Cerebral Venous Sinus Thrombosis and Pachymeningitis in IgG4 Related Disease: Report of Two Cases and Review of Literature

Dear Sir,

Immunoglobulin G4-related disease (IgG4-RD) is a systemic disorder characterized by an inflammatory reaction, rich in IgG4-positive plasma cells associated with sclerosis.[1] The disease spectrum includes autoimmune pancreatitis, Mikulicz disease, pseudotumor of the lung, tubulointerstitial nephritis, and Riedel thyroiditis. Central nervous system involvement in IgG4-RD is rare, and usually manifests with hypertrophic pachymeningitis (HP), hypophysitis, and orbital pseudotumor. Hypertrophic pachymeningitis is also observed in many other conditions including infectious diseases (e.g., neurosyphilis, tubercular, bacterial, and fungal meningitis), inflammatory disorders (e.g., granulomatosis with polyangitis, giant-cell arteritis, rheumatoid arthritis, and neurosarcoidosis), and malignancies (e.g., dural carcinomatosis, metastasis from adjacent skull bone or brain, meningioma, and lymphomas). Hypertrophic pachymeningitis may be the only manifestation in IgG4-RD without involvement of other organs with normal to mildly increased serum IgG4 concentrations. Symptoms include headache, neck pain, cranial nerve palsies,
hydrocephalus, seizure, motor weakness, sensory loss, or features of myeloradiculopathy. In the available medical literature, there is paucity of reports of cerebral venous sinus thrombosis (CVST) secondary to HP in IgG4-RD. In our cohort of 172 patients with CVST, two were due to IgG4-RD pachymeningitis. In this communication, we report these two CVST patients with IgG4-RD hypertrophic pachymeningitis in the light of reported literature.

Patient # 1: A 31-year-old male presented with 4 episodes of recurrent unilateral visual loss in past 21 months. In the first episode, he developed acute onset, painless blurring in left eye which progressively deteriorated to perception of light over 20 days. He did not have any other neurological and systemic symptoms. He was diagnosed as optic neuritis and treated with methyl prednisolone for 5 days followed by oral prednisolone for 10 days. He had three more such episodes, second one in the right eye. His vision improved after the initial three attacks, but visual loss persisted to finger count at 1 meter after the 4th attack. Six months back, he developed one episode of left focal convulsive seizure for 2 min with unconsciousness and received tablet sodium valproate 500 mg twice daily. Three months back, he developed acute paraparesis. There was no paresthesia, bowel bladder involvement, flexor spasms or dysarthria. He was non-diabetic, non-hypertensive, and did not suffer from tuberculosis. His blood pressure was 110/70 mm of Hg, pulse rate 80/minute, and respiratory rate 14/minute. His cardiovascular, respiratory, and abdominal examinations were unremarkable. He was conscious, oriented, and his Mini Mental Status Examination score was 29/30. Vision in right eye was 6/12 and in left eye finger counting at one meter. Color vision was impaired bilaterally, left more than right. Fundus examination revealed temporal pallor bilaterally. He had spastic paraparesis of grade 3, brisk knee, and ankle reflexes with extensor plantar response bilaterally. Sensory and cerebellar examinations were normal. Cranial MRI revealed pachymeningitis along with bilateral frontal gliotic changes. Magnetic resonance venography showed superior sagittal sinus (SSS) and straight sinus thrombosis [Figure A1 and A2]. MRI spine was unremarkable. Laboratory testing revealed normal hemoglobin, blood counts, kidney, liver, and thyroid function tests. Erythrocyte sedimentation rate was 10 mm at first hour. C-reactive protein was 1.10 mg/dl. His cerebrospinal fluid analysis was normal. HIV serology was negative. Serum ACE level was 28U/L (8-52 U/L), vitamin B12 level 1236pg/ml, and homocysteine 13.1µmol/L. Antinuclear antibody, anti-double stranded DNA antibody, antiphospholipid antibody, and p and c-ANCA were negative. Protein C, protein S and antithrombin III levels were within normal limits. Factor V Leiden mutation was negative. Serum IgG level was 2000 mg/dl (normal 800–1800 mg/dl) and IgG4 was 3.2 gram/L (normal 0.03–2.01gram/L). Hence a diagnosis of CVST secondary to IgG4-RD HP was considered. He was prescribed prednisone 40 mg daily, oral anticoagulant, and tizanidine 2 mg three times daily. Sodium valproate was continued. At 5 months of follow up, he had mild spastic lower limb weakness and was independent for activities of daily living. Vision in left eye did not improve and his repeat cranial MRI revealed partial resolution of pachymeningitis and persistence of sinus thrombosis [Figure A3 and A4].

