Neurological Manifestations in Severe Acute Respiratory Syndrome

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Abstract- During the worldwide outbreak of severe acute respiratory syndrome (SARS) in 2002-2003, there were 664 probable SARS patients reported in Taiwan. SARS patients usually present with symptoms related to the respiratory system while neurological manifestations have rarely been described. There were three patients who developed axonopathic polyneuropathy 3-4 weeks after onset of SARS; their clinical condition and electrophysiological studies revealed obvious improvement at follow-up. Two SARS patients have experienced myopathy and three other patients developed rhabdomyolysis. These neuromuscular disorders in SARS patients were considered as critical illness neuropathy and myopathy, but the possibility of direct attack by SARS coronavirus on the nerve and muscle could not be excluded. Large artery ischemic stroke were described in five SARS patients with poor prognosis. Multiple factors contributed to this vascular insult included hypercoagulabe status related to both SARS coronavirous and the usage of intravenous immunoglobulin, septic and cardiogenic shock, and possible vasculitis. The relationship between SARS and above neurological problems still needs further clarification. Pathological and microbiological studies are mandatory to delineate this issue.

Key Words: SARS, Polyneuropathy, Myopathy, Cerebral infarct, Coronavirus

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INTRODUCTION

During the worldwide outbreak of severe acute respiratory syndrome (SARS) from Nov 2002 to July 2003, 8422 SARS patients have been reported around the world[(1)]; 664 patients contracted the illness in Taiwan[(2)]. SARS patients usually presented with fever, nonproductive cough, dyspnea, generalized malaise, and diarrhea with high mortality due to respiratory distress[(3-5)]. Although some drugs have been proposed to treat SARS, none of them has been proved effective and the major therapeutic process seems to be supportive[(6)].

SARS is associated with a novel coronavirus infection[(7-9)]. The coronavirus group is a large group of enveloped RNA virus that can cause respiratory and enteric diseases in animals and humans[(10)]. Among the coronavirus-induced animal diseases, infection with feline infectious peritonitis virus, mouse hepatitis virus,

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and hemagglutinating encephalomyelitis virus can be complicated by encephalitis[10,11], however, whether coronavirus can directly attack the nervous system is not clear.

Up to present, neurological problems in SARS patients have been described in four formal reports, including polyneuropathy, myopathy and rhabdomyolysis, and large artery ischemic stroke[12-15]. These neurological problems mostly developed 2 to 4 weeks after onset of SARS. In this review, we summarized the presentations and discussed the mechanisms of neurological manifestations in SARS patients.

POLYNEUROPATHY

Tsai et al have reported three SARS patients complicated with sensorimotor peripheral nerve disorders[13]. All of them have received intubation for respiratory distress and high dose of steroid therapy for multiple organ failure. They developed distal-predominant weakness in all four limbs with mild decrease in deep tendon reflexes 3 to 4 weeks after onset of SARS. Parasthesia and hypesthesia in the distal limbs were also complained. Nerve conduction velocity (NCV) studies revealed reduced amplitudes of compound muscle action potential, with no evidence of slowing of nerve conduction velocity, prolonged distal motor latency, conduction block, or temporal dispersion. Electromyography (EMG) studies showed acute denervation change with increased polyphasia. These findings were consistent with motor-predominant axonal polyneuropathy. CSF studies in two patients disclosed normal protein level without pleocytosis and negative results for coronavirus antibody determination. Clinical and electrophysiological follow-up 3-7 weeks later showed obvious improvement in all of them.

All the above three SARS patients have undergone intubation, received high-dose steroid and hospitalized in intensive care unit for multiple organ failure. In such a situation, a diagnosis of critical illness polyneuropathy (CIP) was made[13]. CIP, which usually develops during treatment of severe illness with sepsis and multiple organ failure, is a motor-predominant, acute distal neuropathy[16-20]. CIP is monophasic and self-limited, and usually recovers within weeks after the general condition is under control[16,20,21]. NCV and EMG findings in CIP are compatible with those in axonal neuropathies[17-19,20,22]. Considering the serious and protracted nature of SARS, a systemic inflammatory response syndrome (SIRS) can reasonably be applied in these SARS patient. Factors mediating systemic inflammatory response syndrome such as tumor necrosis factor α and nitric oxide are recognized also possibly responsible to cause CIP[17], therefore, peripheral nerve disorder in SARS should be considered as a CIP associated with SARS-related systemic inflammatory response syndrome.

Any possible mechanisms other than CIP should also be considered when confronting a virus-related neuropathy. A viral infection can also cause lesions of the peripheral nervous system (PNS) through postinfectious immune reaction in or direct attacks on the nerves or ganglia[23]. Guillain-Barre syndrome (including acute inflammatory demyelinating polyneuropathy, acute motor sensory axonal neuropathy, and other analogues) are those catastrophic immunological reaction on the PNS. However, the clinical, laboratory and electrophysiological findings in SARS-related neuropathy did not favor a diagnosis of Guillain-Barre syndrome[13]. Varicella-zoster virus[24], cytomegalovirus[25,26], and human immunodeficiency virus (HIV)[25,27] are known able to cause direct PNS damage. Whether direct attacks of PNS exist in SARS-related neuropathy is not known. Further investigations are necessary to delineate the basic mechanisms of SARS-related neuropathy.

