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REVIEW

Cerebrovascular Manifestations of Neurosarcoidosis – An Overview

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Abstract: Neurosarcoidosis (NS) is defined as involvement of either central or peripheral nervous system by non-caseating granulomatous inflammation. They are seen clinically in 5–10% of those with sarcoidosis, though sub-clinical involvement is commoner. Cerebrovascular manifestations of neurosarcoidosis (CVNS) are considered even rarer but availability of novel imaging techniques and awareness of potential imaging markers for NS (yet to be validated), has resulted in better recognition. CVNS can occasionally be the presenting manifestation of sarcoidosis. Despite being rare, those with CVNS may have higher morbidity and mortality compared to other forms of NS. In this review, we aim to describe the clinical features, approach to diagnosis, mimics, investigation and management of CVNS, while attempting to identify features that differentiate central nervous system vasculitis associated with NS (CNSV-NS) from primary central nervous system vasculitis (PCNSV), a close diagnostic mimic.

Keywords: neurosarcoidosis, cerebrovascular neurosarcoidosis, vasculitis, stroke, NS

Introduction

Sarcoidosis is a multisystem inflammatory disease of unknown etiology. Sarcoidosis can literally affect any organ system in the body, with pathological hallmark being non-caseating granulomas resulting from exaggerated cell mediated immune response to hitherto unidentified antigens.[1,2] It predominantly affects lungs, lymph nodes (with a predilection for thoracic, mediastinal and cervical region), eyes and skin, with lymphatic system being involved in almost all cases.[1] However it can often pose a diagnostic dilemma due to its diverse clinical manifestations and poor specificity of positive tests.[2,3] The annual incidence of Sarcoidosis globally ranges between 1–15 per 100,000 population,[1–4] with higher rates among African-Americans (5–10/100,000)[5] and Northern Europeans (Scandinavian) (11–15/100,000).[6]

Neurosarcoidosis (NS) is defined as involvement of either central (CNS) or peripheral nervous system (PNS) by the pathological process of sarcoidosis. It becomes clinically evident over time in 5–10% of those with sarcoidosis.[1–4] However, asymptomatic magnetic resonance imaging (MRI) lesions of brain and/or spinal cord are seen in 10–15% and in up to 25% on autopsy.[1–3] The latter observation may be explained by the close communication between cervical lymphatics and perivascular cerebrospinal fluid (CSF) spaces in the brain.[1,3] The disease can spread through blood which is possibly supported by the perivascular distribution of cerebral granulomas.[1,3,4] Men may be more susceptible to develop NS in contrast to women who have predilection for systemic sarcoidosis, with median age of 43 years.[4] Neurological manifestations could be the very first symptom in approximately 50–70% of NS.[2,4] Over time up to 80% of the cohort of NS will eventually manifest systemic sarcoidosis, while 10–20% remain as isolated NS.[4] Diagnostic criteria have evolved from the Zajicek criteria[7] to the proposed NS consortium consensus group diagnostic criteria,[8] with major diagnostic limitation being obtaining a tissue for making a diagnosis of definite NS. The Zajicek criteria (1999) introduced a three-tier system—definite, probable and possible based on clinical, imaging and histologic evidence emphasizing on exclusion of mimics.[7] The 2018 International Neurosarcoidosis Consortium refined this by standardizing definitions, incorporating detailed MRI and CSF profiles, systemic evaluation and explicit diagnostic pathways for both

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CNS and PNS involvement.[8] Despite aggressive immunomodulation, approximately one third of NS do not improve.[4,9] 10-year neurological relapse free survival (RFS) rate for those with NS is 28%, with encephalic presentation associated with shorter RFS and worsening of disability at 60 months.[9]

