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Case Report

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Multiple Sclerosis Presenting as Intracranial Hypertension in the Setting of COVID-19 Infection

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Abstract

Background: *Multiple sclerosis (MS) and idiopathic intracranial hypertension (IIH) occur more commonly in women of childbearing age. There are altered cerebrospinal fluid dynamics in both diseases, causing them to have similar presentations at times. Coronavirus disease 19 (COVID-19) has also been reported to affect the central nervous system (CNS) of any age.*

Case Presentation: *We report a19 year old male who initially presented with headaches and fever, and was diagnosed with COVID-19 infection. A few days later, he developed acute severe left eye pain, blurred vision, diplopia, and left ear tinnitus. The patient was found to have reduced visual acuity, left sixth nerve palsy, esotropia and asymmetric bilateral papilledema. Later, he developed left facial nerve palsy. MRI of the brain showed extensive demyelinating lesions. Lumbar puncture revealed significantly increased intracranial pressure (ICP) and positive oligoclonal bands.*

Conclusion: *This is a unique case of MS presenting with intracranial hypertension (IH) in the setting of COVID-19 infection that could have been the trigger for the MS clinical attack.*

Keywords: Multiple Sclerosis, Idiopathic Intracranial Hypertension, Intracranial Pressure, Papilledema, COVID-19.

Abbreviations

MS:Multiple Sclerosis (MS); IIH: Idiopathic Intracranial Hypertension; CSF: cerebral spinal fluid; ICP:intracranial pressure; COVID-19: coronavirus disease 19; BMI: Body Mass Index; MOG: Myelin Oligodendrocyte Glycoprotein; LP: Lumbar puncture; CBC: Complete Blood Count; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive Protien; TSH: Thyroid Stimulation Hormone; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; CR: Creatinine; RF: Rheumatoid Factor; ANA: Antinuclear Antibody; C-ANCA: Cytoplasmic Antineutropil Cytoplasmic Antibody; P ANCA: Peripheral Antineutropil Cytoplasmic Antibody; ENA: Extractable Nuclear Antigen; Anti-RNP: Anti-Ribonucleoprotein; Anti-SM: Anti-Smith; SSA: Sjogren Syndrome A; Scl-70: ,Scleroderma; ds-DNA: Double Stranded Deoxyribonucleic Acid; DMT: disease modifying therapy; GBS: Guillain Barre Syndrome.

1. Background

MS is an autoimmune disease affecting the central nervous system myelin [1]. MS is typically found in females of childbearing age, with greater prevalence in Caucasian women [1,2]. IIH, on the other hand, is a disorder of unknown etiology resulting in isolated raised ICP [3]. It typically presents in obese females of childbearing age [3]. Patients usually present with a gradual onset of headache, transient visual loss, pulsatile tinnitus, back pain, dizziness, neck pain, visual blurring, cognitive disturbances, and typically horizontal diplopia [4]. IIH and MS can present with overlapping symptoms such as headaches and diplopia [5]. Furthermore, with the emergence of SARS-CoV-2 that is responsible for the outbreak of COVID-19 infection, neurological manifestations of the infection have also been reported. [6,7,8].

When patients present with overlapping symptoms of multiple disorders, it makes it difficult for clinicians to differentiate between these disorders. Our patient presented with symptoms of increased ICP. This increased ICP could be caused by MS, IIH, or COVID-19 infection. After an extensive work up, we strongly believe that the increased ICP was caused by MS and presented as a clinical attack in this patient.

2. Case Presentation

A19 year old middle-eastern male who initially presented to the primary care clinic with a four-day history of headaches and fever. He was seen by a primary care physician who diagnosed him with COVID-19 infection, confirmed on a fast antigen test.

The patient was treated with dexamethasone and azithromycin. A few days later, the patient presented to the neurology center after developing acute severe left eye pain, blurred vision, diplopia, and left ear tinnitus. He was also complaining of intermittent shortness of breath associated with palpitation. The patient is a non-smoker with body mass index of BMI) 21. There was no significant past medical history and he was not taking any medications prior to this event. There was no family history of neurological disorders.