MYOPATHY AND RHABDOMYOLYSIS

In a review of clinical usages of intravenous immunoglobulin (IVIG) in neuromuscular diseases, Engel briefly mentioned an aged-physician suffered from a radiologically-proved atypical pneumonia after returning from a trip to China[28]. Several weeks later, the patient developed respiratory distress syndrome and required mechanical ventilation. At the same time, he also had diffuse muscle weakness. Both the weakness and pneumonia responded surprisingly well to IVIG

therapy. Engel thought that he had treated a possible lesion of atypical pneumonia in SARS. Despite lack of detailed information, this may be the first report on muscle disorders related to SARS.

There were 2 SARS patients undergoing detailed neurological examination and proved to have myopathy 3-4 weeks after the onset of SARS[13]. The first patient had been intubated and received treatment in intensive care unit for respiratory distress and multiple organ failure. The second patient was treated in general medical ward without intubation. Both of them had received a large amount of methyprednisolone therapy with accumulation doses of 2520 mg and 1400 mg, respectively. Cisatracurium, a neuromuscular blockade, was also given in the first patient, too. In addition to diffuse limb weakness, there were also elevated serum creatine kinase (CK) levels and myopathic changes on EMG study. Their muscle powers improved remarkably within 2-3 weeks. According to the medication history and clinical features of their muscle weakness, the authors made a diagnosis of critical illness myopathy (CIM). To prevent CIM, the authors suggested that current standard treatment for SARS with high-dose or pulsed methyprednisolone might need modification.

Wang et al observed rhabdomyolysis in three patients with probable SARS[15]. All 3 patients had a markedly elevated serum CK level (9050, 339750, and 7659 U/L, respectively). Detailed neurological examinations were not performed. High-dose intravenous methylprednisolone had been given before development of rhabdomyolysis. Muscle specimes from two patients revealed necrotic muscle fibers, basophilic change of sarcoplasm, and centrally located nuclei but no inflammatory cell infiltration. Two patients passed away from multiple organ failure, while the other gradually recovered from acute renal failure and respiratory distress.

Viral infections can sometimes cause rhabdomyolysis, most notably influenza virus A and B[29], HIV[30], coxsackie virus[31], cytomegalovirus[32], West Nile virus[33], and dengue virus[34]. Among them, rhabdomyolysis related to influenza-associated myositis has been well described[29]. The mechanism for muscle damage during viral infection is still poorly understood. Two most commonly proposed mechanisms are direct muscle invasion by viral particles and immune-mediated muscle damage triggered by the virus[29]. Since specimens of muscle biopsy from these 2 SARS patients with rhabdomyolysis did not show evidence of inflammatory cell infiltration, an immune-mediated muscle damage may be less likely. However, there is still no enough evidence of direct invasion of SARS coronavirus into the muscle cells.

CEREBRAL INFARCTION

Of 206 SARS cases in Singapore, five patients (two men, three women, age ranged 39 to 68 years) developed cerebral infarction[12]. Only two patients had stroke risk factors. Cerebral infarct was apparent on brain CT or at autopsy. Two patients had an infarction area involving the territories of more than two large cerebral arteries. Other thrombotic events such as acute myocardial infarction and disseminated intravascular coagulation were noted in 3 cases and generalized hypotension before onset of stroke in 4 patients. Their prognosis was extremely poor (three died and one bedridden). The authors postulated that these large infarctions resulted from a hypercoagulabe state in tandem with factors such as systemic hypotension and cardiac dysfunction.

SARS patients seemed to be susceptible to thromboembolic events. About one third of critical-ill SARS patients developed deep vein thrombosis or pulmonary embolism[35]. In an autopsy study of SARS patients, infarction has been recognized in the brain, heart, kidney, and spleen[36]. In addition, pulmonary thromboemboli within the main pulmonary artery or segmental pulmonary arteries were found in 4 of 8 autopsy specimens[36]. Micro-thrombosis in the pulmonary capillaries and intracardial or widespread intravascular thrombi have also been noted[36-39].

Infection with some viruses, such as HIV[40], herpes simplex virus[41], cytomegalovirus[42], Epstein-Barr virus[43], and Japanese encephalitis virus[44], is known to be associated with hypercoagulibility. The proposed mechanisms for such a hypercoagulable state included: presence of antiphospholipid-anticardiolipin antibodies, decreased activities of natural anticoagulants (especially

protein S), and enhancement of thrombin formation and platelet activation[40,41,45]. However, the actual mechanisms for SARS-related cerebral infarction are not clear.

