THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021), No 3, p. 16-21

CLINICAL OBSERVATION OF RARE NEUROLOGICAL COMPLICATIONS OF COVID-19: ACUTE DEMYELINATING POLYNEUROPATHY AND CRITICAL ILLNESS NEUROPATHY

Sabahgoulian C.B.[1], Manvelyan H.M.[1,2*]

[1] Department of Neurology, Astghik Medical Center, Yerevan, Armenia
[2] Department of Neurology, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

Receive 07.08.2021; accepted for printing 15.08.2021

Abstract

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has predominant clinical presentation with respiratory disease or acute pneumonia, but neurological manifestations and complications have started being reported just recently.

During recent year of pandemic more clinical reports and growing evidence proves the involvement of peripheric nervous system in COVID-19 virus induced and mediated inflammation, with threatening increase of numbers of patients with acute demyelinating polyneuropathies, or Guillain-Barré syndrome; moreover, SARS-CoV-2 has been detected in the CSF of some patients; leading to development of Critical Illness Polyneuropathies in many of patients in reanimation departments.

Careful clinical, diagnostic, and epidemiological studies must be performed to help define the manifestations and burden of neurological disease caused by SARS-CoV-2. Precise case definitions must be used to distinguish non-specific complications of severe disease (eg, hypoxic-toxic encephalopathy and/or critical illness neuropathy) from those caused directly or indirectly by the virus, including infectious, para-infectious, and post-infectious encephalitis, hypercoagulable states leading to stroke, and acute neuropathies such as Guillain-Barré syndrome.

Although the proportion of COVID-19 infections leading to neurological disease will probably remain small, these patients might be left with life long severe neurological complications and sequelae. With large numbers of people infected, the overall number of neurological patients, and their associated health burden and social and economic costs might be large too.

So, in-time detection or prophylaxis of those complications could be life-saving and economically reasonable.

Keywords: *COVID-19, acute polyneuropathy, Guillain-Barré syndrome, critical ilness neuropathy, ENMG*

Rationale

As of June 5, 2021, the COVID-19 pandemic, caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 174 million confirmed cases worldwide and more than 3.74 million deaths. Today it is clear, that it is the largest and most severe pandemic since the 1918 influenza pandemic [*Baj J et al, 2020*]. Although the most common and important presentation is with respiratory disease, reports of neurological features are increasing. Current data suggest that patients with severe COVID-19 infections are at risk of developing neurological complications [*Ellul et al., 2020*].

Anosmia and ageusia are most common, and can occur in the absence of other clinical features, and became hallmarks of the COVID-19.

Current data mostly focused around encephalopathy, which has been reported for majority of patients, with severe decline in cognitive functions, including majority of all reported hospitalised patients with COVID-19 worldwide.

Neurological manifestations occur in about 36.4% of patients infected with SARS-Cov-2 and span several domains within the central and pe-

Address for Correspondence:
Hovhannes M. Manvelyan, MD, PhD
Yerevan State Medical University, 2 Koryun st., Yerevan, 0025, Armenia
Tel.: (+374 10) 530562
E-mail:manvelian@yahoo.com

ripheral nervous system [*Ftiha F et al., 2020*]. These features appear to be a combination of non-specific complications of systemic disease, the effects of direct viral infection, or inflammation of the nervous system and cerebral vasculature, which can be para-infectious or post-infectious [*Niazkar HR et al., 2020*].

Peripheral neuropathy has a multitude of causes, many of which can be diagnosed by careful clinical and electrophysiological evaluation. Typically polyneuropathy will cause the combination of several hallmarks of symptoms, as distal limb muscle weakness, loss of tendon reflexes, and reduced distal limb sensation. There is variable involvement of the autonomic innervation, damage to which causes trophic changes on foot or hand. Loss of tendon reflexes is a cardinal sign of polyneuropathy, often restricted to the ankle jerks in axonal degeneration, but involving more proximal reflexes in acquired demyelinating neuropathies which may involve more proximal segments or the nerve roots.