Initial examination showed reduced visual acuity, left sixth nerve palsy, esotropia and asymmetric bilateral papilledema; being worse on the left side. The rest of his examination was normal. These findings were confirmed by an ophthalmologist, who also excluded the presence of optic neuritis. Two weeks later, the patient developed left seventh nerve palsy with slight worsening of the left sixth nerve palsy.

3. Imaging

MRI of the brain was done on the same day he was seen at the neurology center, revealing multiple T2/FLAIR hyperintense plaques predominantly at the subcortical and juxtacortical regions. Neither of these plaques showed restricted diffusion nor displayed enhancement post contrast administration. Mild kinking of both optic nerves was noted (worse on the left) without radiological signs of optic neuritis. Partial empty sella turcica was also noted (Figure 1 and 2). The contrast images showed focal stenosis of both transverse sinuses (Figure 3).

Repeat MRI the brain with and without contrast three weeks later (after the development of new onset of seventh nerve palsy) was unchanged from the initial one. MRI of the cervical and thoracic spine with and without contrast was also done at this time and was unremarkable.

At six-month follow up, repeat MRI of the brain without contrast was unchanged from the initial one. Magnetic Resonance Venography (MRV) of the brain at this time showed a smaller left venous system (left transverse, sigmoid and upper part of jugular vein), compared to the right one, with smooth tight narrowing of the distal parts of both transverse sinuses. There was no evidence of thrombosis (Figure 4).

4. Other Investigations

A lumbar puncture (LP) was performed showing an elevated opening pressure of 420 mmH_2O, confirming the presence of intracranial hypertension. CSF analysis revealed 0 WBC, 0 RBC, 26.6 protein and 81 glucose. Oligoclonal bands were seen. LP was repeated three weeks later and showed an opening pressure of 230 mmH_2O. CSF was also checked for myelin oligodendrocyte glycoprotein (MOG) antibodies, which were negative.

Extensive laboratory testing was performed and was normal. The blood work included: complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protien (CRP), thyroid stimulating hormone (TSH), vitamin B12, vitamin D, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine (Cr), rheumatoid factor (RF), antinuclear antibody (ANA), cytoplasmic antineutropil cytoplasmic antibody (C-ANCA), and peripheral antineutropil cytoplasmic antibody (P-ANCA).

4.1 Extractable Nuclear Antigen (ENA Profile) was normal including anti-PM/Scl, anti-Mi2-beta (CHD4) antibodies, anti-Ku antibodies, anti-mitochondrial M2 antibodies, anti-Jo-1 antibodies, anti-ribonucleoprotein (Anti-RNP) antibodies, anti-Smith (Anti-Sm) antibodies, anti-Sjogren syndrome A (SS-A) antibodies, anti-Sjogren syndrome B (SS-B) antibodies, scleroderma (Scl-70) antibodies, antihistidyl transfer RNA synthase (Anti-Jo-1) antibodies, and double stranded deoxyribonucleic acid (ds-DNA) antibodies.

5. Management and Follow Up

The patient was treated with methylprednisolone 1000mg intravenously once daily for 5 days. For increased ICP, he was started on acetazolamide 250mg twice daily and increased two weeks later to 500 mg twice daily. For the COVID-19 infection, the patient had already finished a course of dexamethasone and azithromycin prior to presenting to the neurology center. The patient's headaches and diplopia improved within a week of starting the therapy. However, blurred vision persisted.

Two weeks after the initial presentation, the patient presented with a new onset of left-sided facial droop and diplopia. Neurologic examination revealed mild left cranial nerve six and seven palsy. LP was repeated and the opening pressure was found to be 230 mmH_2O. MRI of the brain with and without contrast was repeated and was unchanged from the initial one. The patient was kept on acetazolamide at a dose of 500 mg twice daily. The new symptoms and blurred vision improved within a week.

The patient was referred to a local government's hospital to initiate disease modifying therapy (DMT) for MS, due to the high cost of these medications. The patient received rituximab while there. The choice of rituximab was based on their neurologist's decision and the availability of the DMT at the time.

At a three-month follow up, the patient complained only of mild blurred vision, but no other symptoms. He was continued on acetazolamide at 500 mg twice daily. Throughout this time, the patient was closely followed by the ophthalmologist who documented gradual and significant improvement of the bilateral optic disc edema. At six-month follow up, the patient did not have any complaints, and ophthalmological examination revealed very mild optic nerve edema. Repeat MRI of the brain without contrast was unchanged from the initial one. The acetazolamide dose was reduced to 250 mg twice day.