The clinical spectrum of NS is diverse with the more common ones being cranial neuropathy (50–75%) [facial nerve and optic nerves being commonly affected], inflammatory brain parenchymal disease (5–50%) [encephalopathy, seizures, focal neurological deficits], lepto/pachymeningitis (10–20%) [sub-acute/chronic meningitis, hydrocephalus] and spinal cord inflammation (5–25%) [sub-acute/chronic myelopathy].[2,4] Cerebrovascular manifestations of NS (CVNS) (encompassing ischemic stroke, hemorrhagic strokes, central nervous system vasculitis associated with NS [CNSV-NS], cerebral venous sinus thromboses and sub-arachnoid hemorrhage [SAH]), are historically considered to be rare within the clinical spectrum of NS, possibly due to under-recognition.[10–20] CVNS related strokes may also be more severe. In this review we aim to describe the clinical features, approach to diagnosis, mimics, investigation and management of CVNS, with emphasis on CNSV-NS. We also attempt to identify features that differentiate CNSV-NS from primary central nervous system vasculitis (PCNSV), a close diagnostic mimic. Search strategy included PubMed using search words "Neurosarcoidosis," "Cerebrovascular Neurosarcoidosis," "Neurosarcoidosis" and "Stroke" for relevant articles written in English from 2000 to 2025.

Cerebrovascular Manifestations of Neurosarcoidosis (CVNS)

CVNS has been traditionally considered to be rare with literature evidence confined to individual case reports and case series.[2–4,10–20] Males are more affected with clinical spectrum encompassing ischemic strokes (predominantly small vessel sub-type),[10–14] hemorrhagic strokes (extremely rare),[15] and CNSV-NS.[16–19] Very rare presentations include Moya-Moya vasculopathy,[20] SAH and cerebral venous sinus thromboses.[10–12] However there has been recent increase in reports of CVNS with roughly 14% of NS cases being affected eventually.[21] Though rare, stroke mortality rates can reach up to 23% in those CVNS compared to 5% in those without.[13] Salient features of the spectrum of CVNS is highlighted in Table 1.

Pathogenic Mechanism of CVNS

Sarcoidosis is believed to result from exaggerated cell mediated immune response to as yet unidentified antigens, with the hallmark pathological feature being non-caseating granulomas.[3] Genetic predisposition, environmental factors as well as auto-immunity are considered to play pivotal roles in making an individual susceptible to develop sarcoidosis.[1,3,4] Granulomas are constituted by CD4+T helper cells and macrophages with a rim of B cells, CD8+ T helper cells as well as fibroblasts.[1,3] Tumor necrosis factor - alpha (TNF – α) secreted by macrophages is the major cytokine responsible for maintainence of sarcoid granulomas, thereby forming the basis for anti TNF-α agents in sarcoidosis treatment.[2] Interferon

Table 1 Salient Features of Spectrum of CVNS Depicting Clinical, Imaging Characteristics as Well as Natural Course of Individual Subtypes

CVNS Subtype	Typical Imaging Features	Associated Morbidity/Mortality
Ischemic Stroke	Small vessel infarcts (basal ganglia, pons), perivascular enhancement (PVE), leptomeningeal enhancement	High recurrence (20–70%), long-term disability
Hemorrhagic Stroke	Lobar hemorrhages, cerebral microbleeds (CMB) on SWI, deep medullary vein engorgement (DMVE)	Mortality up to 33%, risk of cognitive decline with CMBs
CNS Vasculitis (CNSV-NS)	HR-VWI may exhibit circumferential vessel wall enhancement, diffuse meningeal involvement	High relapse rates, severe deficits if untreated, diagnostic delays common
Cerebral Venous Sinus Thrombosis	Cerebral venous sinus occlusion; leptomeningeal inflammation in adjacent areas	Rare, may cause raised intracerebral pressure, hemorrhagic venous infarcts/hemorrhage
Moya-Moya-like Vasculopathy	Narrowing/stenosis of basal arteries with abnormal collaterals seen on cerebral angiogram	Extremely rare, outcomes poorly described

gamma (IFN-ϒ) and Interleukin-2 (IL-2) produced by the T Helper cells accentuate cytotoxicity and immune cell proliferation respectively, resulting in sustainence of granulomatous inflammation.[3] CVNS is postulated to be due to either granulomatous inflammation of the vessel wall or direct mechanical effects of perivascular granulomas on the arteries and/or veins (accounted by presumptive hematogenous spread into CNS in systemic sarcoidosis).[10] Granulomatous inflammation results in upregulation of TNF-α, IFN-ϒ and IL-2, which in-turn upregulates the expression of endothelin-1 (ET-1) resulting in sustained vasoconstriction of the cerebral arterioles.[11] Endothelial dysfunction due to circulating inflammatory mediators (ET-1) and Immunoglobulin G (Ig G) deposition on the blood vessel walls may lead to enhanced arterial stiffness, contributing to cerebrovascular events (CVE) in NS.[10–13,15–19] Rarely, cardiac sarcoidosis can lead to embolic ischemic strokes secondary to arrythmias or systolic dysfunction.[14] Table 2 summarizes the postulated pathological mechanisms contributing to CVE in NS.