Patient # 2: A 46-year-old male presented with headache since 6 months. He is non-diabetic, non-hypertensive, and did not have any systemic features. His blood pressure was...
130/80 mm Hg and pulse rate 78/minute. Systemic and neurological examinations were normal. Cranial MRI revealed diffuse pachymeningeal thickening. Magnetic resonance venography revealed straight sinus and anterior two-thirds SSS thrombosis [Figure B1 and B2]. His blood count, kidney, liver, and thyroid function tests, urine examination and radiograph of chest were normal. Erythrocyte sedimentation rate was 30 mm at first hour and C-reactive protein was 2.64 mg/dl. His vitamin B12 and homocysteine levels were normal. Protein C activity was 126% (70–130%), protein S 76% (65–140%), and antithrombin III 120% (80–120%). Autoimmune profile including antinuclear antibody, anti-double stranded DNA, antiphospholipid antibody, p and c-ANCA were negative. Factor V Leiden mutation was negative. His serum IgG level was 2020 mg/dl and IgG4 level was >3.6 gram/L (0.03–2.01 gram/L). A diagnosis of CVST secondary to IgG4-RD HP was made, and he was advised tablet prednisone 0.5 mg/kg body weight along with oral anticoagulant. His international normalized ratio was maintained between 2.5 to 3. At one-month follow up, his headache has resolved completely and repeat MRI with MRV at 3 months revealed partial resolution of pachymenigitis and incomplete recanalization of SSS [Figure B3 and B4].

Both patients had CVST due to IgG4-RD hypertrophic pachymeningitis which was confirmed by raised serum IgG4 level and absence of other CVST risk factors. IgG4-RD is a systemic inflammatory disease characterized by elevated serum IgG4 levels, abundant infiltration of IgG4-positive plasma cells and high-grade sclerosis of the affected region. B-cell–dependent activation of pathogenic CD4+ T cells mediates inflammation and fibroblast activation which lead to collagen deposition, resulting in tissue hypertrophy and increased dural thickness. Meningeal IgG4-RD manifests mainly as pachymeningitis of the brain or spinal cord. Pachymeningitis patients have variable manifestations; supratentorial HP

| Author/Years | Age/Gender | Thrombosed Sinuses | Treatment | Recanalization |
|--------------|------------|--------------------|-----------|---------------|
| Kioumehr et al., 1994 | 35/M | Transverse sinus | NA | NA |
| Goyal et al., 1997 | 19/F | Dural sinus thrombosis | Steroid | NA |
| Yutente et al., 1999 | 30/F | Pan sinus thrombosis | Steroid, azathioprine | No recanalization |
| Hamada et al., 2000 | 64/M | Dural AVF of straight sinus | Embolization, excision of straight sinus, steroid | |
| Lee et al., 2003 | 23/F | Straight sinus | Prednisolone and azathioprine | NA |
| Oiwa et al., 2004 | 44/M | Pan sinus thrombosis | Anticoagulant | No recanalization |
| Lampropoulos et al., 2006 | 63/M | Cerebral venous sinus thrombosis | Oral steroid + azathioprine | NA |
| Singh et al., 2009 | 49/f | Posterior SSS, bilateral transverse and sigmoid sinuses. | Oral steroid | NA |
| Bhatia et al., 2009 | 38/M | Posterior SSS, torcula, bilateral transverse and sigmoid sinuses. | Pulse steroid followed by oral steroid | No recanalization |
| | 23/M | Posterior SSS, right transverse sinus, right sigmoid, and straight sinus. | Intravenous dexamethasone for 1 week followed by oral prednisolone with tapering doses | Recanalized except partial recanalization of straight sinus |
| Xia et al., 2010 | 42/F | SSS | Steroids, azathioprine, mycophenolate, adalimumab and methotrexate | No recanalization |
| Saito T et al., 2014 | 72/F | Confluence of sinus, straight sinus, right transverse sinus | Steroid | NA |
| Zhao et al., 2014 | 44/F | Stenosis | Steroid | NA |
| | 40/F | Occlusion | Steroid | NA |
| | 41/M | Occlusion | Steroid, azathioprine | |
| | 17/F | Stenosis | Steroid | |
| | 71/F | Stenosis | Steroid | |
| Nayak R et al., 2018 | 23/M | Left transverse and sigmoid sinus, left jugular vein | Ceftazidime, cotrimoxazole | NA |
| Kuribayashi et al., 2019 | 58/M | SSS | Steroid, cyclophosphamide | Recanalized |
| Di Stefano V, et al., 2019 | 47/F | SSS, transverse and sigmoid sinus | Steroid, cyclophosphamide, rituximab | Recanalized |