6. Discussion

This is a very complex patient who presented with three separate entities: COVID-19 infection, demyelinating lesions on MRI and increased ICP with positive oligoclonal bands on LP. It was unclear if these are three separate entities co-existing in one patient, or one entity presenting with different symptoms. The patient's initial presentation of fever and headaches was typical of COVID-19 infection, which was confirmed with the fast antigen

test. His symptoms were very mild and improved within days. A few days later, the patient started having new and acute symptoms, typical of increased ICP. MRI of the brain and LP findings were most consistent with MS. This made us question whether COVID-19 infection was causing his symptoms.

CNS manifestations of COVID-19 have been extensively reported [9,10]. There are many different neurological effects of COVID-19, including: encephalopathy, encephalitis, ischaemic strokes, haemorrhagic strokes, and Guillain Barre Syndrome (GBS) [6,7,8]. In a series from Wuhan, 78 of 214 COVID-19 patients developed neurological manifestations such as agitation, confusion and corticospinal tract signs. These patients, however, tended to be more severely affected, older and with more comorbidities [11]. The typical neurological manifestations could be due to the viral infection, causing loss of smell and taste, or to the consequences of severe systemic illness such as sepsis, hypoxia, vasculitis, and hypercoagulability [11]. There are rare, isolated case reports of demyelination [12]. Cerebral venous thrombosis is another rare complication [13]. Patients may develop this neurological sequela due to the prothrombotic state triggered by COVID-19 [14-16]. Brain MRI changes noted were meningeal enhancement, ischaemic strokes, and perfusion changes [15-17]. CSF examination of white cell response and other immunological features are typically absent [17]. In a study of 52 patients with CNS COVID-19 infection, ICP ranged between normal and slightly elevated in most cases. Less than one third of the patients had slightly increased ICP [18]. Only patients with meningitis or meningoencephalitis had increased mononuclear leukocytes and 30% had elevated protein [18]. Based on the above data, we do not believe that COVID-19 contributed to our patient's CNS symptoms. At most, it could have been a trigger for his main entity.

We believe that the increased ICP in our patient is directly due to MS, rather than to IIH coexisting with MS. The patient's clinical presentation and diagnostic work up do not fit the typical picture for IIH. First, he is a male with ideal body weight (BMI 21). Second, following the revised criteria published by Friedman et al in 2013 (table 1), our patient does not fit the "probable" nor the "definite" diagnosis of IIH. Out of the five criteria, he only fits three of them. He does not have a normal MRI of the brain or normal CSF composition [4]. Based on these criteria, the diagnosis of IIH is excluded in this patient. Third, according to Chen et al, our patient's presentation is atypical for IIH. This is because he has asymmetric papilledema and unilateral facial nerve palsy [19]. Peripheral facial weakness is an uncommon finding among IIH patients. A series of 30 children with IIH identified only one child with unilateral facial nerve palsy [20]. Another series of 140 adults and children with IIH, identified only two patients with unilateral facial nerve palsy [21]. When our patient developed facial nerve palsy three weeks from his initial presentation, his LP opening pressure was only 230 mmH_2O, making IIH less likely to be causing his neurological symptoms. Based on the above, we believe that the clinical presentation of increased ICP in our patient was due to MS, rather than IIH.

It is possible that multiple sclerosis and IIH exist on a spectrum, as both alter CSF fluid dynamics, most often through arachnoid granulations and venous stenosis [22,23]. In patients with MS, increased areas of transverse and sagittal sinuses can be seen due to outflow stenosis associated with reduced venous sinus compliance [23,24]. Although not clearly understood, the increased ICP in IIH is due to disruption in CSF equilibrium. This occurs either due to overproduction or inadequate reabsorption of CSF [3,4]. The area of the superior sagittal sinus has been shown to differ between IIH and MS, with no appreciable change and an increase in size, respectively [23,24]. Bateman et al suggested that MS alters CSF fluid dynamics, most often through arachnoid granulations and venous stenosis, and therefore can cause increased ICP [22,23]. The initial MRI with contrast showed focal areas of stenosis in both transverse sinuses. These areas of stenosis persisted six months later, evident on the MRV, supporting the notion that the increased ICP is due to MS. If it was due to IIH, it should have resolved or improved after normalizing the ICP.