Clinical Phenotypes of CVNS

Ischemic Strokes

Stroke constitutes the most common CVNS, but is extremely rarely reported in literature, with only 51 cases of 63 CVE reported over a duration of 60 years, with earliest description in 1953.[10–13] Nevertheless strokes can be the presenting manifestation of NS, with 65% diagnosed to have NS either during or after the stroke. The diagnosis of NS is even more even more challenging in those with isolated NS.[11] Ischemic strokes are the predominant subtype (up to 70%) affecting males more commonly (upto 65%) with mean age of 41–46 years.[10–13] They predominantly affect the small vessel vascular territories supplied by the deep perforators without collateral flow, thereby resulting in small infarcts, even though the exact reason for this predilection is unclear.[10–13] One possibility is the spread of granulomatous inflammation from the inflamed perivascular connective tissue along the basal meninges, brain sulci and deep grey matter along the Virchow-Robin (VR) spaces.[10] This notion is substantiated by predominant involvement of the lenticulostriate territories and pontine perforators among NS associated strokes resulting in a caudo-rostral distribution.[11,12] Cortical strokes are rarer, attributed to either spread of cortical leptomeningeal or parenchymal inflammation into the cortex along the VR spaces or through hematogenous seeding.[10–12] Multi-territorial small vessel territory strokes have also been reported in NS in the setting of vasculitis discussed below.[16–18] Large/medium vessel strokes are rarer due to unknown reasons with potential mechanisms being cardioembolic (secondary to cardiac sarcoidosis),[12–14] mechanical compression by perivascular granulomas,[10–13] and vasculitis as well as vasculopathy of Moya-Moya type (extremely rare to involve the medium/large sized vessels in NS).[19,20] High resolution intracranial vessel wall MRI (HR-VWI) shows vascular abnormalities in 69%, with perforator vessel involvement (defined as visibly tortuous or dilated vessels reaching upto the subependymal region) in 46% and circumferential vessel wall enhancement involving the large/medium vessels in 23%.[22] Tortuous/

Table 2 Postulated Pathogenic Mechanisms of CVNS

Mechanism	Pathological Process	Cerebrovascular Consequence
Granulomatous inflammation	Infiltration of vessel walls by granulomas	Vasculitis, vessel wall damage
Mechanical compression	Perivascular granulomas exerting pressure on arteries or veins	Vascular narrowing or obstruction
Endothelial dysfunction	Mediated by inflammatory agents (eg, endothelin-1)	Disrupted vascular tone, arterial stiffness Increased risk of ischemia
Immunoglobulin G (IgG) deposition	Immune complex deposition in vessel walls	Chronic inflammation, vascular injury Arterial stiffness, predisposing to infarcts
Cardiac sarcoidosis (secondary cause)	Myocardial involvement leading to arrhythmias or systolic dysfunction	Embolic ischemic stroke from cardiac thrombi

Table 3 Depicts the Different Pathogenic Mechanisms Involved in the Causation of Ischemic Strokes in Neurosarcoidosis

Mechanism	Pathological Feature	Vascular Effect	Frequency
Leptomeningeal & perivascular granulomas	Granulomas adjacent to vessels without direct invasion	Compression of small vessels	Common
Granulomatous invasion of vessel walls	Granulomas invade vessel walls	Vasculitis (granulomatous inflammatory vessel wall damage)	Less common
Vascular/perivascular inflammation without granulomatous invasion	Inflammatory response without granulomas	Vasculitis / Perivasculitis	Rare

visibly dilated lenticulostriate perforator vessels are not common in those with cerebrovascular small vessel disease secondary to traditional vascular risk factors and hence larger studies incorporating HR-VWI are needed to see if it can be an imaging surrogate for cerebrovascular involvement in NS.[22]

