Diffuse Proliferative Cerebral Angiopathy: A case report and review of the literature

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ABSTRACT

Diffuse proliferative cerebral angiopathy is a distinct entity from cerebral arterio-venous malformations; characterized by multiple small arterial feeders and draining veins with normal brain parenchyma seen in-between the abnormal vessels. It is usually seen in younger age group. Here we report a case of diffuse cerebral proliferative angiopathy in a 78-year-old female patient along with discussion of the neuro-imaging findings and review of the literature. It is important to recognize this entity to avoid aggressive surgery or intervention and thus preventing permanent damage to the normal intermingled brain tissue.

CASE REPORT

A 78-year-old female patient presented with multiple seizures. Past medical history included DM, HTN and dementia. Laboratory evaluation was unremarkable with no electrolyte imbalance. Electroencephalogram showed findings consistent with diffuse encephalopathy. There was no family history of cerebral arteriovenous malformations, and no skin lesions were seen.

Imaging Findings

Non-contrast computed tomography of the head performed as a part of dementia workup in 2007 was essentially normal (Fig. 1). The repeat non-contrast CT brain done during the recent admission (2014) however revealed multiple linear/serpiginous calcifications in both cerebral hemispheres (Fig. 2). No perilesional edema was seen.

Magnetic resonance imaging demonstrated multiple tortuous vessels in the deep white matter and cortical surface of the brain on post contrast T1W sequences (Fig. 3 and Fig. 4). Normal interspersed brain parenchyma was seen in-between vascular malformations. No nidus was demonstrated, and no susceptibility artifact suggesting hemosiderin deposition was seen on GRE sequence. T2W and T2 FLAIR sequences showed age appropriate involutional changes with deep white matter leukoaraiosis along with tubular signal voids suggestive of abnormal vessels (Fig. 5). No gliosis was seen. MRA showed mild stenosis of the M2 segment of the right middle cerebral artery and P2 segments of bilateral posterior cerebral arteries (Fig. 6).

The electroencephalogram demonstrated features consistent with diffuse encephalopathy (Fig. 7).

Treatment

The decision was made for conservative management in view of the patient age. Follow up did not occur as the patient died shortly after diagnosis was made secondary to hospital-acquired pneumonia.
Etiology & Demographics
The prevalence rate of cerebral vascular malformation is hard to estimate. In a population-based study in Olmsted County, Minnesota, the detection rate for AVMs was 1.1 per 100,000 when autopsy cases were excluded and 2.1 per 100,000 for all cases including autopsy cases [1]. It is hypothesized that these malformations are mostly congenital and result of an anomalous cerebral development. Cerebral vascular malformations are classified based on the pathophysiology and natural history into many types such as arteriovenous malformations (AVM), cavernous malformations, venous malformation and capillary telangiectasia. The AVMs are dilated tortuous vessels with direct connection between arteries and veins without intervening capillary network [2]. Cavernous malformations are abnormal cluster of enlarged capillaries with no significant feeding arteries, veins and without any recognizable intervening neural parenchyma. Venous malformations are abnormal group of dilated veins resembling spoke of wheel with no feeding arteries. Capillary telangiectasias are small areas of abnormal dilated capillaries within otherwise normal brain tissue.

Diffuse cerebral proliferative angiopathy is regarded as a different entity from cerebral AVMs. The pathogenesis of diffuse cerebral proliferative angiopathy remains unclear, but it is presumably induced as a response to cortical ischemia with the feeding arteries having altered internal elastic lamina and smooth muscle cells [3]. No case reports of cerebral proliferative angiopathy in the geriatric population are found.

Clinical & Imaging findings
Characteristic angiographic features of diffuse cerebral proliferative angiopathy include multiple small arterial feeders and numerous small draining veins with no dominant feeders or nidus (abnormal tangle of small vessels) seen. Unlike the typical AVMs, these lesions contain normal cerebral tissue in-between the abnormal vessels [4].

Possible complications include 45% chance of seizures, 41% of headaches, 16% of neurological deficits such as stroke-like symptoms including transitory ischemic attacks and 12% of hemorrhage [3]. In our case, the patient presented with the episode of seizures.

The non-contrast CT brain performed in 2007 failed to show any abnormality probably because all the abnormal vascular channels were isodense to the brain parenchyma. However, the repeat CT done in 2014 shows multiple vascular calcifications in both cerebral hemispheres. The exact cause of these calcifications are not known but it could be attributed to same mechanisms which cause calcification in AVMs where it is proposed that either arterial steal phenomenon or persistent venous congestion cause calcification in chronic hypoperfused brain or these are caused secondary to dystrophic changes in the walls of congested veins [5].