Using the revised 2017 McDonald criteria, the diagnosis of MS was confirmed in this patient. He had one clinical attack, objective evidence of more than two lesions on MRI, and positive oligoclonal bands in CSF [25]. We considered the current presentation as a clinical MS attack. The symptoms of increased ICP are too acute to be due to IIH. The patient also developed seventh nerve palsy which is very atypical for patients with IIH. When he developed the left seventh cranial nerve palsy, his LP opening pressure was only 230 mmH2O. The lack of enhancement on MRI could have been due to him receiving steroids prior to presenting to us. Burnham et al showed that receiving methylprednisolone prior to the MRI completely suppressed gadolinium enhancement of acute MS demyelinating lesion in the majority of patients [26]. The lack of enhancement could be because this acute relapse is presenting with increase intracranial pressure, rather than focal white matter lesion. Based on these facts, we chose to treat the patient with intravenous methylprednisolone.

7. Conclusion

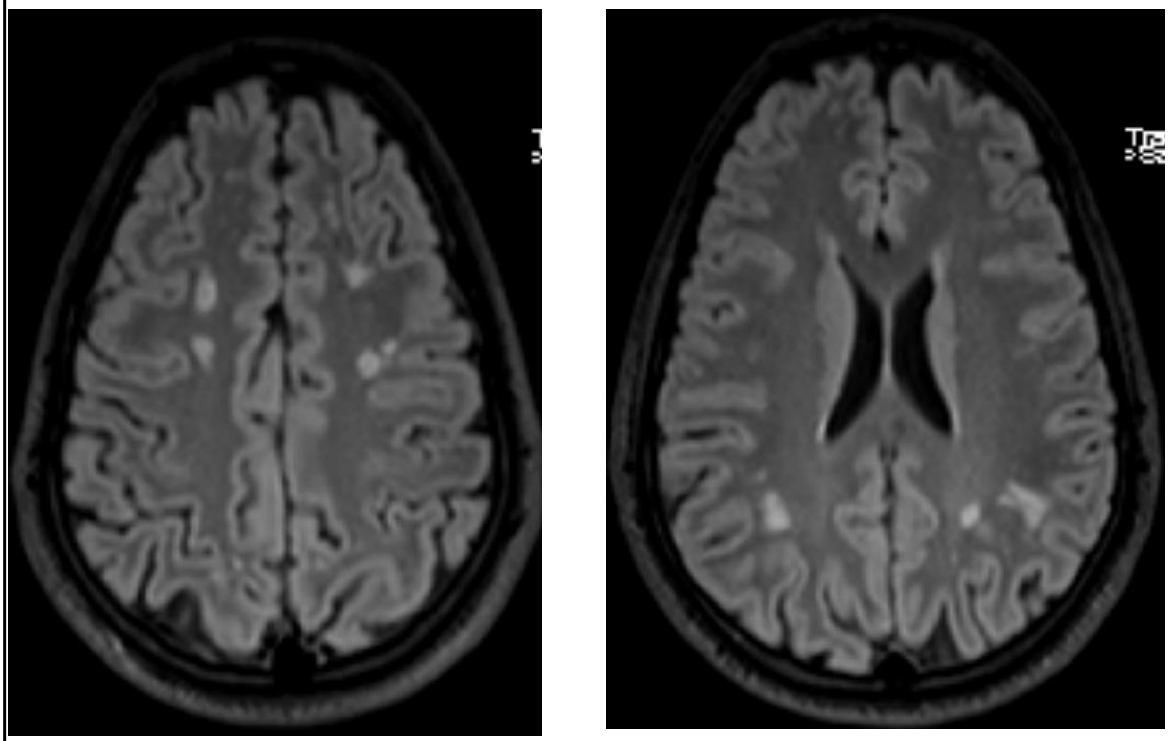
MS, IIH, and COVID-19 infection can coexist. However, our patient did not fit the definite or probable criteria for IIH, and fulfilled the McDonald's criteria for MS. COVID-19 infection was very mild and should not have caused significant symptoms. We have done extensive work up on the patient to rule out any other pathologies that can fully explain his presentation. We believe that the MS caused the increased ICP, rather than IIH co-existing with MS, or COVID-19 infection causing the symptoms. Further work is required to confirm that MS can cause an increase in ICP and set criteria to differentiate it from other causes. This will also help draw better diagnostic and treatment guidelines for those patients.

