DOI: 10.7860/JCDR/2024/74167.19879

Case Report

Internal Medicine Section

A Diagnostic Conundrum in Case of Primary Central Nervous System Vasculitis Presenting as Young Stroke

PRAKASH SHENDE[1], SUBASHINI VADIVEL[2], KUNAL MODI[3]

ABSTRACT

Primary Central Nervous System Vasculitis (PCNSV) is a rare inflammatory condition affecting the blood vessels in the brain and spinal cord, without signs of systemic vasculitis. The symptoms of PCNSV are typically non-specific and varied. This case involves a 16-year-old female who arrived at the emergency department with tingling and numbness in her left upper and lower extremities since waking up that morning. Within hours, she developed significant weakness in her left arm and leg. She had no significant medical history, comorbidities, or history of substance use. On examination, her vitals were stable, and she was fully conscious and oriented. Neurological examination revealed right-sided mouth deviation and decreased muscle power in her left limbs, while sensory function remained normal. Routine blood tests were normal, except for mildly elevated Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). Autoimmune markers and complement levels were within normal limits. Cerebrospinal Fluid (CSF) analysis showed lymphocytic pleocytosis and mildly elevated protein levels. Magnetic Resonance Imaging (MRI) brain imaging revealed multiple small, acute, non-haemorrhagic infarcts in the right frontoparietal and temporo-occipital regions. MR angiography indicated thrombosis in the right internal carotid artery, with extensive thickening and constriction in various segments, consistent with PCNSV. She was treated with dual antiplatelet therapy, antiepileptics, methylprednisolone pulse therapy, and intravenous cyclophosphamide, followed by maintenance therapy with methotrexate and oral steroids. This case underscores the importance of early recognition and aggressive treatment of PCNSV to prevent long-term neurological deficits. Reporting this case is crucial as it highlights an atypical presentation in a young female, emphasising the need for awareness and comprehensive diagnostic approaches.

Keywords: Cerebrovascular disorders, Immunosuppressive therapy, Magnetic resonance imaging, Thrombosis

CASE REPORT

A 16-year-old female was brought to the emergency department with complaints of tingling and numbness in her left upper and lower extremities since waking up that morning, which progressed to weakness in her left arm and leg within a few hours of admission. There was no substantial family or medication history and she denied having any comorbidities, drug abuse or alcohol consumption. On assessment, her vitals were stable. She was conscious and oriented to time, place and person. CNS examination revealed an angle of mouth deviation to the right with no other cranial nerve involvement. Motor examination revealed decreased power (grade 2/5, movements possible only with gravity eliminated) and reduced tone in the left upper and lower limbs sensory examination on all four limbs was within normal limits. Other systemic examinations were normal.

Routine investigations were within the normal range. ESR and CRP were mildly elevated [Table/Fig-1]. The Antinuclear Antibody (ANA) profile (ANA by blotting and ANA by immunofluorescence) and complement levels (C3, C4) were within normal limits [Table/Fig-2]. CSF examination showed lymphocytic pleocytosis with mildly elevated protein levels.

Investigation	Lab values	Reference range
Vit D	10	20-40 ng/mL
B12	540	160-950 pg/mL
Homocysteine	10.3	5-15 micro mol/L
HbA1c	5.6	<5.7%
Erythrocyte Sedimentation Rate (ESR)	39	<20 mm/hr
C-Reactive Protein (CRP)	3.2	0.3-1 mg/dL

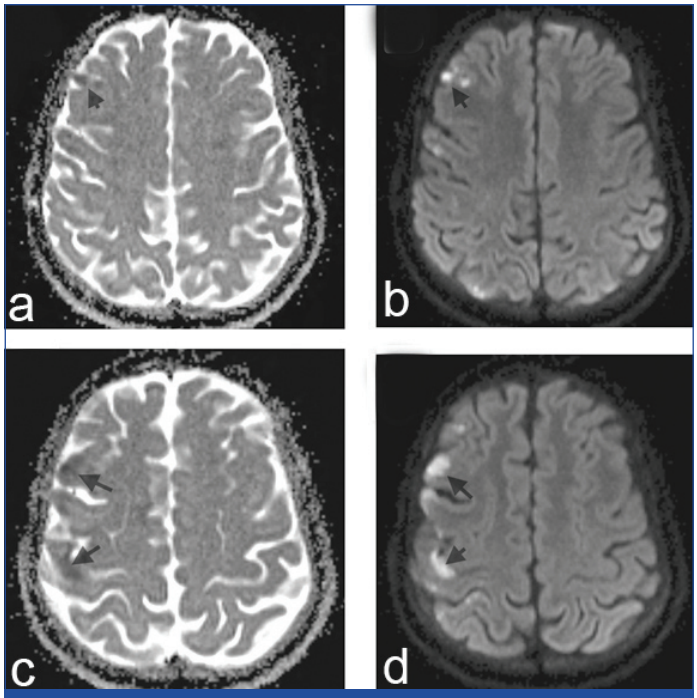
[Table/Fig-1]: Routine blood investigations.