To summarize, the mechanisms of ischemic stroke in NS seems to be multifactorial (Table 3).[10–14,16–20] Theoretically chronic inflammation in NS as well as steroid use in those with pre-existent diagnosis of sarcoidosis might contribute to accelerated atherosclerosis, in-turn priming the smaller calibre blood vessels to occlude.[12] A high index of suspicion is needed to diagnose stroke due to CVNS in those with previously undiagnosed Sarcoidosis/NS. Diagnostic clues include leptomeningeal enhancement (44–90%), cerebral periventricular white matter abnormalities (20–69%) as well as spinal cord abnormalities (18%) and inflammatory CSF (defined as > 5 cells/μL and/or protein levels above 45 mg/dl) noted in 67–79% of cases, with CSF oligoclonal bands noted in 27%.[11–13] Novel neuroimaging markers such as perivascular enhancement (PVE) (defined as linear intraparenchymal enhancement along the lumen or expected course of arterial perforators) is seen more commonly in NS subjects who develop CVE as against those who do not (50% vs.18%; p value <0.05), thereby reinstating its value as a neuroimaging surrogate for CVE in NS.[23] Ischemic stroke recurrence rates varied between 20–70% in the literature, with persistent leptomeningitis serving as a predictor for stroke recurrence, with early use of stronger immunomodulators targeting TNF – α inhibitors like Infliximab potentially reducing recurrence risks.[11,12]

Hemorrhagic Strokes (Arterial and Venous)

Hemorrhagic strokes constitute roughly 30% of strokes in NS, with approximately 30 documented cases in literature.[10,11,13,15] In contrast to the ischemic lesions in NS, the intraparenchymal hemorrhage (IPH) tends to have predilection for lobar cortex with relative sparing of basal ganglia due to unclear reasons.[10,11,13,15] Hemorrhagic spectrum of CVNS includes both IPH and SAH, with shared pathological mechanisms.[10,15] Unlike ischemic strokes, the predominant pathological mechanism contributing to IPH/SAH in NS seems to be vasculitis affecting both the arteries and veins, resulting in clinically silent cerebral microbleeds (CMB – defined as less than 10 mm in maximum dimension), occasional macrobleeds and microaneurysms.[10,13] The atypical location of IPH in NS could be partially attributed to the concomitant yet variable involvement of arteries and veins in NS.[21] Approximately 30% of those presenting with IPH have isolated NS, thereby posing a diagnostic challenge, with potential clues being presence of concomitant neuroimaging abnormalities suggestive of NS such as intense leptomeningeal/pachymeningeal/PVE or non-enhancing white matter lesions.[10] In addition NS subset with IPH were likelier to have PVE on contrast enhanced MRI Brain along the distribution of deep medullary veins, potentially indicating underlying granulomatous venous/perivenous phlebitis.[21] CMB were noted in 54% of NS subjects who underwent HR-VWI, with prominent deep medullary vein engorgement (DMVE) noted in 46%, both in 3D T1 weighted black blood fast spin echo imaging and susceptibility weighted imaging (SWI) sequences.[22] DMVE is defined as engorged, tortuous veins in parallel configuration at the region of corona radiata with radial orientation around the atria and frontal horns.[22,24] Another study demonstrated DMVE in 33% of NS subjects undergoing routine MRI on SWI, with CMB occurring more commonly in those with DMVE (P – 0.009).[24] Eventhough DMVE may also be seen in dural venous sinus thromboses as well as dural arteriovenous fistula, they are increasingly considered as a neuroimaging marker of venous involvement in NS, especially

in presence of concomitant neuroimaging findings suggestive of NS as mentioned above.[22,24] Yet another interesting observation is that CMB also tends to be more prevalent in those with DMVE, thereby indicating a possible continuity in the spectrum of venous imaging abnormalities in NS.[22,24] The presence of CMB increases the possibility of recurrence of IPH, with its progressive increase contributing to cognitive decline and resultant morbidity.[10,11,13]