Table 1 Diagnostic Criteria for IIH	
A	Papilledema.
B	Normal neurologic examination except for cranial nerve abnormalities.
C	Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (obese women), and MRI, with and without contrast, and MRV for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used.
D	Normal CSF composition.
E	Elevated lumbar puncture CSF opening pressure (≥25 cm CSF in adults and ≥28 cm CSF in children [25 cm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture.

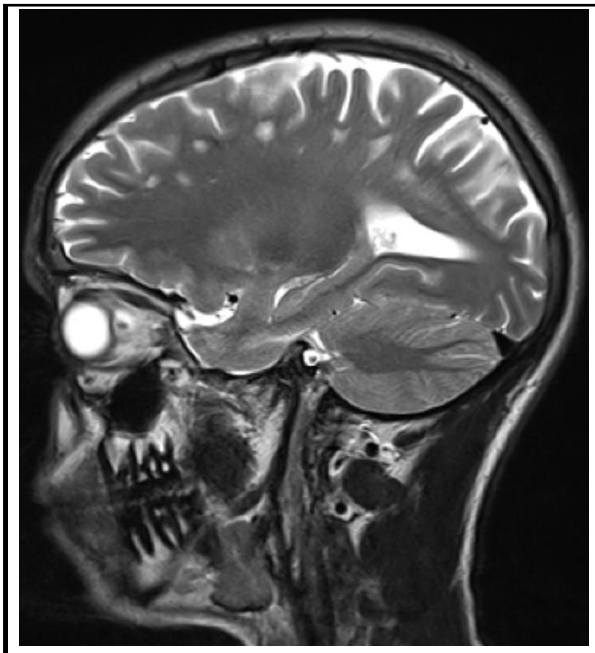
Definite Diagnosis	If the patient fulfills criteria A-E.
Probable Diagnosis	If criteria A-D are met, but the measured CSF pressure is lower than specified for a definite diagnosis.

CSF*=Cerebrospinal fluid,* ***CT****=Computed tomography,* ***MRI****=Magnetic resonance imaging,* ***MRV****=Magnetic resonance venography*

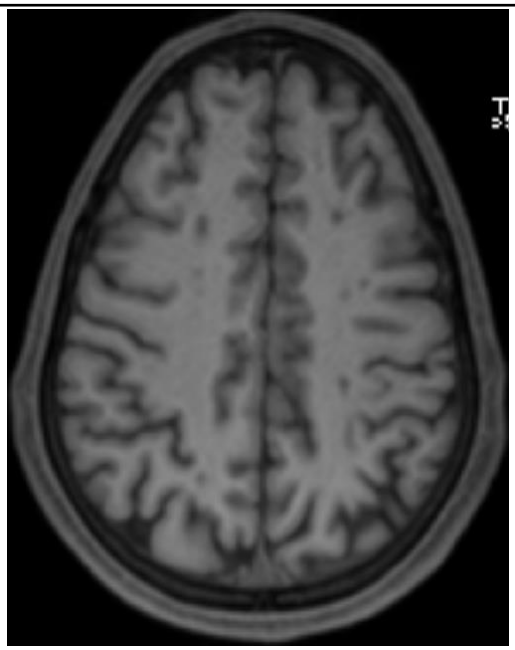
Firgure 1 MRI of the Brain; FlAIR and T2



