Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

COVID-Related Leukoencephalopathy: Unusual MRI Features and Comparability to Delayed Post Hypoxic Ischemic Encephalopathy ☆

Manzoor Ahmed, M.D[a], *Waqar Haider Gaba, FRCP*[b,*], *Fahim M Khan*[a], *Rabab Al Mansoori*[a], *Abd Al Kareem Adi*[b]

[a] *Department of Radiology, Sheikh Khalifa Medical City, Abu Dhabi, UAE*
[b] *Department of Internal Medicine, Sheikh Khalifa Medical City, Karamah Street, Abu Dhabi, 51900, UAE*

ARTICLE INFO

Article history:
Received 15 May 2021
Revised 21 November 2021
Accepted 21 November 2021

Keywords:
COVID-19
Leukoencephalopathy
delayed post-hypoxic
leukoencephalopathy (DPHL)

ABSTRACT

COVID-19 related leukoencephalopathy can be multifactorial given the systemic effects of the viral disease. We present couple of cases with typical clinico-imaging stigmata of COVID-19 resulting in severe respiratory insufficiency. MR brain imaging revealed confluent diffuse supratentorial white matter T2 hyperintensity with restricted diffusion during the sub-acute course of the disease. The MR imaging pattern of leukoencephalopathy was non-specific but more comparable to delayed post-hypoxic leukoencephalopathy (DPHL) as also previously reported in COVID-19. Interestingly, T2 imaging showed unusual but peculiar finding of "accentuated medullary veins" in the superficial zones. No dural venous sinus thrombosis or micro-hemorrhages were present to explain "dots and stripes" due to dilated medullary veins. The patho-mechanism of this findings is not clear but may possibly be related to demyelination as DPHL has shown to be a demyelinating process. We present a review of COVID-related leukoencephalopathy with discussion on hypoxia-induced demyelinating process with accentuated medullary veins as possible associated marker.

Introduction

COVID-19 pandemic has been caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2). Neurologic or Neuroimaging manifestations related to COVID-19 (NMC) are being increasingly reported [1–6]. Diffuse white matter T2 signal abnormality is generally termed as leukoencephalopathy in acute or sub-acute settings. Such findings described in COVID-related encephalopathy are non-specific with various potential pathogenesis: toxic, metabolic, posterior reversible encephalopathy due to patient system illness, critical illness encephalopathy, post-infectious demyelination and potentially direct infection causing cerebritis due to neuro-tropism of COVID-19 virus. However, 1one of the most plausible explanation can be delayed post-hypoxic leukoencephalopathy

☆ Competing Interests: The authors have declared that no competing interests exist.

* Corresponding author.
E-mail address: drgaba@hotmail.co.uk (W.H. Gaba).

https://doi.org/10.1016/j.radcr.2021.11.059

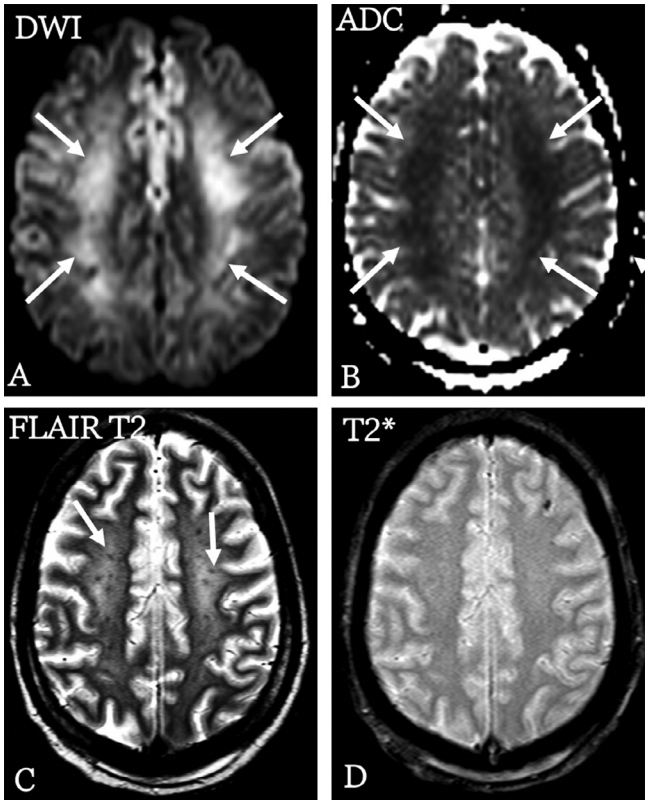

Fig. 1 – Axial DWI (B1000) (A), ADC (B), T2 (C) and GRE/T2* (D). Bilateral fronto-parietal white matter confluent diffuse white matter T2 hyperintensity (leukoencephalopathy) with restricted diffusion (A & B, arrows) is shown. Note tiny T2 hypointense foci (arrows, C) representing accentuated medullary veins. No corresponding susceptibility foci to represent micro-hemorrhages on gradient echo image (D).

