Differential diagnosis in brain abnormalities with a miliary enhancing pattern

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Learning objectives

To give an overview of the differential diagnosis of miliary enhancing pattern brain abnormalities and, where possible, summarize disease specific findings from both a radiological and clinical perspective in order to minimize the number of patients selected for invasive diagnostic procedures such as brain biopsy.
Background

Miliary enhancing pattern of brain abnormalities refers to a rare type of multiple small, monomorific enhancing foci. When confronted with this type of enhancement, the radiologist and referring clinician face the challenge to narrow down the broad differential diagnosis.

Miliary enhancing brain abnormalities can be found in multiple disorders, ranging from inflammatory, genetic disorders, malnutrition to neoplastic syndromes. A lack of a systematic approach when confronted with miliary enhancing brain abnormalities could result in ongoing uncertainty regarding the diagnosis, and might lead to considering and even undertaking an unnecessary or possibly preliminary brain biopsy.

Distinguishing whether or not there is a specific distribution pattern of miliary enhancing brain lesions suggestive of involvement within the perivascular space (PVS), also known as Virchow Robin spaces (VRS), is essential when making a differential diagnosis. The PVS is a periarterial compartment accompanying small and middle size arteries as they penetrate the brain. This compartment drains the interstitial fluid and has no relation to cerebrospinal fluid (CSF). The PVS is oriented along the lenticostriatale arteries entering the basal ganglia, along the medullary arteries over the high convexities and at the level of the mesencephalodiencephalic junction (Kwee and Kwee, 2007).
Miliary enhancing pattern brain abnormalities and disease specific findings on imaging will be provided for most of the, biopsy proven, differential diagnosis of 13 diseases.

Diseases with miliary enhancing brain lesions

<table>
<thead>
<tr>
<th>PVS involvement +</th>
<th>Neurosarcoidosis</th>
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<tbody>
<tr>
<td></td>
<td>CNS angiitis</td>
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<tr>
<td></td>
<td>LYG</td>
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<td></td>
<td>Erdheim Chester Disease</td>
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<td></td>
<td>Lyme’s disease</td>
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<td></td>
<td>Vitamin B12 deficiency</td>
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<td>CLIPPERS</td>
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<td>PVS involvement -</td>
<td>Neuro Tuberculosis</td>
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<td></td>
<td>Histoplasmosis</td>
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<td></td>
<td>Behcet</td>
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<td></td>
<td>Susac's disease</td>
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<td></td>
<td>Mitochondrial disease</td>
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</tbody>
</table>

Box1: Overview of diseases which could show miliary enhancing brain lesions, subdivided into 3 groups; distribution pattern suggestive of perivascular space (PVS) involvement, without PVS involvement and either with or without PVS involvement

Diseases showing a miliary enhancing brain lesions distribution pattern suggestive of PVS involvement.

1) Neurosarcoidosis:

Neurosarcoidosis has a known predilection for the basal leptomeninges, commonly affecting cranial nerves. Therefore cranial nerve palsy and complaints of headache are common clinical presentations (30-50% of cases). Mainly nerve VII is involved, less commonly nerve V and VIII. The spectrum of MRI abnormalities consist of periventricular white matter lesions and nodular or diffuse parenchymal and basal leptomeningeal enhancement (Nowak and Widenka, 2001). A distribution pattern consistent with PVS
involvement has been reported (Groeschel et al., 2006) and our cases too suggest involvement of the PVS (Fig 1-4).

2) **Primary CNS angiitis:**

MR findings in primary CNS angiitis are: multiple bilateral supratentorial high intensity lesions affecting both grey and white matter. A normal MRI-study is a very strong argument against, or even excludes primary angiitis. Ischemic infarction are seen most often, together with white matter microangiopathy (Zuber et al., 1999).

Focal vessel lesions can result in aneurysms and haemorrhage due to vessel wall rupture while, the more common, segmental vessel lesions can cause stenosis, infarction and occlusions. Angiography is considered the cornerstone procedure and can reveal multiple arterial occlusions, segmental stenosis, narrowing or beading of intracranial vessels sometimes separated by dilatations, avascular areas and intracerebral aneurysms (Ferro, 1998, Zuber et al., 1999). PVS involvement is postulated in segmental necrotizing angiitis (Kwee and Kwee, 2007). Leptomeningeal biopsy can provide a definitive diagnosis, but is usually not performed (Zuber et al., 1999). (fig 5-7)

3) **Lymphoid granulomatosis (LYG):**

On MR imaging both mass type lesions and diffuse punctuate, linear parenchymal distributions, leptomeningeal enhancement, dural and cranial nerve enhancement is reported (Lucantoni et al., 2009).