A B



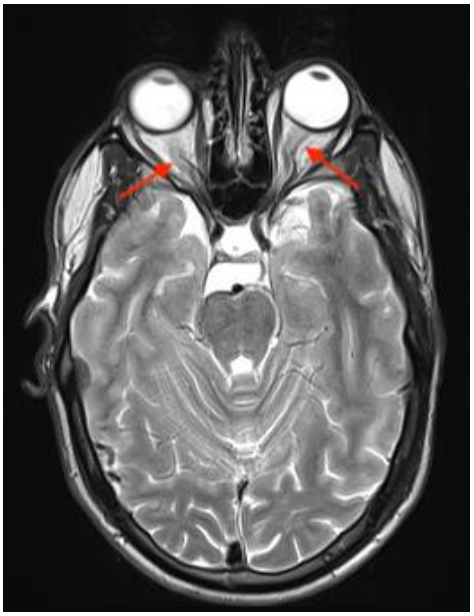
C



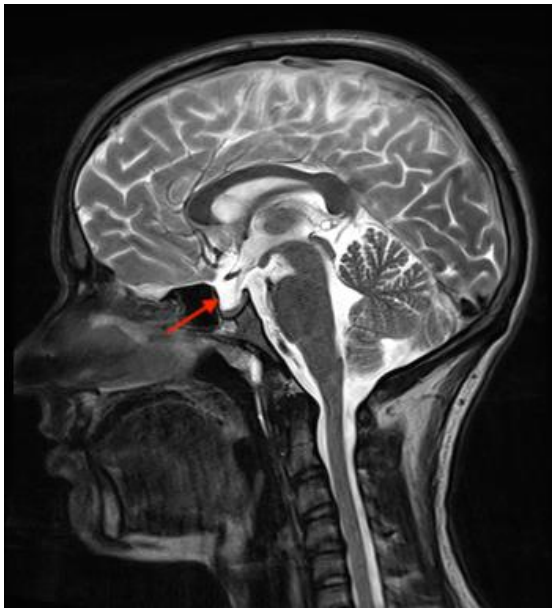
D

MRI of the brain demonstrating multiple hyperintense plaques predominantly the subcortical and juxtacortical regions evident on FlAIR sequences (A, B) and T2 sequences (D). Hypointense lesions (black holes) were noted on T1 sequence (D).
A: Axial FlAIR B: Axial FlAIR C: Sagittal T2 D: Axial T1

Figure 2 MRI of the Brain; T2



A

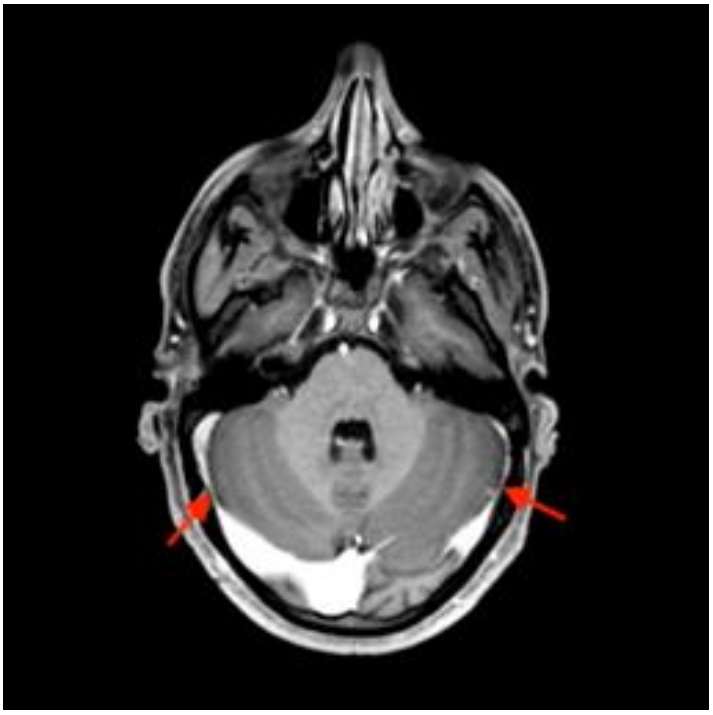


B

A: Axial T2: Kinking of the optic nerves.