Hence the hemorrhagic spectrum of CVNS also warrants early institution of aggressive immunotherapy in order to minimize eventual morbidity and mortality.[10,11,13,15] The closest differential to be considered is PCNSV, which will be discussed in the below section, with other considerations being cerebral amyloid angiopathy (CAA) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in appropriate clinical scenario. Cerebral venous sinus thromboses (CVST) in NS resulting in ICH is extremely rare with only five cases documented in literature thus far, with predilection for superior sagittal sinus.[10] Presumed pathological process responsible for CVST in NS is granulomatous leptomeningeal involvement resulting in secondary thromboses.[10] Hemorrhagic spectrum of CVNS warrants upfront aggressive immunomodulation, preferably with TNF – α inhibitors in view of mortality rates as high as 33% in this subgroup.[15]

Central Nervous System Vasculitis Associated with Neurosarcoidosis (CNSV-NS)

CNSV-NS is extremely rare, with information available only as case reports or short case series in literature.[16–19] Similar to the other CVNS, they tend to involve the small to medium sized vessels in the cerebral vasculature due to unclear reasons, thereby limiting the diagnostic utility of conventional cerebral angiogram studies in this subset.[16–19] Nevertheless there are case reports of involvement of large vessels in CNSV-NS, even though they are extremely rare.[19] Advent of novel imaging tools like HR-VWI has enabled better identification of potential CNSV-NS cases in addition to providing potential imaging clues to differentiate from other diagnostic mimics such as PCNSV.[22] In a study analyzing the findings of HR-VWI on a cohort of 13 NS patients with low pre-test suspicion for CNSV-NS and without stroke-like syndrome at baseline (6 definite, 5 probable and 2 possible),[7,8] 23% had circumferential vessel wall enhancement involving the large/medium vessels, thereby pointing towards the possibility of higher prevalence of CNSV-NS in the NS cohort.[22]

The clinical manifestations of CNSV-NS tend to be broad with headaches, confusion, stroke like symptoms, cranial neuropathy, seizures as well as encephalopathy.[16–19] Ischemic strokes are commoner, with high index of suspicion to be exercised in the setting of recurrent multifocal infarcts in combination with other neuroimaging findings such as leptomeningeal enhancement, diffuse white matter abnormalities, hypothalamic-pituitary involvement as well as spinal cord abnormalities.[16–19] Hemorrhagic forms include macrobleeds, CMB as well as granulomatous phlebitis causing linear enhancement along the paraventricular veins along the lateral and third ventricle.[10,16–19]

Pathological mechanisms of CNSV-NS is postulated to be either granulomatous vasculitis (non-caseating granulomas in the tunica adventitia), spread of inflammation from surrounding perivascular granulomas to the vessel walls or rarely necrotizing fibrinoid vasculitis.[16–19] The common final pathway of all the above-mentioned mechanisms is destruction of tunica intima, fibrosis, stenosis and occlusion of vascular lumen.[18,23] In the rarer large vessel subtype of CNSV-NS, the pathological mechanism involves vessel wall inflammation eventually resulting in stenosis or ectasia.[18] On account of the low sensitivity of neuroimaging (MRI), CSF findings as well as conventional cerebral angiogram in small/medium vessel subtype of CNS Vasculitis, a low threshold should be kept for performing cortico-meningeal brain biopsy, which is still the gold standard for diagnostic evaluation of any patient with suspected CNS Vasculitis.[16–19,23] As all the above-mentioned pathological mechanisms hold good in causation of PCNSV as well, diagnosis of CNSV-NS could be challenging unless there is unequivocal histopathological confirmation of sarcoidosis from an extra neural tissue.[23] Timely diagnosis and prompt institution of appropriate immunomodulation tends to improve the outcomes in this otherwise disabling subset of CVNS which is historically associated with high morbidity and mortality.[16–19]

Differentiation of CNSV-NS from PCNSV

Both CNSV-NS and PCNSV are steroid responsive inflammatory disorders affecting the CNS, sharing clinical and histopathological features, thereby posing significant diagnostic challenge on many occasions, especially in the setting of isolated NS.[2–4,16–18,23,25–29] Eventhough both the disease entities shows response to corticosteroids used as the initial

