Letters to the Editor

Case Report: Need for Vigilance in Recognizing Neurologic Presentations of COVID-19

To the Editor: Case reports and clinical studies have suggested neurologic consequences of severe acute respiratory syndrome coronavirus 2 infection—most commonly headache, anosmia, and ageusia—in addition to the more well-recognized respiratory findings. Other manifestations include stroke, impairment of consciousness, coma, seizure, and encephalopathy.[1] An early case series from Wuhan, China, identified neurologic features in 78 of 214 patients (36.4%) who were diagnosed with coronavirus disease 2019 (COVID-19),[2] and a systematic study in France found neurologic signs in 49 of 58 patients (84.4%), including abnormalities in magnetic resonance imaging (MRI) and cerebrospinal fluid.[3] In a case-control study, COVID-19 was implicated as an independent risk factor for acute ischemic stroke (odds ratio [OR] = 3.9).[4] Another study demonstrated an association between COVID-19 and large vessel occlusion strokes (OR = 2.4).[5]

An 88-year-old woman with a history of hypertension, pulmonary embolism (receiving apixaban [Eliquis]), hypothyroidism, and chronic kidney disease presented with three hours of slurred speech, dizziness, and blurred vision. On arrival, her symptoms improved, and she was afebrile. She denied experiencing fever, chills, cough, dyspnea, chest pain, nausea, or vomiting. Computed tomography (CT) of the brain, CT angiography of the head and neck, and an MRI of the brain showed no acute findings. Findings on chest radiography and laboratory tests, including urinalysis, were within normal limits. She was monitored overnight with complete symptom resolution and was diagnosed with a transient ischemic attack.

Seven hours after discharge, she returned to the emergency department with slurred speech, confusion, dizziness, and syncope. Vital signs, including orthostatic vital signs, and test results, including vitamin B_{12} and folate, were within normal limits. A repeat chest radiograph and CT of the head showed no acute findings. Shortly after arrival, her symptoms returned to baseline. Echocardiography showed a normal ejection fraction. Electroencephalography was normal.

On day 4 after the initial presentation, she developed vomiting. A COVID-19 polymerase chain reaction test was positive. She subsequently developed a temperature of 100.3°F (37.9°C). By day 7, she was afebrile, tolerating food, and was discharged.

In people presenting with neurologic signs and symptoms, COVID-19 may be overlooked as a possible underlying etiology, delaying appropriate treatment and potentially contributing to high-risk exposures for staff and other patients. Twenty-four staff members treated this patient before COVID-19 was diagnosed. However, no viral transmission occurred due to universal precautions (surgical mask and eye covering) among staff, emphasizing the importance of personal protective equipment in treating all patients regardless of symptoms.

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References

1. Zubair AS, McAlpine LS, Gardin T, et al. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019. *JAMA Neurol.* 2020;*77*(8):1018-1027.
2. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;*77*(6):683-690.
3. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med.* 2020;382(23):2268-2270.
4. Belani P, Schefflein J, Kihira S, et al. COVID-19 is an independent risk factor for acute ischemic stroke. *AJNR Am J Neuroradiol.* 2020;41(8):1361-1364.
5. Kihira S, Schefflein J, Mahmoudi K, et al. Association of coronavirus disease (COVID-19) with large vessel occlusion strokes: a case-control study. *AJR Am J Roentgenol.* 2020;1-6. ■

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This series is coordinated by Kenny Lin, MD, MPH, deputy editor.

Case Reports: Rhabdomyolysis Associated with COVID-19

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To the Editor: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has caused a global health crisis. COVID-19 can present with a variety of complications during the course of infection. Rhabdomyolysis is characterized by muscle necrosis and the release of intracellular muscle constituents into the systemic circulation. A prompt diagnosis is a prerequisite for successful treatment and avoiding complications.