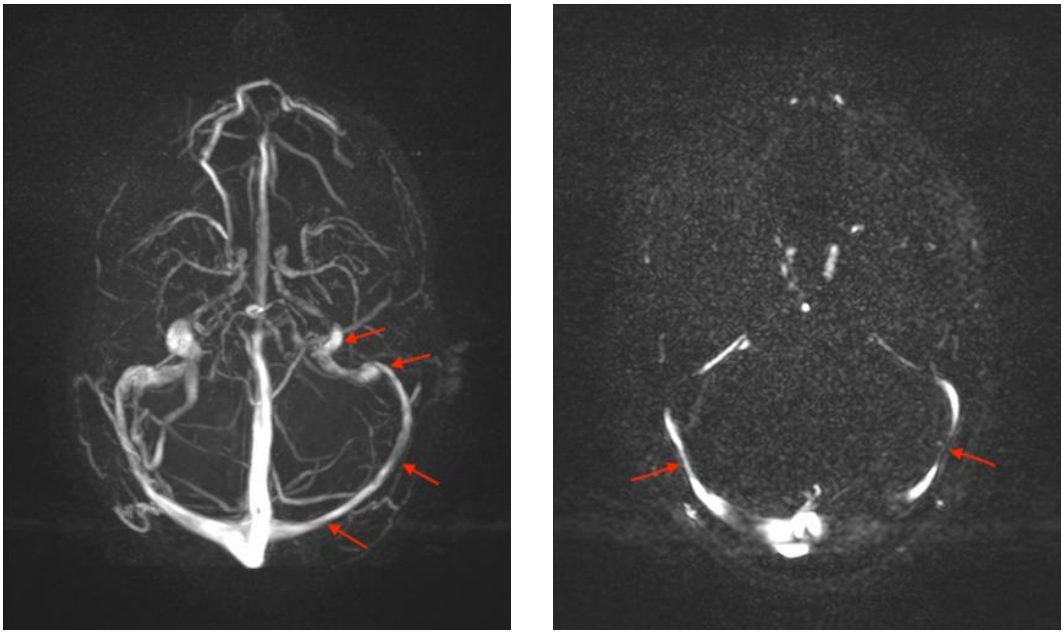
B: Sagittal T2: Partial empty sella turcica.

Figure 3 MRI of the Brain with Contrast



MRI of the brain with contrast showing focal stenosis of bilateral sagittal sinuses.

Figure 4 MRV of the Brain



A B

A: Left transverse and sigmoid sinuses overall narrower than the right.
B: Focal stenosis of bilateral transverse sinuses.

Authors' Contributions

MH designed the study, analysed the data, reviewed, revised and finalized the manuscript. MA collected the data and did the first draft. Both authors approved the final manuscript.

Author Details

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Declarations

Ethics Approval and Consent to Participate

The subject in the case report was fully informed of the study objectives and written consent was obtained from him.

Consent for Publication

Written informed consent to publish this information was obtained from study participant. Proof of consent to publish from study participant can be requested at any time.

Competing Interests

The authors declare that they have no competing interests.

Availability of Data and Materials

The dataset is available upon the reasonable request to corresponding author.