AVF= arteriovenous fistula, CSF= cerebrospinal fluid, F=female, M=male, NA=not available, SSS= superior sagittal sinus
Conflicts of interest
There are no conflicts of interest.

Varun K. Singh, Jayantee Kalita¹, Usha K. Misra¹, Sunil Kumar⁴
Department of Neurology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, ⁄Department of Neurology, and ⁄Radiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareli Road, Lucknow, Uttar Pradesh, India

Address for correspondence: Dr. Jayantee Kalita, Professor, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow - 226 014, Uttar Pradesh, India. E-mail: jayanteek@yahoo.com

References
1. AbdelRazek MA, Venna N, Stone JH. IgG4‑related disease of the central and peripheral nervous systems. Lancet Neurol 2018;17:183‑92.
2. Ekizoglu E, Coban O, Ulukan C, Gezen Ak D, Dursun E, Tuzun E, et al. Intracranial hypertension related to cerebral venous thrombosis; and acute ischemic stroke with micro‑infarcts associated with IgG4‑related disease. Int J Neurosci 2018;128:1097‑9.
3. Sireesha Y, Uppin MS, Ganti S, Alagolu R, Mudumba VS, Bhattacharjee S, et al. A series of biopsy‑proven patients with immunoglobulin g4‑related neurological disease. Ann Indian Acad Neurol 2019;22:73‑8.
4. Huang K, Xu Q, Ma Y, Zhan R, Shen J, Pan J. Cerebral venous sinus thrombosis secondary to idiopathic hypertrophic cranial pachymeningitis: Case report and review of literature. World Neurosurg 2017;106:105.
5. Kioumehr F, Rooholamini SA, Yaghmai I, Verma R. Idiopathic hypertrophic cranial pachymeningitis: A case report. Neuroradiology 1994;36:292‑4.
6. Goyal M, Malik A, Mishra NK, Gaikwad SB. Idiopathic hypertrophic pachymeningitis: spectrum of the disease. Neuroradiology 1997;39:619‑23.
7. Yunten N, Oran I, Calli C, Parildar M. Hypertrophic cranial pachymeningitis involving dural sinuses: A pseudo signal‑void appearance on MRI. Eur J Radiol 1999;31:188‑92.
8. Hamada J, Yoshinaga Y, Korogi Y, Ushio Y. Idiopathic hypertrophic cranial pachymeningitis associated with a dural arteriovenous fistula involving the straight sinus: Case report. Neurosurgery 2000;47:1230‑3.
9. Lee YC, Chuang YC, Hsu SW, Liu CC. Idiopathic hypertrophic cranial pachymeningitis: Case report with 7 years of imaging follow‑up. AJNR Am J Neuroradiol 2003;24:119‑23.
10. Oiwa Y, Hyotani G, Kamei I, Itakura T. Idiopathic hypertrophic cranial pachymeningitis associated with total occlusion of the dural sinuses: case report. Neurol Medicochir 2004;44:650‑4.
11. Lampropoulos CE, Zain M, Jan W, Nader‑Sepahi A, Sabin IH, D’ Cruz DP. Hypertrophic pachymeningitis and undifferentiated connective tissue disease: A case report and review of the literature. Clin Rheumatol 2006;25:399‑401.
12. Singh C, Kesavadass C, Nair MD, Sarada C. Acquired anterior basal encephalocele in idiopathic hypertrophic pachymeningitis. Neuroradiol 2009;21:791‑4.
13. Bhatia R, Tripathi M, Srivastava A, Garg A, Singh MB, Nanda A, et al. Idiopathic hypertrophic cranial pachymeningitis and dural sinus occlusion: Two patients with long‑term follow‑up. J Clin Neurosci 2009;16:937‑42.
14. Xia Z, Chen‑Plotkin A, Schmahlmann JD. Hypertrophic pachymeningitis and cerebral venous sinus thrombosis in inflammatory bowel disease. J Clin Neurosci 2010;17:1454‑6.
15. Saito T, Fujimori J, Yoshida S, Kaneko K, Kodera T. Rinsho Shinkeigaku 2014;54:827‑30.
16. Zhao M, Geng T, Qiao L, Shi J, Xie J, Huang F, et al. Idiopathic hypertrophic pachymeningitis: Clinical, laboratory and neuroradiologic features in China. J Clin Neurosci 2014;21:1127‑32.
17. Nayak R, Patel B, Raju K. Chronic pachymeningitis with dural venous sinus thrombosis: An unusual presentation of cranial melioidosis. Neurol India 2018;66:1185‑7.
18. Kuribayashi T, Manabe Y, Fujiwara S, Onote Y, Narai H, Abe K. Combined hypertrophic pachymeningitis and cerebral venous thrombosis in a case of granulomatosis with polyangiitis. Case Rep Neurol 2019;11:252-5.