Investigations	Results
Thyroid function test	Normal
Fasting lipid profile	Normal
HIV/HbsAg/HCV	Non-reactive
ANA IF	Negative
ANA BLOT	Negative
ANCA	Negative
APLA profile	Negative

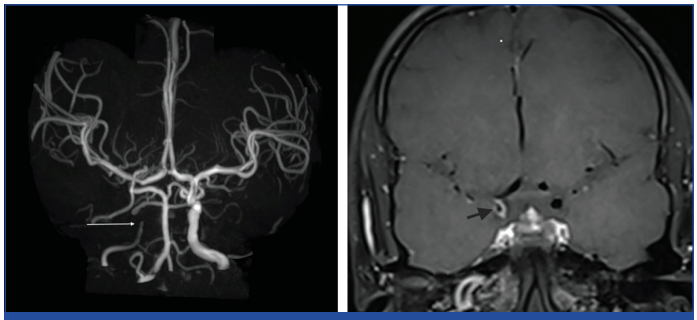
[Table/Fig-2]: Special investigation including ANA blot and APLA.

MRI brain imaging revealed multiple small acute non-haemorrhagic infarcts in the cortical and subcortical regions of the right frontoparietal and temporo-occipital areas (right middle cerebral artery/posterior cerebral artery watershed areas) [Table/Fig-3]. MR angiography revealed reduced flow in all segments of the right internal carotid artery distal to the origin of the ophthalmic artery, indicating thrombosis [Table/Fig-4].

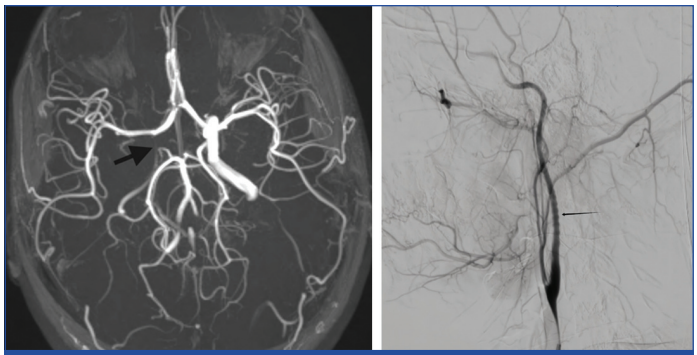
According to the MRI vessel wall study [Table/Fig-5], the right internal carotid artery had extensive circumferential thickening and substantial constriction from the cervical section to the petrous, lacerum, cavernous, clinoid, and supra-clinoid regions. Postcontrast enhancement was seen along the thicker walls of the right carotid artery, especially in the cavernous and clinoid segments. The clinoid and supra-clinoid segments were significantly narrower with noticeable wall thickening and reduced flow signal within the lumen [Table/Fig-6]. Additionally, short-segment occlusion was observed in these areas. Subtle wall enhancement was also seen in the right ophthalmic and middle



[Table/Fig-3]: a,b) MRI brain shows multiple small acute non-haemorrhagic infarcts in the frontoparietal area; c,d) Shows in the temporo-occipital area.



[Table/Fig-4]: MR Angiography showing reduced flow in the right internal carotid artery (white arrow).
[Table/Fig-5]: MR vessel wall showing circumferential thickening of the right internal carotid artery. (Images from left to right)



[Table/Fig-6]: MR vessel wall showing absent flow in the right internal carotid artery.
[Table/Fig-7]: Cerebral angiography showing chronic occlusive changes in the right supra-clinoid part of the internal carotid artery. (Images from left to right)

cerebral arteries. Cerebral angiography showed chronic occlusive changes in the right supra-clinoid part of the internal carotid artery suggesting vasculitis [Table/Fig-7].

An extensive workup was conducted to rule out other differential diagnoses such as CNS vasculitis secondary to systemic inflammation, infectious vasculitis, Takayasu arteritis, and drug-induced vasculitis. In the absence of any underlying disease, a diagnosis of PCNSV was established.