treatment option, responsiveness to second/third line immunomodulation tends to vary between CNSV-NS and PCNSV, thereby highlighting the importance of prompt differentiation while making an initial diagnosis on account of the therapeutic implications.[16–18,23,27–29] PCNSV is increasingly identified as a heterogenous disease with large/medium vessel (having abnormalities on cerebral angiogram) and small vessel subtype (with no abnormalities on cerebral angiogram).[23,29] CNSV-NS too affects the small vessels more often with overlapping histopathological features, thereby posing diagnostic dilemma in differentiating from small vessel subtype of PCNSV.[16–18,23,27,29] A study by Saygin et al specifically addressed to provide clues to differentiate between CNSV-NS (definite or probable)[7,8] and PCNSV (biopsy proven or with positive cerebral angiogram and inflammatory CSF) on the basis of clinical and imaging characteristics as outlined in Table 4.[27] Eventhough PVE and DMVE are postulated to be neuroimaging markers suggestive of CNSV-NS in combination with other neuroimaging findings, it is unclear as of now as to whether they could aid in differentiating CNSV-NS from PCNSV.[21,22,24] In view of the theoretical possibility of higher chances of involvement of veins in CNSV-NS as against PCNSV, DMVE and PVE oriented radially at the level of lateral/third ventricles could potentially be of diagnostic value.[2–4,16–19,21–24,27]

However, on account of the rarity of both CNSV-NS and PCNSV, larger cohort studies are required to validate the diagnostic utility of neuroimaging markers to reliably differentiate between the diagnostic entities.

Management of CVNS

There are no established guidelines for diagnosis and management of CVNS.[2–4,9–20] In a systematic review on 63 CVE in 51 cases of stroke in sarcoidosis, 63% were on immunomodulators post stroke, with Corticosteroids alone being the treatment regimen in 41%.[11] Seventeen percent were on Corticosteroids with other immunomodulators, with Methotrexate being the most commonly used steroid sparing agent (11%).[11] Interestingly in this review roughly 20%

Table 4 Salient Clinical, Imaging, Histopathological and Therapeutic Features of CNSV-NS Vs PCNSV

Feature	CNSV-NS	PCNSV
Demographics	Middle-aged males; African-American predominance	Middle-aged males; no strong ethnic predilection
CSF Profile	Higher cell counts and protein; OCBs may be present	Mild pleocytosis; protein elevated; OCBs rare
Clinical Features	Cranial neuropathies, encephalopathy, recurrent strokes	Headache, seizures, cognitive decline, multifocal deficits
MRI Findings	Pachymeningeal/basal leptomeningeal enhancement more likely; brain-stem/cerebellar/pituitary/ hypothalamic/cranial nerve involvement; PVE, DMVE commoner	Cortical/subcortical white matter lesions; occasional grey matter involvement; infarcts; CMB; leptomeningeal enhancement (less likely)
Spinal cord involvement	Commonly involved (Cervical and Thoracic segments likelier)	Less common
Vessel Involvement	Small to medium vessels; venous involvement common	Small to medium/large vessels; venous involvement uncommon
Histopathology	Non-caseating granulomas in adventitia; granulomatous vasculitis	Granulomatous, lymphocytic or necrotizing vasculitis
Systemic Association	Often associated with systemic sarcoidosis	No systemic disease
Response to TNF-α Inhibitors	Responsive	Variable response; often steroid-dependent
Recurrence Risk	High (especially if untreated or undertreated)	Moderate to high recurrence
Common Mimics	PCNSV, tuberculosis, neurosyphilis	CNS infections, lymphoma, paraneoplastic vasculopathy

Abbreviations: OCB, Oligoclonal bands; PVE, Perivascular enhancement; DMVE, Deep medullary vein engorgement; CMB, Cerebral microbleeds.

of cases did not receive any specific immunomodulatory therapy due to unclear reasons.[11] Despite having no dedicated large scale data pertaining to management of CVE in NS, there is ample evidence of utility of immunomodulation with Cyclophosphamide (HR 0.26; 95% CI, 0.11–0.59; p – 0.001), Methotrexate (HR 0.47; 95% CI, 0.25–0.87; p – 0.02) and Infliximab (HR 0.16; 95% CI, 0.02–1.24; p – 0.08) to reduce relapse rates in NS cohort.[9]