TABLE 1

Clinical Characteristics of Patients with COVID-19 and Rhabdomyolysis

Characteristics	Case 1	Case 2	Case 3	Case 4
Age (years)	54	54	34	71
Sex	Male	Male	Male	Male
Race	Hispanic	White	White	Black
Medical history	Asthma, diabetes mellitus, hypertension, obesity	None	Obesity, prediabetes,	Hypertension, schizophrenia, seizures
Presenting signs and symptoms	Cough, SOB, fever	Myalgias, fever, cough, SOB	Fever, cough, SOB, weakness	Fever, cough, SOB
CK on presentation (U per L/μkat per L)	4,590 (76.65)	3,068 (51.24)	623 (10.40)	5,498 (91.82)
Peak CK total/corresponding day	7,337 (122.53)/4	3,068 (51.24)/1	5,454 (91.08)/4	10,247 (171.12)/3
Potassium (mEq per L) on presentation	5.0	3.9	3.6	3.8
Phosphorus (mg per dL/mmol per L) on presentation	3.6 (1.16)	ND	2.8 (0.90)	5.5 (1.78)
Creatinine (mg per dL/μmol per L) on presentation	0.7 (61.88)	1.1 (97.24)	0.89 (78.68)	4.1 (362.44)
Acute renal replacement therapy	No	No	Yes	No
Aspartate transaminase/alanine transaminase on presentation (U per L)	25/28	100/48	100/86	125/44
Peak aspartate transaminase/alanine transaminase (U per L)	161/59	91/231	100/86	128/120
C-reactive protein (mg per dL/mg per L)	48 (480)	2.14 (213.6)	12.89 (128.9)	30.90 (309)
Erythrocyte sedimentation rate (mm per hour)	69	111	87	73
Ferritin (ng per mL)	602	4,462	639	327
Fibrinogen (mg per dL/g per L)	ND	992 (29.16)	797 (23.43)	675 (19.84)
Outcome	Died	Discharged	Died	Died

Note: Reference ranges are CK 30 to 223 U per L (0.50 to 3.72 μkat per L), potassium 3.5 to 5 mEq per L (3.50 to 5.0 mmol per L), phosphorus 2.5 to 5 mg per dL (0.81 to 1.61 mmol per L), creatinine 0.6 to 1.30 mg per dL (53.04 to 114.92 μmol per L), aspartate transaminase 13 to 39 U per L (0.22 to 0.65 μkat per L), alanine transaminase 7 to 52 U per L (0.12 to 0.87 μkat per L), erythrocyte sedimentation rate 0 to 32 mm per hour, C-reactive protein less than 10 mg per dL (100 mg per L), fibrinogen 183 to 503 mg per dL (5.38 to 14.79 g per L), and ferritin 12 to 300 ng per mL (12 to 300 mcg per L).

CK = creatine kinase; COVID-19 = coronavirus disease 2019; ND = not done; SOB = shortness of breath.

We report on 10 patients with rhabdomyolysis associated with COVID-19 who presented to our hospital through the emergency department. COVID-19 diagnosis was made by polymerase chain reaction assay. Pertinent clinical characteristics are summarized in *Table 1*.

The median age of the participants was 55 years and all were male. Presenting symptoms included cough, shortness of breath, fever, myalgias, and confusion. None of the patients were receiving statins or other medications known to cause rhabdomyolysis or had risk factors for rhabdomyolysis. The median creatine kinase level on presentation was 4,460 U per L (74.48 μkat per L). Three patients had acute kidney injury on presentation and liver enzymes were elevated in all patients except one. Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, fibrinogen, and ferritin) were elevated in all patients. Influenza was negative in five patients and other viral causes of rhabdomyolysis (e.g., parainfluenza, enterovirus, adenovirus) were negative in four patients.[1] Eight out of 10 patients died.

Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
88	56	57	64	36	39
Male	Male	Male	Male	Male	Male
White	Hispanic	Hispanic	White	White	Black
Diabetes, hypertension	Hypertension, prediabetes	None	None	None	Hypertension
Confusion	Fever, cough, SOB	Cough, fever	Myalgias, fever, cough, SOB	Fever, cough, SOB	Myalgias, fever, cough, SOB
2,628 (43.89)	5,388 (89.98)	4,643 (77.54)	1,793 (29.94)	5,388 (89.98)	4,330 (72.31)
2,628 (43.89)/1	5,388 (89.98)/1	37,524 (626.65)/14	6,435 (107.46)/4	5,531 (92.37)/5	4,330 (72.31)/1
3.9	3.1	4.0	4.8	4.0	4.0
2.8 (0.90)	3.4 (1.10)	2.4 (0.78)	8.5 (2.75)	2.4 (0.78)	ND
2.25 (198.90)	0.8 (70.72)	1.1 (97.24)	1.01 (89.28)	1.03 (91.05)	3.8 (335.92)
No	No	No	No	Yes	No
115/60	299/170	125/44	101/80	154/111	131/65
117/63	299/170	511/153	113/79	177/101	131/65
6.76 (67.6)	9.58 (95.8)	15.4 (154)	24.7 (247)	29.7 (297)	8.5 (85)
33	81	40	34	35	43
106	836	7,500	ND	4,746	1,170
392 (11.52)	ND	760 (22.34)	559 (16.43)	784 (23.05)	ND
Died	Discharged	Died	Died	Died	Died

Acute viral infections associated with rhabdomyolysis include influenza A and B, coxsackieviruses, Epstein-Barr virus, herpes simplex, parainfluenza, adenovirus, echovirus, HIV, and cytomegalovirus.[2] Others have reported cases of rhabdomyolysis associated with COVID-19.[3,4] The pathologic mechanism leading to this complication is currently unknown. Clinicians should be aware of this life-threatening manifestation of COVID-19 so that prompt and appropriate interventions can be undertaken if it is suspected or confirmed. Further studies are needed to characterize the muscle injury consequences of SARS-CoV-2 infection.