She was started on dual antiplatelet therapy and antiepileptics. Induction therapy included intravenous methylprednisolone, 500 mg once daily for three days, followed by intravenous cyclophosphamide, 500 mg once a month for six months. Over six months, the steroids were gradually tapered. She maintained well on oral prednisolone, 5 mg once daily, and methotrexate, 15 mg once a week.

She showed gradual improvement over six months, with regular physiotherapy. The power in her upper and lower limbs increased to 4/5, meaning she could move her limbs against resistance.

DISCUSSION

The PCNSV is characterised by inflammation within the walls of blood vessels in the CNS, often resulting in destructive changes, occlusion, and infarction. Although relatively rare, this condition is serious and potentially life-threatening [1].

A cohort study conducted at the All India Institute of Medical Sciences (AIIMS) in New Delhi by Agarwal A et al., investigated the age of onset for PCNSV in India. The study found that the median age of onset in India is 28.6 years, with a significant male predominance, indicated by a ratio of 4.8 males to 1 female [1]. In contrast, globally, the median age of onset for PCNSV is typically around 40 to 50 years [2]. The present case report underscores an even younger onset of PCNSV, highlighting the variability in age at presentation across different populations.

PCNSV lacks pathognomonic symptoms and can present with a wide range of clinical manifestations. The most common symptoms include seizures (70.7%), headaches (59.8%), hemiparesis (54.9%), cognitive impairment (29.3%), visual impairment (21.9%), ataxia (20.7%), and paraparesis (13.4%) [1]. Globally, spinal cord involvement occurs in a small percentage of cases (<5%), causing vasculitic myelopathies [2]. The prevalence of cervical myelopathies in India is a subject of debate. In a study conducted at AIIMS by Agarwal A et al., with 82 patients, reported a prevalence of 38.3% [1]. In contrast, Sundaram S et al., found cervical myelopathies to be rare in their study of 45 patients [3]. Although tingling and numbness are not typically associated with PCNSV, they can occasionally occur, as observed in this case.

The clinical course of PCNSV can vary significantly, manifesting as acute, chronic, chronically progressive, relapsing, or remitting. The specific clinical subtypes and symptomatology depend on the type of vessels involved. Small vessel involvement often leads to encephalopathy, cognitive impairment, or seizures and relapses are commonly seen in this subtype whereas, large vessel vasculitis typically presents with stroke and focal deficits [2,4].

The diagnostic criteria by Calabrese LH and Mallek JA for PCNSV include the presence of a newly acquired, otherwise unexplained neurological deficit. It is essential to exclude any evidence of systemic vasculitis or other conditions that could account for the patient's neurological symptoms. The diagnosis is supported by evidence of an inflammatory process within the CNS, demonstrated either by angiography showing vasculitis (such as vessel narrowing or occlusion) or by brain biopsy revealing granulomatous inflammation, lymphocytic infiltration, or necrotising vasculitis [5]. The diagnosis of PCNSV typically faces an average delay of 23 months, primarily because it is a diagnosis of exclusion, necessitating the elimination of other potential conditions [1,3]. This prolonged delay can lead to severe neurological deficits. This case report emphasises the vital importance of early diagnosis and prompt management to mitigate long-term complications and improve patient outcomes.

The differential diagnosis of PCNSV includes various conditions with similar clinical and imaging presentations. Secondary CNS vasculitis due to systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, neurosarcoidosis, and infectious vasculitis from

bacterial, tuberculosis, viral (e.g., HIV), fungal, Lyme, or syphilitic infections must be considered. Drug-induced vasculitis from illicit drugs or medications is also possible [3]. Moyamoya disease, a progressive cerebrovascular disorder, and atherosclerosis, a chronic vascular disease, both present with vascular stenosis and occlusion. Reversible Cerebral Vasoconstriction Syndrome (RCVS) features reversible cerebral artery narrowing, often with thunderclap headaches [6]. Multiple sclerosis, an autoimmune demyelinating disease, and CNS neoplasms, including primary brain tumours or metastases, can present similarly. Other important differentials include cerebral amyloid angiopathy, primary CNS lymphoma, autoimmune encephalitis (e.g., anti-NMDA receptor encephalitis), and radiation vasculopathy from prior cranial irradiation [7].

After a comprehensive evaluation and ruling out all other possibilities, the laboratory investigation for PCNSV may include mildly elevated inflammatory markers such as ESR and CRP. The tests are likely to be negative for ANA, Antineutrophil Cytoplasmic Antibodies (ANCA), antiphospholipid antibodies, and other serological tests [2,4] CSF analysis in PCNSV often shows features of inflammation, such as mild lymphocytic pleocytosis or elevated protein levels, while oligoclonal bands or raised IgG levels are occasionally observed [2,4,8].