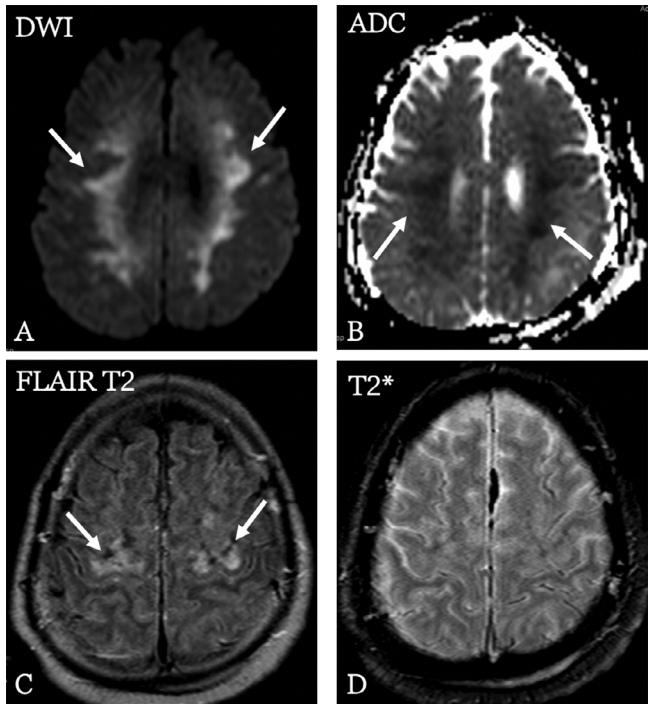

Fig. 2 – Axial DWI (B1000) (A), ADC map (B), T2 FLAIR (C) and GRE/T2* (D). Bilateral fronto-parietal white matter confluent diffuse white matter T2 hyperintensity (leukoencephalopathy) with restricted diffusion (A & B, arrows) is shown. Note tiny T2 hypointense foci (arrows, C) representing accentuated medullary veins. No corresponding susceptibility foci to represent micro-hemorrhages on gradient echo image (D).

(DPHL) [4], given the high risk of hypoxemic injury in these patients and further corroborated by confluent symmetric diffuse white matter T2 signal change with restricted diffusion, typical for DPHL in proper settings [7–9].

We present here two such cases of COVID-related leukoencephalopathy with confluent symmetric diffuse white matter signal change and corresponding homogenous restricted diffusion, specifically in the fronto-parietal centrum semi-ovale region. The highlight of both cases is accentuated medullary veins manifesting in the affected white matter as hypointense T2 stripes and spots with in the hyperintense white matter. This may not only add peculiarity to COVID-related leukoencephalopathy but also point to possible pathogenesis perhaps hypoxia related demyelination. The MR findings of symmetric and diffuse white matter changes with restricted diffusion matches the recently reported findings in COVID-related leukoencephalopathy, attributing it to delayed post hypoxic injury [4,5]. However, prominent medullary veins is an unusual observation and rarely reported in diffuse leukoencephalopathy [10].

Cases with Specific Neuro-imaging Findings

Case 1: A 43 years old COVID positive healthy male presenting with mild symptoms but moderate burden of disease on chest imaging. Progressive worsening culminated in requirement for critical care due to respiratory insufficiency and systemic disease. The patient had low Glasgow Coma Score and showed diffuse leukoencephalopathy on MRI with restricted diffusion and unusual finding of accentuated medullary veins (Fig. 1). COVID-19 related leukoencephalopathy was the diagnosis of exclusion. Patient passed away after 7 weeks of hospitalization.

Fig. 1: Axial DWI (B1000) (A), T2 (B) and GRE/T2* (C). Bilateral fronto-parietal white matter confluent diffuse white matter T2 hyperintensity (leukoencephalopathy) with restricted diffusion (arrows, A) is shown. Note tiny T2 hypointense foci (arrows, B) representing accentuated medullary veins. No corresponding susceptibility foci to represent micro-hemorrhages on gradient echo image (C).