IVIG therapy has been advised and widely used in SARS patients[46]. A thromboembolic event such as stroke or TIA is an uncommon complication related to IVIG treatment[47,48]. IVIG infusion can induce high levels of immunoglobulin G, immune complex formation, increased platelet aggregation, and elevated blood viscosity[49,50]. The risk of IVIG-induced thromboembolic complications is increased in patients with pre-existed high blood viscosity, hypercoagulable status, impaired cardiac output, etc[49,51]. In addition, combined use of IVIG and corticosteroids would play a synergistic role in thrombosis development[52]. IVIG therapy (with or without methylprednisolone) seemed to play an important role in SARS-related cerebral infarction.

Some viruses such as varicella-zoster virus[53], HIV[54] and hepatitis C virus[55] may cause vasculitis which in turn is able to induce cerebral stroke. The equine arteritis coronaviruses can cause lymphocytic infiltration, necrosis of smooth muscle and occlusion of vessel wall (cited in 12). Systemic vasculitis has been found in SARS patients at autopsy[39]. However, the possibility of SARS-related stroke through a mechanism of vasculitis is still unknown.

CONCLUSION

Figure summarizes the proposed mechanisms of neurological manifestations in SARS patients. Polyneuropathy, myopathy, and rhabdomyolysis may result from systemic inflammatory response syndrome secondary to critical illness or high dose steroid, while the pathogenetic role of direct attack of SARS coronavirus on the peripheral nerves and muscles could not be excluded. Multiple factors of cerebral infarct in SARS patients included: hypercoagulabe status related to both SARS coronavirous and the usage of IVIG, septic and cardiogenic shock, and possible viral vasculitis. Because of small reported case number of SARS patients with neurological presentations, the clear pathogenesis of these neurological problems in SARS could not be well clarified. We should pay attention to these neurological manifestations in the face of SARS in the future.

There are few disorders that spare the nervous system[56] and neurologists should more actively pay attention to a newly rising disease, especially its neurological

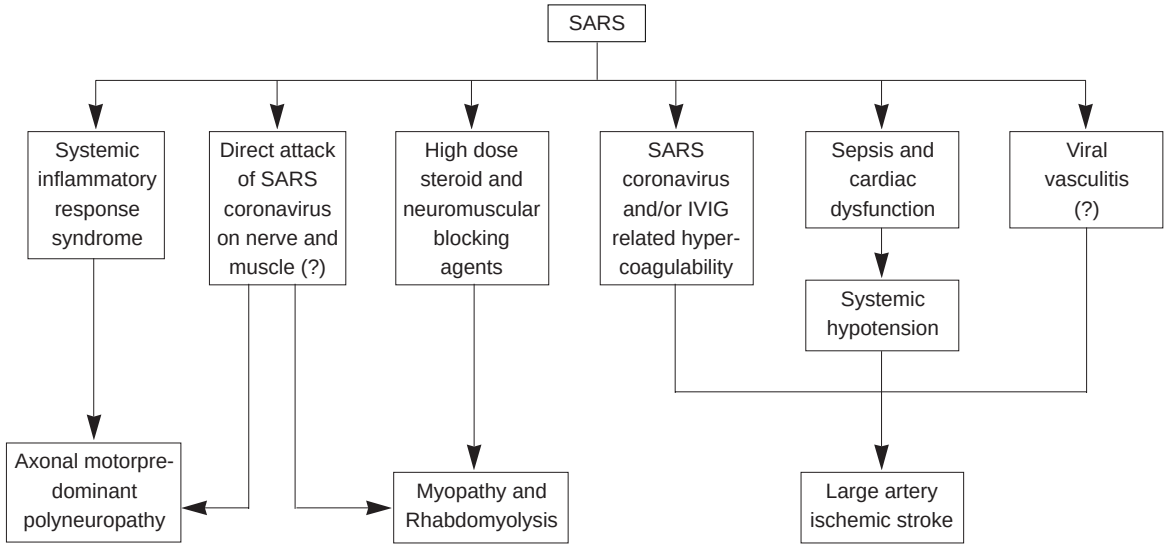

Figure. Proposed pathogenesis of neurological problems in severe acute respiratory syndrome. SARS: severe acute respiratiory syndrome; IVIG: intravenous immunoglobulin.

manifestations and complications. We believe that much more neurological problems related to SARS would be found and described if neurologists could participate in the clinical investigations of SARS patients from the very beginning.

After reviewing the SARS-related neurological problems, we suggest: (1) rhabdomyolysis may be an important clinical feature of SARS and SARS patients should receive regular examination of serum CK level during the acute phase; (2) to avoid CIM, current standard treatment with high-dose methylprednisolone for SARS might need further modification if possible; (3) SARS may be associated with hypercoagulibility and prophylactive use with antiplatelets or anticoagulant to prevent strokes might be considered; (4) because of risks to develop thromboemboli, IVIG for SARS patients should be given with precaution, preferably a smaller dose at lower rates; (5) further pathological and microbiological studies are mandatory to investigate the possibility of direct attack of SARS coronavirus on the nerves and muscles as well as SARS-related vasculitis.

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