Imaging modalities including MRA and CT angiogram are sensitive but not entirely specific for diagnosing PCNSV. Conventional cerebral angiography and MRI vessel wall imaging are diagnostically superior. Features such as alternate narrowing and dilatation of vessels, multilocular occlusions or fusiform arterial dilatations indicate CNS vasculitis. Vessel wall beading is common but non-specific [9-11]. Despite advancements in imaging technology, biopsy remains the gold standard for diagnosing PCNSV. In cases where imaging findings are inconclusive or when there is a need for definitive histological confirmation, biopsy should be considered as an essential diagnostic tool [2,4].

Pathophysiological types of PCNSV can be classified based on histopathological findings and the size of the affected vessels. The most common type is granulomatous vasculitis, marked by granuloma formation involving medium and small-sized blood vessels. Lymphocytic vasculitis, another prevalent type, involves lymphocytic infiltration into the vessel wall and also predominantly affects small to medium-sized vessels. Necrotising vasculitis, although less common, is more severe and characterised by the destruction of blood vessel walls leading to necrosis, involving both small and medium-sized vessels [1,3,6]. Biopsy was not performed for this case; the diagnosis was achieved through radiological evaluation. Given the absence of other risk factors or secondary diseases, treatment was initiated based on the radiological findings.

The treatment strategy for PCNSV involves induction therapy with steroids and cyclophosphamide, which has shown efficacy in preventing relapse compared to steroid monotherapy. Early detection and aggressive treatment with combined therapy has been associated with a significant reduction in disability [12,13]. Steroids including intravenous methylprednisolone pulse therapy or oral prednisone are commonly used in induction therapy. Intravenous cyclophosphamide is preferred in rapidly progressive disease [2,12,13]. Biological agents such as Rituximab and TNF-alpha blockers are considered in cases intolerant to steroids or non-responsive to conventional therapies [12-15]. Maintenance therapy typically begins 4-6 months after initiation and involves disease-modifying agents such as azathioprine, mycophenolate mofetil, or methotrexate, with the primary goal of reducing disability and preventing relapse [2,12-15]. The available treatment options are summarised in [Table/Fig-8] [12-15].

Treatment	Dosage
High-dose steroids (injectable methylprednisolone)	500 mg- 1 gm/day given over 3 to 5 days [12,13]
Cyclophosphamide	Intravenous 15 mg/kg, once a month for 6 doses [13]
Azathioprine	2-3 mg/kg/day [13,14]
Methotrexate	15-25 mg/week [13,14]
Mycophenolate mofetil	2-3 g/day [14]
Rituximab	Rituximab is given at a dose of 375 mg/m^2 weekly for 4 weeks, with maintenance doses of 500 mg to 1 g every six months if needed [15]
Oral prednisolone	Administer 1 mg/kg during the acute phase. Begin tapering steroids once the acute phase subsides. Achieve a dose of 30 mg of prednisone over four weeks. Reduce the dose by no more than 2.5 mg every two weeks. If symptoms recur, return to the last effective dose plus an additional 10 mg [12,13]

[Table/Fig-8]: The available treatment options for PCNSV listed [12-15].

CONCLUSION(S)

The PCNSV manifests with a diverse range of symptoms, ranging from headache to stroke. Diagnosis of PCNSV typically relies on MRI and cerebral angiography or brain biopsy. Initial management often involves the administration of steroids and antiplatelet agents. In cases of recurrent stroke, immunosuppressants such as azathioprine, methotrexate or immunomodulators like Rituximab may be considered. The combination of immunosuppressants and dual antiplatelet therapy plays a crucial role in mitigating the risk of recurrent stroke. Timely diagnosis and targeted treatment are essential for reducing long-term disability and mortality associated with PCNSV.

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PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of General Medicine, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India.
2. Resident, Department of General Medicine, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India.
3. Resident, Department of General Medicine, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Subashini Vadivel,
A 201, Anandi Baugh, Kharalwadi, Pimpri, Pune-411018, Maharashtra, India.
E-mail: subineethi@gmail.com

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 10, 2024
- Manual Googling: Jul 23, 2024
- iThenticate Software: Jul 31, 2024 (7%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

Date of Submission: **Jul 09, 2024**
Date of Peer Review: **Jul 20, 2024**
Date of Acceptance: **Aug 01, 2024**
Date of Publishing: **Sep 01, 2024**