Case 2: A 45 years old COVID positive healthy male presented with severe symptoms and biochemical evidence of severe disease after two weeks of onset and required critical care due to respiratory insufficiency with severe burden of disease on chest imaging. The patient sustained low Glasgow Coma Score resulting in MR Brain imaging which showed diffuse leukoencephalopathy with restricted diffusion and the unusual finding of accentuated medullary veins (Fig. 2 and 3). COVID-19 related leukoencephalopathy was the diagnosis of exclusion. Patient was eventually discharged to long term fa-

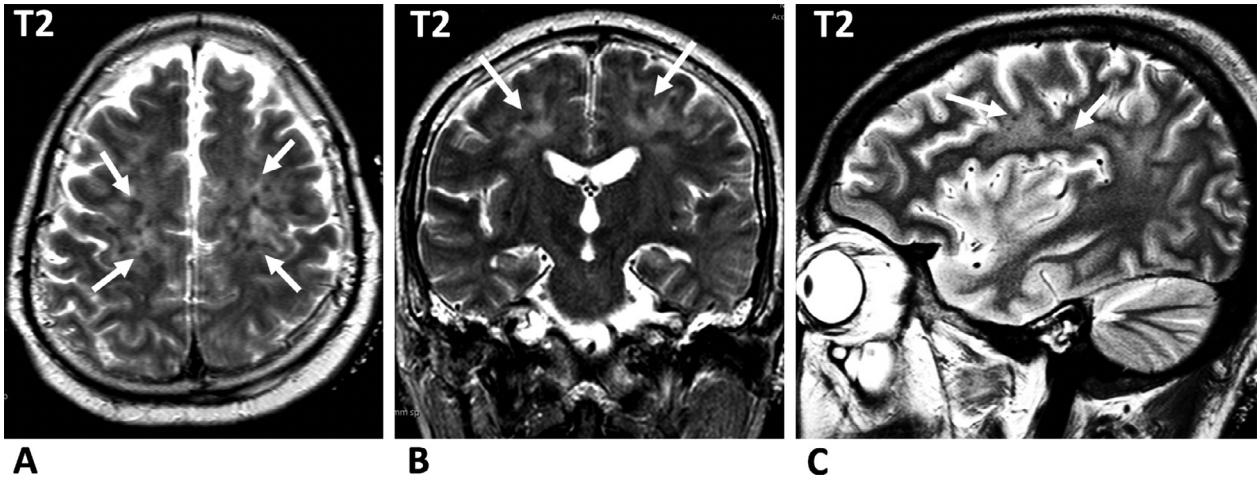

Fig. 3 – Multi-planar T2 images. Bilateral diffuse supratentorial sub-cortical and deep white matter T2 hyperintense signal changes (leukoencephalopathy) with diffuse accentuation of sub-cortical and superficial zone deep medullary veins (arrows, A, B and C)

cility due to dependence on mechanical ventilation and neurologic disability.

Discussion

Severe cases of COVID-19 patients are at risk of developing leukoencephalopathy seen in critically ill patients. There can be complex interplay of pathogenetic pathways particularly related to toxic, metabolic, infectious, and hypoxic causes which can typically result in an imaging manifestation of confluent supratentorial white matter disease pattern with relative sparing of sub-cortical zones [1–6]. Additional imaging stigmata can be helpful in further understanding the pathogenesis of the leukoencephalopathy in this critically ill cohort of patients.

Our two cases of COVID-19 with confluent, symmetric and diffusion-restricted fronto-parietal leukoencephalopathy revealed accentuated medullary veins in the affected white matter. The findings may potentially point to a pathogenetic relationship rather than representing as a coincidental finding. Certainly, there is some relationship of demyelination with veins, at least a relationship of vicinity as pathogenetic relationship is not very clear [11]. Demyelinating disorders specifically Multiple Sclerosis is generally considered a "perivenous disease" [12,13] and lately, supported by manifestation of "Central Vein Sign" on high field MRI. More interesting would be the potential role of hypoxemic injury causing demyelinating COVID-19 related leukoencephalopathy in the setting of sustained respiratory dysfunction. Demyelinating injury has been previously described in delayed post-hypoxic leukoencephalopathy (DPHL) [9,14] and our highlighted observation of prominent medullary veins can be postulated as marker of demyelination. There was no evidence of cerebral venous thrombosis to account for accentuated medullary veins.