Clinical features suggestive of demyelinating or conduction block polyneuropathy include:

a) a relative lack of muscle wasting in relation to the degree of weakness because no denervation has occurred; b) weakness of proximal muscles as well as distal, because of nerve root involvement; and c) disproportionate loss of joint position and vibration sensations compared to relative preservation of pain and temperature sensations which are carried by unmyelinated fibres [*Donaghy M 2011a, 2021b*].

Acute idiopathic polyneuropathies and the Guillain–Barré syndrome produce acute and diffuse demyelination or conduction block, or less frequently axonal degeneration affecting the spinal roots and peripheral nerves, and occasionally the cranial nerves. They are usually post-infective and recover spontaneously. The term Guillain–Barré syndrome includes two main entities now recognized as distinct: acute idiopathic demyelinating polyradiculoneuropathy and acute motor axonal neuropathy [*Donaghy M 2011a, 2021b*].

The Guillain–Barré syndrome is one of the most common forms of polyneuropathy. The condition may occur in either sex, with slight male preponderance, and at any age, occasionally including infancy. The mean age of onset is around 40 years, there is no obvious seasonal clustering of cases. The crude average annual incidence rate varies in different countries from 0.6 to 1.9 per 100 000 people [*Ropper AH, 1991; Chio A et al. 2003*]. Over half of Guillain–Barré syndrome patients experience symptoms of viral respiratory or gastrointestinal infections during the 1–3 weeks prior to the onset of neurological symptoms [*Donaghy M, 2011*].

Serological studies have implicated a wide range of infective agents. Cytomegalovirus and Campylobacter jejuni, in approximately 30 per cent, are the commonest [*Hadden et al., 2001*]. Epstein–Barr virus, Mycoplasma pneumoniae, human immunodeficiency virus, and childhood exanthems are also reported [*Chio A et al. 2003*]. The Guillain–Barré syndrome may accompany primary infection with HIV at a stage before viral antibodies are detectable in the serum; measurement of the p24 capsid antigen proving the underlying infection, precipitate differing forms of Guillain–Barré syndrome [*Visser L et al. 1996, 1999*].

The Guillain–Barré syndrome may occasionally appear in patients already being treated with substantial doses of steroids too [*Chio A et al. 2003*].

Critical illness polyneuropathy (CIP). Sensorimotor polyneuropathy can develop in patients being ventilated for cardiorespiratory disease who develop multi-organ failure or sepsis. Prospective electrophysiological examination of patients with severe sepsis shows that abnormalities are common at the time of admission to intensive care, and predict subsequent development of critical illness neuropathy and myopathy [*Frithiof R et al. 2021*]. The compound muscle action potentials and sensory nerve action potentials are reduced in amplitude, and needle electrodes show evidence of limb muscle denervation. This neuropathy usually comes to light

To overcome it
is possible, due to the
uniting the knowledge and
will of all doctors in the world

when patients fail to wean from the ventilator. The mortality in such patients is high, but those who recover neurologically do so over 3–6 months [*Cheung K. et al., 2021*]. This rapidity of recovery is faster than might be expected from a dense axonal degeneration polyneuropathy and suggests a degree of potentially reversible conduction failure. The disorder should be distinguished from Guillain–Barré syndrome by normal spinal fluid protein levels and the electrophysiological characteristic of axonal degeneration rather than demyelination [*Chio A et al. 2003*]. In a critically ill patient in the intensive care setting, the principal differential diagnosis is a critical illness myopathy, occurring most commonly in acute respiratory disorder such as asthma treated with non-depolarizing neuromuscular-blocking agents or high-dose steroids. Critical illness polyneuropathy and myopathy may coexist, and given that the creatine kinase level often remains normal, muscle biopsy is the only reliable way to diagnose the myopathy [*Cheung K. et al, 2021*].

During calendar year of COVID-19 pandemic in our clinic we observed four cases of acute Guillain–Barré syndrome and three cases of CIP, associated with respiratory infection.

All Guillain–Barré syndrome patients were diagnosed and in-hospital treated of COVID-19, and admitted to our clinic after being discharged of infectious hospitals in 2-4 weeks, presented with relatively symmetrical areflexic ascending tetraparesis, and general weakness.