Diffuse proliferative angiopathy can be diagnosed using MRI and MRA though DSA remains the "gold standard" as it allows direct vessel visualization, shunt estimation and possibility of intervention if required [2, 6]. On MRI, cerebral proliferative angiopathy are seen as tubular flow voids on T1W and T2W sequences with abnormal, enlarged serpiginous vessels seen on contrast-enhanced images. Secondary features such as dilated proximal intracranial or extracranial arteries are also demonstrated. Chronic hemorrhage, gliosis, or both can be seen in the brain tissue adjacent to the abnormal vessels [4]. Diffuse cerebral proliferative angiopathy often has arterial supply from multiple vascular distributions [7]. In our case, as no digital subtraction angiography was performed hence it was difficult to confirm the arterial supply accurately however it seems to be originating from the bilateral carotid and vertebral arteries.

Genetic disorders such as hereditary hemorrhagic telangiectasia (Rendu Osler Weber syndrome), Sturge Weber syndrome and Wyburn Mason Syndrome show cerebral angiopathy [2, 4, 8, 9]. None of these syndromes or any cutaneous lesions were seen in our patient.

Diffuse cerebral proliferative angiopathy is the presumed diagnosis in our case as evidenced by normal intermingled brain parenchyma in-between vascular malformations and absence of large arterial feeders or nidus.

Treatment & Prognosis
The treatment options for patients with diffuse cerebral proliferative angiopathy largely depend on the clinical presentation (hemorrhage, intractable seizures and disabling headaches). There is a risk of permanent neurological damage to the normal interspersed brain parenchyma if surgery or radiosurgery is performed hence patients with controlled seizures and headaches can be monitored expectantly with the understanding that the patient would have small risk of hemorrhage (12%) or other neurological symptoms such as seizures or focal deficit [3]. Limited arterial embolization in noneloquent areas can be performed for patients presenting with uncontrolled seizures and headaches. Calvarial burrhole surgery that increases cortical blood supply by recruiting additional dural vessels can also be performed for patients with disabling headaches [3].

Differential Diagnosis
Few differentials for cerebral proliferative angiopathy include hereditary hemorrhagic telangiectasia (HHT), Sturge Weber Syndrome (SWS) and Wyburn Mason Syndrome (WMS). In hereditary hemorrhagic telangiectasia apart from cerebral angiopathy, affection of a first degree relative, or telangiectatic skin lesions, epistaxis is required [10]. In Sturge Weber Syndrome (SWS), patients usually have facial cutaneous angiomomas also known as port wine stain, meningeal calcification and enlargement of the choroid plexus along with leptomeningeal arteriovenous shunts and retinal pathology. Moreover, up to 75% of these patients experience epileptic seizures before the age of 1 year or mental retardation [11]. In Wyburn Mason Syndrome (WMS), telangiectatic skin lesions are seen and the cerebral arteriovenous shunts are mainly located centrally in the midbrain region [7].
**TEACHING POINT**

Diffuse proliferative cerebral angiopathy should be considered as a separate entity from "classical" brain AVMs. It is characterized by presence of normal interspersed brain parenchyma, absence of large dominant arterial feeders or nidus and in few cases presence of transdural blood supply. Clinically also it differs from classical AVMs as there is a lesser chance of hemorrhage and the usual presentation is in the form of seizures and headache. Diffuse proliferative cerebral angiopathy is presumably induced as a response to cortical ischemia.

**REFERENCES**


Figure 1: 78-year-old female patient with diffuse cerebral proliferative angiopathy. Findings: A, B, C) Non-contrast axial images (done in year 2007) show no significant abnormality. No linear or tubular hyperdensities are seen. Technique: Marconi, Philips Medical system, slice thickness 5mm, kvP 120, mAs 275.
Figure 2: 78-year-old female patient with diffuse cerebral proliferative angiopathy.
Findings: A, B, C) Non-contrast axial images (done in year 2014) show tubular and linear parenchymal and subcortical hyperdensities (arrows) in both cerebral hemispheres. No surrounding perilesional hypodensity suggestive of edema is seen. Technique: Marconi, Philips Medical system, slice thickness 5mm, kVp 120, mAs 275.
Figure 3: 78-year-old female patient with diffuse cerebral proliferative angiopathy.
Findings: Contrast enhanced T1-weighted (A, B, C, D) axial sequences showing multiple enhancing tubular vascular channels (arrows) involving parenchymal/subcortical cerebral hemispheres. Some of the vessels are more ectatic than others (arrowheads). Normal interspersed brain parenchyma is seen with no nidus demonstrated.
Technique: GE Medical systems 1.5 Tesla, TR 7.04, TE 2.05, ST 3, slice spacing 3, 10ml of Dotarem as contrast.
Figure 4: 78-year-old female patient with diffuse cerebral proliferative angiopathy. Findings: Contrast enhanced T1-weighted (A, B) Sagittal and (C, D) Coronal sequences showing multiple enhancing tubular vascular channels (arrows) involving parenchymal/subcortical cerebral hemispheres. Normal interspersed brain parenchyma is seen with no nidus demonstrated.
Technique: GE Medical systems 1.5 Tesla, TR 7.04, TE 2.05, ST 3, slice spacing 3, 10ml of Dotarem as contrast.
Neuroradiology: Diffuse Proliferative Cerebral Angiopathy: A case report and review of the literature