The MR imaging of our 2 cases unequivocally represented prominent medullary veins. The hypointense T2 flow voids can cause significant image contrast and appear as filling defects in the background field of homogenous T2 hyperintense white matter changes. Close similarity of the pattern on MRI can be seen in lysosomal or hypo-myelinating disorders of the white matter describes as "tigroid or leopard pattern" [15]. Van der Voorn et al [16] used correlative histopathologic evidence to prove these stripes on MRI as either caused by perivenular sparing of the myelin or lipid laden glial/globoid cells in three patients of metachromatic leukodystrophy (MLD), infantile GM1 gangliosidosis (GM1) and globoid cell leukodystrophy (GLD). The prominent superficial medullary veins in our 2 cases can potentially represent peri-venular sparing by the white matter disease (like above disorders) and or related to venous pathophysiology of presumed demyelinating leukoencephalopathy.

Supratentorial parenchymal veins include superficial and deep draining veins with occasional trans-cerebral veins [17]. Superficial parenchymal veins include intra-cortical, subcortical, and superficial medullary veins. The superficial medullary veins runs perpendicular to the cortex and traverse through it to drain into pial veins. Deep medullary veins on the other hand drain into the deeper veins via pattern of convergence and passing through four zones or segments. The two most superficial zones include bamboo branch union (Zone-I) and candalebra zone (II), which is the most prominent of the four, all these eventually drain into subependymal zone. The accentuated veins in our cases likely represented these two superficial zones. Demyelinating plaques in multiple sclerosis have been well described around medullary veins represented by the well-established term of "Dawson's fingers" and lately as "Central vein sign" on high field MRI. Even, increased propensity of plaques have been described along developmental venous anomalies (DVA) in multiple sclerosis by [18]. Tomura et al reported angiographic evidence of dilated medullary veins in progressive multifocal leukoencephalopathy- a demyelinating disease [10].

Demyelination can have multiple etiologies- inflammatory, viral, metabolic, compressive effects & hypoxia [19]. DPHL is a rare and relative less recognized disorder manifesting as

neurologic relapse after weeks of stability following hypoxic event- usually mild to moderate rather than severe hypoxic injury [7]. The pathophysiology may not be very clear, but histopathology has shown extensive demyelination with sparing of the axons, U-fibers and cortex [14]. The post-hypoxic time interval coincides with the 19 days half-life turn-over for myelin-related lipids and proteins [20]. DPHL most likely result from necrosis of oligodendrocytes in susceptible watershed zones causing failed myelin turn-over but sparing the axons and no associated myelin vacuolization. The other contributing mechanism is hypoxia-induced dysfunction of adenosine triphosphate-dependent enzymes responsible for myelin maintenance [9]. Most of the previously reported cases were related to carbon monoxide poisoning, cardiac arrest or drug over-dose [8,9]. Like the case series by Radmanesh et al [3,5], our cases suffered sustained respiratory distress due to COVID-19 and required assisted ventilation for weeks till MRI was performed. The MR findings typically consist of diffuse symmetric white matter T2 hyperintensity with corresponding restricted diffusion [7–9].

Further validation is needed especially histo-pathologic correlation to confirm COVID-related leukoencephalopathy. Presence of accentuated medullary veins can be coincidental but certainly present a peculiar appearance on MR imaging. Axial T2 imaging initially suggested microhemorrhages but there was no susceptibility present on T2* imaging as recently described as one of the neuro-imaging manifestations of COVID-19 ([3], [21]).

In summary, persistent or delayed hypoxic injury is a plausible contributory patho-mechanism for COVID-related leukoencephalopathy with imaging features identical to DPHL. Furthermore, accentuated medullary veins is a peculiar finding with possible association with underlying pathophysiology of leukoencephalopathy in critically ill COVID-19 cases.

Authors' contribution

Dr Manzoor Ahmed: Conceptualization, Writing-Review & Editing. Dr Waqar Haider Gaba: Writing-Review & Editing. Dr Fahim Khan: Writing- Review & Editing. Dr Rabab Al Mansoori: Writing- Review & Editing. Dr Abd Al Kareem Adi: Writing-Review & Editing

REFERENCES

[1] Sachs JR, Gibbs KW, Swor DE, Sweeney AP, Williams DW, Burdette JH, et al. COVID-19-associated Leukoencephalopathy. Radiology 2020;296(3):E184–5.

[2] Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology 2020;296(2):E119–20.