All patients developed progressive limb weakness, first noted as difficulty in walking and balance, in one case the weakness was fast progressive started from toe numbness in the morning and culminated with bilateral facial nerve palsy in the evening.

All patients have been loaded with high doses of methylprednisolone as a part of their COVID-19 caused pneumonia treatment, and had the history of mask-oxigenation. The patient with rapid deterioration had decompensated hypothyreosis and second type diabetes mellitus.

Three of patients immediately started Plasma exchange treatment upon admitting to the hospital, as protocoled method of treatment, which shortens the time taken for patients with Guillain–Barré syndrome to start to improve, to regain functional abilities such as walking, and reduces their requirement for assisted ventilation [*Winer JB, 2002*]. Data proves, that Plasma exchange enables the median patient to walk independently at 53 days compared to 85 days for controls, and allows 82 per cent to walk independently at 6 months compared to 71 per cent of controls, and to be maximally effective, plasma exchange needs to be started within the first week of neurological symptoms [*Winer JB, 2002*].

Plasma exchange was performed using a continuous-flow technique, given on sequential days, as recommended. Four or five exchanges were done, and fast recovery was noticed.

All patients had a complain of severe back pain, which was resistant even to intravenous administration of anti-inflammatory non steroid medicines.

Intravenous immunoglobulin (IvIg) was given at 2 *g/kg* body weight/day for 5 days for patient with rapid deterioration and risk of development of pulmonary arrest and failure.

IvIg has become the treatment of choice because it is immediately available, does not require cannulation of a major vessel, has fewer side effects than plasma exchange, and does not carry the same risks of exacerbating circulatory disturbances due to autonomic neuropathy. Also the choice for IvIg in this particular case was done because it could be more effective than plasma exchange for the motor axonal subgroup resulting from immunocompromised patients [*Visser et al. 1999*].

All four patients were discharged from the hospital on days 7-14th, according to their improvement and substantial recovery of motor functions. Upon completion of treatment all patients were independent or had minor mobility issues, continued their treatment with kinesiotherapy and motor rehabilitation.

Follow up was done in three patients after three and six months, total recovering was registered, although patient with diabetes had developed lower limb neuropathic pain syndrome and was suffering of the pain. Additional pharmacological treatment with gabapentine was initiated.

Critical illness neuropathy was diagnosed in three patients with COVID-19 infection in Reanimation department, with severe respiratory failure, ventilated, unconsciousness.

Due to absence of contact, motor response of those patients were noticed to be extremely weak or absent, and they rapidly developed muscular atrophies and trophic changes, including bedsores. The hallmark of those neuropathies was growing symmetric muscular weakness, from legs to arms, with loss of tendon reflexes. Due to coma state the sensory deficit was out of measuring.

Although at present, there are no recommended pharmacologic interventions in preventing or treating critical illness polyneuropathy [*Shepherd SJ et al.,2016*], the use of intravenous immunoglobulin was thought to be promising [*Mohr M et al., 1997*].

All patients with CIP in ICU among reanimation treatment and critical care had received IvIg therapy, within first weeks (2-3) of clinical signs, with standard dose of 2*g/kg* divided on several days Iv administration. The choice of IvIg therapy was based on fact of clinical evidence that plasma exchange is not effective if started later then second week of disease onset, and serious limitations for patients with COVID-19 in their functional mobility from one department to another.

All patients with motor polyneuropathy were referred to the department of clinical neurophysiology or ICU patients had their electrophysiological examinations performed *in situ.* Motor nerve conduction studies were performed in the median and ulnar nerves of one arm and in the fibular and tibial nerves of both legs.

Electromyography with a concentric needle electrode was performed in upper and lower limb muscles and in one case one facial skeletal muscle, in order to detect abnormal spontaneous activity at rest (fibrillations and/or positive sharp waves) and if possible, if the patients could collaborate, analyze the presence of myopathic (polyphasic, short duration, low amplitude) motor unit potentials [*Lacomis et al., 2000*]. Presence of edema, primarily of the lower limbs, was regularly evaluated, and if present reported, since this could influence the nerve conduction studies studies.

