------------|-------|----------|----|-----|----|
| 887 | nr  | nr  | myalgia         | nr    | nr       | nr | nr  | nr |
| 164 | nr  | nr  | myalgia, fatigue| nr    | >200 in 90| nr | nr  | nr |
| 67  | nr  | nr  | myalgia         | nr    | nr       | nr | nr  | nr |
| 48  | nr  | nr  | myalgia         | nr    | normal   | nr | nr  | nr |
| 23  | nr  | nr  | muscle injury   | nr    | nr       | nr | nr  | nr |

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| Patient | Gender | Age | Weakness | CK | EMG | NOP | Diagnosis |
|---------|--------|-----|----------|----|-----|-----|------------|
| 18      | nr     | nr  | myalgia  | nr | nr  | nr  | nr[9]     |
| 11      | nr     | nr  | myalgia  | nr | nr  | nr  | br[21]    |
| 10      | nr     | nr  | nr       | nr | nr  | nr  | myositis  |
| 5       | nr     | nr  | myalgia  | nr | nr  | nr  | nr[30]    |
| 4       | 8-15   | 2m, 2f | weakness | nr | nr  | nr  | myogenic  |
| 1       | 60     | m   | weakness | tenderness | 11842 | >12000 | nr  | nr[22]    |
| 1       | 58     | f   | weakness | PT, DTR | 700   | nr   | fibrillations | myositis |
| 1       | 36     | f   | weakness | PT   | nr   | nr   | nr[7]     |
| 1       | 42     | f   | weakness, DV, DP | weakness | nr | nr | nr | nr[6] |
| 1       | 71     | m   | weakness, myalgia | none | 8720 | 2079 | nr | nr[10]    |
| 1       | 16     | m   | myalgia, fatigue | tenderness | 427656 | 45µg/L | nr | nr[11] |
| 1       | 38     | m   | myalgia | normal | 42670 | nr | nr | nr[23] |
| 1       | nr     | m   | myalgia, weakness | weakness | 25384 | nr | nr | nr[24] |
| 1       | 49     | m   | myalgia | normal | 22740 | nr | nr | nr[26] |
| 1       | 38     | m   | myalgia | nr | 33000 | nr | nr | nr[27] |

CK: creatine-kinase, DP: dysphagia, DTR: diminished tendon reflexes, DV: double vision, EMG: electromyography, MB: muscle biopsy, MG: myoglobin, NOP: number of patients, nr: not reported, PT: ptosis