[3] Radmanesh A, Derman A, Lui YW, Raz E, Loh JP, Hagiwara M, et al. COVID-19 -associated Diffuse Leukoencephalopathy and Microhemorrhages. Radiology 2020;Oct;297(1)(223–227):202040 In press. doi:10.1148/radiol.2020202040.

[4] Lang M, Buch K, Li MD, Mehan WA Jr, Lang AL, Leslie-Mazwi TM, et al. Leukoencephalopathy Associated with Severe COVID-19 Infection: Sequela of Hypoxemia? Am Journal Neuroradiology 2020;Sep;41(9):(1641–1645). doi:10.3174/ajnr.A6671.

[5] Radmanesh A, Derman A, Ishida K. COVID-19-associated delayed posthypoxic necrotizing leukoencephalopathy. Journal Neurologic Sciences 2020;415:116945.

[6] Agarwal S, Jain R, Dogra S, Krieger P, Lewis A, Nguyen V, et al. Cerebral Microbleeds and Leukoencephalopathy in Critically Ill Patients With COVID-19. Stroke 2020;Sep;51(9):(2649–2655). doi:10.1161/STROKEAHA.120.030940.

[7] Beeskow AB, Oberstadt M, Saur D, Hoffmann KT, Lobsien D. Delayed Post-hypoxic Leukoencephalopathy (DPHL)-An Uncommon Variant of Hypoxic Brain Damage in Adults. Frontiers in Neurology 2018;9:708.

[8] Kim JH, Chang KH, Song IC, Kim KH, Kwon BJ, Kim HC, et al. Delayed encephalopathy of acute carbon monoxide intoxication: diffusivity of cerebral white matter lesions. Am Journal Neuroradiology 2003;24(8):1592–7.

[9] Zamora CA, Nauen D, Hynecek R, Ilica AT, Izbudak I, Sair HI, et al. Delayed posthypoxic leukoencephalopathy: a case series and review of the literature. Brain & Behav 2015;5(8):e00364.

[10] Tomura N, Watanabe M, Kato T, Nishino K, Kowada M. Case report: Progressive multifocal leukoencephalopathy with prominent medullary veins on angiogram. Clin Radiology 1994;49(1):66–8.

[11] Awad AM, Marder E, Milo R, Stüve O. Multiple sclerosis and chronic cerebrospinal venous insufficiency: a critical review. Therapeutic Advan Neurol Disorders 2011;4(4):231–5.

[12] Adams CW, Abdulla YH, Torres EM, Poston RN. Periventricular lesions in multiple sclerosis: their perivenous origin and relationship to granular ependymitis. Neuropathol Applied Neurobiol 1987;13(2):141–52.

[13] Bhandari A, Xiang H, Lechner-Scott J, Agzarian M. Central vein sign for multiple sclerosis: A systemic review and meta-analysis. Clin Radiol 2020;75(6):479 e9-479.e15.

[14] Gottfried JA, Mayer SA, Shungu DC, Chang Y. Duyn JH Delayed post-hypoxic demyelination. Association with arylsulfatase A deficiency and lactic acidosis on proton MR spectroscopy. Neurology 1997;49(5):1400–4.

[15] Faerber EN, Melvin J, Smergel EM. MRI appearances of metachromatic leukodystrophy. Pediatric Radiology 1999;29:669–72.

[16] Van der Voorn JP, Pouwels PJ, Kamphorst W, Powers JM, Lammens M, Barkhof F, et al. Histopathologic correlates of radial stripes on MR images in lysosomal storage disorders. Am J Neuroradiol 2005;26(3):442–6.

[17] Taoka T, Fukusumi A, Miyasaka T, Kawai H, Nakane T, Kichikawa K, et al. Structure of the medullary veins of the cerebral hemisphere and related disorders. Radiographics 2017;37(1):281–7.

[18] Rogers DM, Peckham ME, Shah LM, Wiggins RH 3rd. Association of developmental venous anomalies with demyelinating lesions in patients with multiple sclerosis. Am J of Neuroradiol 2018;39(1):97–101.

[19] Love S. Demyelinating diseases. Review. J Clin Pathology 2006;59(11):1151–9.

[20] Meyer MA. Delayed post-hypoxic leukoencephalopathy: case report with a review of disease pathophysiology. Neurol Int 2013;5(3):e13.

[21] Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Brain MRI Findings in Severe COVID-19: A retrospective observational study. Radiology 2020;297(2):(242–251):202222. doi:10.1148/radiol.2020202222.