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References

1. Compston, A., Winedl, H., & Kieseier, B. C. (2008). Coles. Multiple sclerosis. Lancet, 372, 1502-1517.
2. Leray, E., Moreau, T., Fromont, A., & Edan, G. (2016). Epidemiology of multiple sclerosis. Revue neurologique, 172(1), 3-13.
3. Eftekhari, S., Westgate, C. S. J., Uldall, M. S., & Jensen, R. H. (2019). Preclinical update on regulation of intracranial pressure in relation to idiopathic intracranial hypertension. Fluids and Barriers of the CNS, 16, 1-12.
4. Friedman, D. I., Liu, G. T., & Digre, K. B. (2013). Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology, 81(13), 1159-1165.
5. D′amico, D., Curone, M., Ciasca, P., Cammarata, G., Melzi, L., Bussone, G., & Bianchi Marzoli, S. (2013). Headache prevalence and clinical features in patients with idiopathic intracranial hypertension (IIH). Neurological Sciences, 34, 147-149.
6. Umapathi, T., Kor, A. C., Venketasubramanian, N., Lim, C. T., Pang, B. C., Yeo, T. T., ... & Ang, S. P. B. (2004). Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). Journal of neurology, 251, 1227-1231.
7. Tsai, L., Hsieh, S., & Chang, Y. (2005). Neurological manifestations in severe acute respiratory syndrome. Acta neurologica Taiwanica, 14(3), 113.
8. Kim, J. E., Heo, J. H., Kim, H. O., Song, S. H., Park, S. S., Park, T. H., ... & Choi, J. P. (2017). Neurological complications during treatment of Middle East respiratory syndrome. Journal of clinical neurology (Seoul, Korea), 13(3), 227-233.
9. Paterson, R. W., Brown, R. L., Benjamin, L., Nortley, R., Wiethoff, S., Bharucha, T., ... & Zandi, M. S. (2020). The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain, 143(10), 3104-3120.
10. Harapan, B. N., & Yoo, H. J. (2021). Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). Journal of neurology, 268(9), 3059-3071.
11. Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., ... & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology, 77(6), 683-690.
12. Zanin, L., Saraceno, G., Panciani, P. P., Renisi, G., Signorini, L., Migliorati, K., & Fontanella, M. M. (2020). SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta neurochirurgica, 162, 1491-1494.
13. Rigamonti, A., Mantero, V., Piamarta, F., Spena, G., & Salmaggi, A. (2021). Cerebral venous thrombosis associated with coronavirus infection: an underestimated entity?. Neurological Sciences, 42(1), 317-318.
14. Favas, T. T., Dev, P., Chaurasia, R. N., Chakravarty, K., Mishra, R., Joshi, D., ... & Pathak, A. (2020). Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. Neurological Sciences, 41, 3437-3470.
15. Chougar, L., Mathon, B., Weiss, N., Degos, V., & Shor, N. (2020). Atypical deep cerebral vein thrombosis with hemorrhagic venous infarction in a patient positive for COVID-19. American Journal of Neuroradiology, 41(8), 1377-1379.
16. Klein, D. E., Libman, R., Kirsch, C., & Arora, R. (2020). Cerebral venous thrombosis: atypical presentation of COVID-19 in the young. Journal of stroke and cerebrovascular diseases, 29(8), 104989.
17. Edén, A., Kanberg, N., Gostner, J., Fuchs, D., Hagberg, L., Andersson, L. M., ... & Gisslén, M. (2021). CSF biomarkers in patients with COVID-19 and neurologic symptoms: a case series. Neurology, 96(2), e294-e300.
18. Espíndola, O. M., Brandão, C. O., Gomes, Y. C. P., Siqueira, M., Soares, C. N., Lima, M. A. S. D., ... & Silva, M. T. T. (2021). Cerebrospinal fluid findings in neurological diseases associated with COVID-19 and insights into mechanisms of disease development. International Journal of Infectious Diseases, 102, 155-162.
19. Chen, B. S., Newman, N. J., & Biousse, V. (2021). Atypical presentations of idiopathic intracranial hypertension. Taiwan Journal of Ophthalmology, 11(1), 25.
20. Babikian, P., Corbett, J., & Bell, W. (1994). Idiopathic intracranial hypertension in children: the Iowa experience. Journal of Child Neurology, 9(2), 144-149.
21. Capobianco, D. J., Brazis, P. W., & Cheshire, W. P. (1997). Idiopathic intracranial hypertension and seventh nerve

palsy. Headache: The Journal of Head and Face Pain, 37(5), 286-288.
22. Bateman, G. A., Lechner-Scott, J., Bateman, A. R., Attia, J., & Lea, R. A. (2020). The incidence of transverse sinus stenosis in multiple sclerosis: further evidence of pulse wave encephalopathy. Multiple sclerosis and related disorders, 46, 102524.
23. Bateman, G. A., Lechner-Scott, J., Copping, R., Moeskops, C., & Yap, S. L. (2017). Comparison of the sagittal sinus cross-sectional area between patients with multiple sclerosis, hydrocephalus, intracranial hypertension and spontaneous intracranial hypotension: a surrogate marker of venous transmural pressure? Fluids and Barriers of the CNS, 14(1), 1-5.
24. De Simone, R., Ranieri, A., Sansone, M., Marano, E., Russo, C. V., Saccà, F., & Bonavita, V. (2019). Dural sinus collapsibility, idiopathic intracranial hypertension, and the pathogenesis of chronic migraine. Neurological Sciences, 40, 59-70.
25. Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., ... & Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology, 17(2), 162-173.
26. Burnham, J. A., Wright, R. R., Dreisbach, J., & Murray, R. S. (1991). The effect of high-dose steroids on MRI gadolinium enhancement in acute demyelinating lesions. Neurology, 41(9), 1349-1349.