19. Di Stefano V, Dono F, De Angelis MV, Onofrj M. Hypertrophic pachymeningitis and cerebral venous thrombosis in myeloperoxidase-ANCA associated vasculitis. BMJ Case Rep 2019;12:bcr-2018-226780.

20. Chen LY, Wong PC, Noda S, Collins DR, Sreenivasan GM, Coupland RC. Polyclonal hyperviscosity syndrome in IgG4-related disease and associated conditions. Clin Case Rep 2015;3:21726.

To Editor,

Intramedullary spinal cord lesions can result due to varied etiologies such as: infection (tuberculosis, syphilis, viruses, fungal, bacterial), demyelination (acute transverse myelitis, multiple sclerosis-MS, neuromyelitis optica spectrum disorders-NMOSD, ADEM-acute demyelinating encephalomyelitis, MOG-associated-disorders), granulomatous disorders, vascular, syringomyelia, congenital abnormalities, and neoplastic lesions.

[NMOSD is characterized by repeated attacks of optic neuritis and myelitis. The severity of the neurological deficit and the imaging characteristics may mimic intramedullary spinal cord tumor. Hereby, we describe three patients of AQ P4-positive NMOSD misdiagnosed as intramedullary tumor and operated.

Patient-1: A 32-year-old gentleman presented with three episodes of recurrent neurological disturbances between 2003 and 2010 that improved with steroids. In 2013, he developed progressive quadriparesis, MRI showed a C2-C3 intramedullary lesion; possibility of an intramedullary tumor was considered and C1-C3 laminectomy was done. Histopathology was suggestive of demyelination, was treated with steroids. Between 2004 and 2013, he had five more episodes. Totally he had three episodes of optic neuritis and six episodes of myelopathy. He was referred to our institute in Nov 2014. During that time, his neurological examination revealed visual acuity of 6/60 in the right eye and complete blindness in the left eye. Spastic right hemiparesis with 4/5 power and mild distal weakness in left hand. Deep tendon reflexes (DTRs) were brisk in all four limbs with bilateral extensor plantars. His evaluation revealed positive serum AQ P4 antibody. He was diagnosed as AQ P4-positive NMOSD and started on azathioprine.

Patient-2: A 35-year-old lady presented with stiffness of both upper and lower limbs. MRI showed long segment expansile

Figure 1:

MRI findings of the patients. (a, b) MRI images of the Case-1. (a) Sagittal T2 sequence showing the atrophies operated cervical spinal cord across the C2-C3. (b) Axial images of the same showing atrophied cord with T2 hyperintensity involving more than 50% of the cervical cord. (c, d) MRI images of the Case-2. (c) Sagittal T2 sequence showing the MRI changes prior to surgery showing T2 hyperintensity of the cervical cord with edematous cord. (d) Sagittal T2 sequence of the same patient 6 months after the surgery showing the atrophied thinned out cervical cord with brainstem changes across the Pons. (e-h) MRI images of the Case-3. Sagittal T2 sequence pre (e) and Post-surgery (f). (g, h) Axial images of the cervical cord showing T2 hyperintensity with bright spotty lesion

Submitted: 11-May-2020  Revised: 23-Jun-2020  Accepted: 14-Jul-2020

Published: 08-Jan-2021

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

DOI: 10.4103/aijan.AIAN_411_20