Electrophysiological evidence of motor and sensory polyneuropathy with axonal (rather than demyelinating) features, absence of abnormal response on repetitive nerve stimulation among clinical features of critical illness, limb weakness or difficulty weaning from ventilator, were among diagnostic criteria of the critical illness polyneuropathy.

The demyelinating type of polyneuropathy among sensory and motor deficit were diagnosed in patients with Guillain–Barré syndrome.

Conclusion

Among many well-known pathogenetic mechanisms of development of acute polyneuropathies after COVID-19 infection, as inflammation and further autoimmunization, similar to well established bacterial or viral infections, in this particular disease there are certain peculiarities which must be considered as specific.

The most obvious and investigated is a cytokine storm, which leads to the failure of autoregulation and further development of the aggressive substances against different parts of the body, including vulnerable myelin on the peripheric nerves, leading to acute demyelination and/or axonal injury. Although grand efforts are done toward pharmacologically controlling the cytokine storm, the problem of impaired immune response remains unsolved.

Second, the aggressive treatment of COVID-19 infection, aiming at life preservation in critically ill situations includes high doses of antibiotics and hormones, interactions or cross reactions of which somehow could trigger self-immunization in immune-compromised patients.

A growing number of case reports describe a wide array of neurological manifestations, whether symptoms from the peripheral nervous system have been less frequently reported and their characterization requires electrophysiological investigations that are not always readily available in the setting of the ongoing COVID-19 pandemic.

Electromyography investigation must become mandatory method in all patients suspicious for motility arrest or signs of motor peripheric weakness.

So, every patient with COVID-19 respiratory infection must be considered as potential compli-

cator for neurological issues, with life-threatening risks or life-long neurological sequelae.

Although the proportion of COVID-19 infections leading to neurological disease will probably remain small, these patients might be left with life long severe neurological complications and sequelae. With large numbers of people infected, the overall number of neurological patients, and their associated health burden and social and economic costs might be large too. Health-care planners and policy makers must prepare for this eventuality, while the many ongoing studies investigating neurological complications increase our knowledge. So in-time detection or prophylaxis of those complications could be life-saving and economically reasonable.

REFERENCES

1. *Baj J, Karakuła-Juchnowicz H, Teresiński Get al.:* COVID- 19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. J Clin Med. 2020, 9:1753. 10.3390/jcm9061753
2. *Bureau B L, Obeidat A, Dhariwal M S et al.* (November 12, 2020) Peripheral Neuropathy as a Complication of SARS-Cov-2. Cureus 12(11): e11452. DOI 10.7759/cureus.11452
3. *Cheung K, Rathbone A, Melanson M, Trier J, Ritsma BR, Allen MD.* Pathophysiology and management of critical illness polyneuropathy and myopathy. J Appl Physiol, 2021 May 1;130(5):1479-1489. doi: 10.1152/japplphysiol.00019.2021. Epub 2021 Mar 18. PMID: 33734888; PMCID: PMC8143786.
4. *Chiò A, Cocito D, Leone M, Giordana MT, Mora G, Mutani R;* Piemonte and Valle d'Aosta Register for Guillain-Barré Syndrome. Guillain-Barré syndrome: a prospective, population-based incidence and outcome survey. Neurology. 2003 Apr 8;60(7):1146-50. doi: 10.1212/01.wnl.0000055091.96905.d0. PMID: 12682322.
5. *Donaghy M* (2011a) (editor) Brain's Diseases of the Nervous System (12 ed.) Publisher: Oxford University Press, Print Publication Date: Mar 2009, Print ISBN-13: 9780198569381 Published online: Jul 2011 1376P, DOI: 10.1093/med/9780198569381.001.0001
6. Donaghy M (2011b) Polyneuropathy (Section 3; Disorders of special senses, Chapter 21) in "Brain's Diseases of the Nervous System" (12 ed.) Publisher: Oxford University Press, Print Publication Date: Mar 2009, Print ISBN-13: DOI: 10.1093/med/9780198569381.003.0453
7. *Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T.* Neurological associations of COVID-19. Lancet Neurol. 2020 Sep;19(9):767-783. doi: 10.1016/S1474-4422(20)30221-0. Epub 2020 Jul 2. PMID: 32622375; PMCID: PMC7332267.
8. *Frithiof R, Rostami E, Kumlien E, Virhammar J, Fällmar D, Hultström M, Lipcsey M, Ashton N, Blennow K, Zetterberg H, Punga AR.* Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: A prospective study. Clin Neurophysiol. 2021 Apr 1:S1388-2457(21)00489-2. doi: 10.1016/j.clinph.2021.03.016. Epub ahead of print. PMID: 33875374; PMCID: PMC8012169.
9. *Ftiha F, Shalom M, Jradeh H:* Neurological symptoms due to Coronavirus disease 2019 . Neurol Int. 2020, 12:8639. 10.4081/ni.2020.8639
10. *Hadden RD, Gregson NA.* Guillain--Barré syndrome and Campylobacter jejuni infection. Symp Ser Soc Appl Microbiol. 2001;(30):145S-54S. doi: 10.1046/j.1365-2672.2001.01363.x. PMID: 11422570.
11. *Lacomis D, Zochodne DW, Bird SJ.* Critical illness myopathy. Muscle Nerve. 2000 Dec;23(12):1785-8. doi: 10.1002/1097-4598(200012)23:12<1785::aid-mus1>3.0.co;2-j. PMID: 11102901.