In a systematic review by Pua et al on strokes associated with sarcoidosis, antiplatelets and anticoagulation were given in 19% and 6% subjects respectively, with no mention regarding the subtype or dosage of the same.[11] Follow up data was available for 45% of the study population with median follow up duration of 6.5 months, with 71% of the cohort either dead or disabled at last follow up.[11] More specific information was available in the retrospective cohort analysis of 11 ischemic stroke patients with NS by Hutto etal[12] 73% (7/11) received high dose intravenous Methylprednisolone (1000 mg daily for 3–5 days) followed by prolonged oral Steroids (0.5–1 mg/kg/day) in 90.9% (10/11). Steroid sparing immunomodulators were started in 90.9% (10/11) with 27% (3/11) requiring more than one agent eventually.[12] Infliximab (3–7 mg/kg IV at weeks 0,2,6 followed by every 4–8 weeks) was the most commonly used steroid sparing agent in 80% (8/10), with remission achieved in 87.5% (7/8) of them.[12] Concomitant Aspirin was given in 54.5% (6/11), Clopidogrel in 9% (1/11), Statins in 36% (4/11) with none receiving anticoagulation.[12] The median follow up duration of the study was 52 months, with recurrent strokes noted in 72.7% (8/11), the latter being more common in those with persistent leptomeningeal enhancement or recurrent neuroinflammatory attacks during follow up.[12] Similar observations were also noted in the review by Jachiet et al on 51 NS subjects with CVE, with 85% (33/39) and 36% (14/39) receiving corticosteroids and additional immunomodulatory drug respectively after sustaining a CVE.[13] 70% of the cohort were either dead (23%) or disabled (47%) after a median follow up of 12 months, thereby reinstating the high morbidity and mortality associated with CVE in NS.[11–13] On account of the small sample size of all the above mentioned retrospective studies, larger cohort studies preferably multi-centric are warranted before the above-mentioned observations can be generalized.[11–13]

Due to the rarity of CNSV-NS, there are no established guidelines for its management, with broad framework shared with management of other vasculitis such as PCNSV.[23,28] Induction phase treatment includes high dose steroids (Intravenous Methylprednisolone 1000 mg daily for 3–5 days) followed by prolonged oral steroids (0.5–1 mg/kg/day) with gradual taper and early introduction of steroid sparing agent for remission induction as well as maintainence.[16–19,28] There are no current guidelines favoring one steroid sparing agent over the other, but ancillary evidence suggest efficacy of Cyclophosphamide (pulse regimen – 15 mg/kg IV maximum dose of 1200 mg at weeks 0,2,4,7,10,13), Infliximab (3–7 mg/kg IV at weeks 0,2,6 followed by every 4–8 weeks), Azathioprine (2–2.5 mg/kg/day orally), Methotrexate (10–25 mg weekly oral or subcutaneous), Mycophenolate mofetil (500–3000 mg/day in two divided doses) and Rituximab (375 mg/m^2 IV at days 0,7,14,21 followed maintainence doses in 6 months) to reduce the relapse rates, with Infliximab being the most commonly used agent.[16–19] Periodic clinical and neuroimaging monitoring is essential to monitor for relapses, worsening or development of side effects to the immunomodulators, so that appropriate modification of treatment regimen could be instituted. Formulation of a uniform therapeutic algorithm for CNSV-NS warrants large scale preferably randomized controlled trials, which will be a significant deterrent in view of rarity of the diagnostic entity.

Mortality

NS with cerebrovascular manifestations tend to portray the aggressive subset on majority of occasions with mortality rates increasing from 5–10% in those without CVE to 23–33% in those with CVE, with recurrent CVEs noted on follow up ranging from 20–70%.[9,11,12,15,21] Hence those NS subjects with CVE warrant aggressive and prompt institution of immunomodulation to minimize morbidity and mortality.

Conclusion

The CVNS cases reported in literature are likely just “tip of the iceberg”. Despite being rare, the heterogenous phenotypic spectrum of CVNS, can have devastating consequences in terms of overall functional outcomes. Increasing awareness of imaging tools such as HR-VWI and imaging markers such as PVE and DMVE could potentially pave way in the future

for increasing recognition of CVNS, even though their diagnostic utility needs to be tested in larger cohort studies. Prompt recognition and early institution of aggressive immunomodulatory therapy can potentially reduce the high morbidity and mortality associated with CVE in NS. Large scale multi-centre studies are the need of the hour in order to formulate a standardized guideline for evaluation and management of this rarer disease subtype with potentially devastating consequences.

Disclosure

The authors report no conflicts of interest in this work.

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