Rohit et al.

Figure 5: 78-year-old female patient with diffuse cerebral proliferative angiopathy.
Findings: A) T2 FLAIR contrast axial sequence showing multiple tubular enhancing vessels (white arrows) and (B) axial T2 weighted sequence showing multiple tubular signal voids in bilateral brain parenchyma (white arrows) along with chronic microvascular periventricular ischemic changes (black arrows). Normal interspersed brain parenchyma is seen with no adjacent gliosis or perilesional edema. Technique: GE Medical systems 1.5 Tesla, (A) T2 FLAIR contrast TR 9502, TE 127.7, ST 5, slice spacing 7, 10ml of Dotarem as contrast. (B) Axial T2W, TR 2540, TE 93.6, ST 5, Slice spacing 7.

Figure 6: 78-year-old female patient with diffuse cerebral proliferative angiopathy.
Findings: A ,B, C) MRA images showing mild stenosis of M2 segment of right middle cerebral artery (red arrows) and P2 segments of bilateral posterior cerebral arteries (white arrows). Few prominent extracranial vessels are also demonstrated (grey arrows). Technique: GE Medical systems 1.5 Tesla, TR 26, TE 3.4, ST 1.2, slice spacing 1.2, 10ml of Dotarem as contrast.
Neuroradiology: Diffuse Proliferative Cerebral Angiopathy: A case report and review of the literature

Rohit et al.

Etiology: A separate entity from classical cerebral arteriovenous malformation.

Incidence: Few cases reported in literature (less than 15).

Gender Ratio: Slight female preponderance.

Age predilection: Usually congenital with presentation in early age.

Risk Factors: No known risk factors.

Treatment: Usually monitored expectantly with the understanding that the patient would have some risk of hemorrhage (12%) or other neurological symptoms.

Prognosis: Increased chances of intractable seizures and headaches.

Imaging Findings: The characteristic angiographic features include multiple small arterial feeders and multiple small draining veins with no dominant feeders or nidus within the malformation. Normal interspersed brain parenchyma is noted in-between abnormal vessels.

Table 1: Summary table for diffuse proliferative cerebral angiopathy.

<table>
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Figure 7: 78-year-old female patient with diffuse cerebral proliferative angiopathy. Findings: Bipolar montage shows continuous generalized slowing consistent with diffuse encephalopathy.
Table 2: Differential table for diffuse proliferative cerebral angiopathy.

<table>
<thead>
<tr>
<th>Entity</th>
<th>Skin lesions</th>
<th>Clinical presentation</th>
<th>Extent of AVM on CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse proliferative cerebral angiopathy</td>
<td>Nil</td>
<td>Hemorrhage, epilepsy</td>
<td>Diffuse, bilateral</td>
</tr>
<tr>
<td>Hereditary hemorhagic telangiectasia</td>
<td>Skin telangiectasia</td>
<td>Epilepsy</td>
<td>Localized</td>
</tr>
<tr>
<td>Sturge Weber Syndrome</td>
<td>Facial angiomas</td>
<td>Mental retardation, epilepsy</td>
<td>Localized, retinal involvement.</td>
</tr>
<tr>
<td>Wyburn Mason Syndrome</td>
<td>Skin telangiectasia</td>
<td>Epilepsy</td>
<td>Localized</td>
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</tbody>
</table>

ABBREVIATIONS

AVM = Arteriovenous malformation
CT = Computed tomography
DM = Diabetes mellitus
DSA = Digital subtraction angiography
GRE = Gradient recalled echo
HHT = Hereditary hemorrhagic telangiectasia
HTN = Hypertension
MRI = Magnetic resonance imaging
SWS = Struge Weber Syndrome
WMS = Wyburn Mason Syndrome

KEYWORDS

Diffuse proliferative angiopathy; arteriovenous malformation; radiology; hereditary syndrome; epilepsy; cerebral

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