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References

1. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine (Baltimore)*. 1982;61(3):141-152.
2. Pesik NT, Otten EJ. Severe rhabdomyolysis following a viral illness: a case report and review of the literature. *J Emerg Med*. 1996;14(4):425-428.
3. Chong WH, Saha B. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with rhabdomyolysis and acute kidney injury (AKI) [published online July 28, 2020]. *Am J Med Sci*. 2020;S0002-9629(20)30344-X.
4. Valente-Acosta B, Moreno-Sanchez F, Fueyo-Rodriguez O, et al. Rhabdomyolysis as an initial presentation in a patient diagnosed with COVID-19. *BMJ Case Rep*. 2020;13(6):e236719.

Is Cutaneous Cryosurgery the Best Treatment Option for Cutaneous Warts?

Original Article: Cutaneous Cryosurgery for Common Skin Conditions

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See additional reader comments at: https://www.aafp.org/afp/2020/0401/p399.html

To the Editor: In the Strength of Recommendation Taxonomy (SORT) table from their article, Clebak and colleagues gave a SORT Evidence Rating of B (based on inconsistent or limited-quality patient-oriented evidence) to the following recommendation, "Cryosurgery is as effective as daily treatment with salicylic acid in the treatment of plantar warts, with higher reported patient satisfaction." A randomized controlled trial was cited for this information.[1]

In the text of the article, Clebak and colleagues referred to a 2012 Cochrane review[2] that found "no difference in clearance rates in the treatment of warts comparing repeat cryosurgery with daily salicylic acid"; however, they did not mention the review in their recommendation and seemed to give precedence to the aforementioned single randomized controlled trial over a systematic review, which is an inversion of the Levels of Evidence.

The Cochrane review cited a meta-analysis (generally held to be higher level evidence than randomized controlled trials), as well as the single randomized controlled trial cited by Clebak and colleagues. The authors of the Cochrane review concluded the following: "A meta-analysis of cryotherapy versus placebo for warts at all sites favoured neither intervention nor control…One trial showed cryotherapy to be better than both placebo and [salicylic acid], but only for hand warts." The trial cited in the Cochrane review was not the randomized controlled trial cited by Clebak and colleagues, but rather an article by Bruggink and colleagues.[3]

Cryosurgery is not without risks, and high-level evidence suggesting that it is no better than placebo in a disease process that will likely resolve on its own[4] should make us reconsider whether family physicians should offer cryotherapy for cutaneous warts. I believe that the quoted statement from this article is not supported by current evidence and is misleading at best.

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References

1. Cockayne S, Hewitt C, Hicks K, et al. Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial. *BMJ*. 2011;342:d3271.
2. Kwok CS, Gibbs S, Bennett C, et al. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev*. 2012;(9):CD001781.
3. Bruggink SC, Gussekloo J, Berger MY, et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. *CMAJ*. 2010;182(15):1624-1630.
4. Sterling JC, Gibbs S, Haque Hussain SS, et al. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. *Br J Dermatol*. 2014;171(4):696-712.

In Reply: Our article attempted to provide a balanced review of the techniques, indications, contraindications, and complications of cryosurgery in common dermatologic applications. We did not specifically review the clinical question of the optimal approach to cutaneous warts.

The authors of the 2012 Cochrane review summarizing topical treatments for cutaneous warts acknowledged that the included studies were of limited quality and were at a high risk of bias.[1] Only one trial showed cryotherapy to be more effective than salicylic acid and placebo; however, this was only for warts of the hand. A Cochrane review without clear recommendation would be a SORT B, similar to a recommendation from a single, good-quality randomized controlled trial based on the SORT taxonomy.[2]

The "high level evidence" referenced by Dr. Fay represents the 2014 guidelines of the British Association of Dermatologists for the Management of Cutaneous Warts, which includes the 2012 Cochrane review that favors cryotherapy over salicylic acid treatment for warts of the hand.[3]

We encourage family physicians to include the benefits and risks of all procedures, including cryosurgery, with patients as part of an informed and shared decision-making process.

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References

1. Kwok CS, Gibbs S, Bennett C, et al. Topical treatments for cutaneous warts. *Cochrane Database Syst Rev*. 2012;(9):CD001781.
2. Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician*. 2004;69(3):548-556. Accessed June 30, 2020. https://www.aafp.org/afp/2004/0201/p548.html
3. Sterling JC, Gibbs S, Haque Hussain SS, et al. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. *Br J Dermatol*. 2014;171(4):696-712. ■