12. *Mohr M, Englisch L, Roth A, Burchardi H, Zielmann S.* Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis. Intensive Care Med 23: 1144–1149, 1997. doi:10.1007/s001340050471.

13. *Niazkar HR, Zibaee B, Nasimi A, Bahri N.* The neurological manifestations of COVID-19: a review article. Neurol Sci. 2020 Jul;41(7):1667-1671. doi: 10.1007/s10072-020-04486-3. Epub 2020 Jun 1. PMID: 32483687; PMCID: PMC7262683.

14. *Ropper AH.* Ischemic compression paresthesias in Guillain-Barré syndrome. Arch Neurol. 1991 Dec;48(12):1261-2. doi: 10.1001/archneur.1991.00530240065022. PMID: 1845030.

15. *Shepherd SJ, Newman R, Brett SJ, Griffith DM;* Enhancing Rehabilitation After Critical Illness Programme Study Investigators. Pharmacological therapy for the prevention and treatment of weakness after critical illness: a systematic review. Crit Care Med 44: 1198–1205, 2016. doi:10.1097/CCM.0000000000001652.

16. *Visser LH, Schmitz PI, Meulstee J, van Doorn PA, van der Meché FG.* Prognostic factors of Guillain-Barré syndrome after intravenous immunoglobulin or plasma exchange. Dutch Guillain-Barré Study Group. Neurology. 1999 Aug 11;53(3):598-604. doi: 10.1212/wnl.53.3.598. PMID: 10449126.

17. *Visser LH, van der Meché FG, Meulstee J, Rothbarth PP, Jacobs BC, Schmitz PI, van Doorn PA.* Cytomegalovirus infection and Guillain-Barré syndrome: the clinical, electrophysiologic, and prognostic features. Dutch Guillain-Barré Study Group. Neurology. 1996 Sep;47(3):668-73. doi: 10.1212/wnl.47.3.668. PMID: 8797462.

18. *Winer JB.* Treatment of Guillain-Barré syndrome. QJM. 2002 Nov;95(11):717-21. doi: 10.1093/qjmed/95.11.717. PMID: 12391383.

THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021). No 3

CONTENTS

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37410) 580840 Editor-in-Chief
Fax: (+37410) 582532
E-mail: namj.ysmu@gmail.com, ysmi@mail.ru
URL: http//www.ysmu.am

Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO THOMSON REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "collage" LTD
Director: A. Muradyan
Armenia, 0002, Yerevan,
Saryan St., 4 Building, Area 2
Phone: (+374 10) 52 02 17,
E-mail: collageltd@gmail.com