PVS involvement has been described to be an important feature (Lucantoni et al., 2009). Adachi et al. (1996) and Bhagavatula and Scott (1997) reported involvement of small perforates and perivascular tissue in LYG. (fig 8-9).

4) **Erdheim Chester's disease.**

Most extra-axial, intracranial lesions are found in retro-orbital space, pituitary stalk, cerebellopontine angle, choroids plexus, dura and falx. In case of symmetrical hyperintens signal on T2 weighted images in dentate nuclei and peridentate regions, ECD, Multiple Sclerosis and Mitochondrial disease should be considered. No perivascular distribution is reported. However, our case indicates extension along the PVS at the level of the basal ganglia and the pons (fig 10-14).

5) **Lyme's disease:**

Even in case of neurological symptoms, MR imaging rarely reveals brain lesions. Both meningeal and nerve root involvement are comparatively common features. Focal lesions with T2 prolongation of cerebral white matter is also reported in many cases (Agerwal and
Cerebral vasculitis in neuro-Lyme can affect small as well as medium sized and large intracranial arteries. Recent studies report on predominant anterior circulation vasculitis (Topakian et al., 2008) in addition to reported PVS involvement (Kaiser 1998).

( fig 15 on page 22 ).

6) Vitamin B12 deficiency:

Spinal MR classically shows dorsal column involvement and, at later stage, cord atrophy (Renolds, 1992). In a small number of patients, multiple brain parenchymal T2 hyperintense lesions were found.

Vitamin B12 suppletion may resolve the spinal and cranial abnormalities. There are no reports no PVS involvement, however this may be seen to our experience (fig 16-19).

7) Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)

In all 8 patients described in the literature, there were typical MR findings of miliary enhancing pattern brain lesions at the level of the pons, extending to the spinal cord and towards the basal ganglia and cerebellum, showing a pattern consistent with PVS involvement (Pittock et al., 2010).

Diseases showing miliary enhancing brain lesions without a distribution pattern suggestive of PVS involvement.

1) Neuro Tuberculosis:

In case of miliary enhancing lesions, they are mostly distributed along the leptomeninges and to a lesser extent scattered throughout the brain parenchyma, without support for a distribution pattern following the PVS. Leptomeningeal nodules are reported to have a predilection for cerebellar foliae, vermis region and the quadrigeminal cisterns (Janse van Rensburg et al., 2008), though not seen in our two cases. There is no PVS involvement reported, which is supported by our cases. (fig 20-22).

2) Histoplasmosis:

Approximately 10-20% of patients with disseminated histoplasmosis have clinically apparent CNS involvement. Chronic, mainly basilar, meningitis is the most common finding in CNS involvement. Also multiple small ring-enhancing lesions throughout the brain and spine are reported (Kauffman, 2007). In the appropriate endemic context, cerebral histoplasmosis should be a diagnostic consideration when imaging studies show...
multiple brain lesions (Saccente et al., 2003). In the literature there are no reports on distribution along the PVS. (fig 23-25).

3) Behcet’s disease:

Neuro-Behcet most commonly presents with bilateral pyramidal signs, hemiparesis and behavioural changes. Typically the lesions are clustered in the brainstem, basal ganglia, capsula interna and penduncles. Furthermore, venous thrombosis is reported, while cortex and cerebellar involvement is limited. In later stages brain stem atrophy is a specific feature (Akman-Demir, 1999). No distribution following the PVS pattern is reported in Behcet. (fig 26-27).

4) Susac’s Syndrome:

Classically Susac’s syndrome presents as a (clinical) triad consisting of encephalopathy, usually bilateral retinal artery occlusion and bilateral hearing loss. In a recent review article of 27 patients, there is typical involvement of the corpus callosum (in 100% of cases), the periventricular, subcortical and centrum semiovale white matter (in 100% of cases). Grey matter involvement was found in 70% of cases, enhancing grey and white matter lesions were also found in 70% of cases. Leptomeningeal enhancement is reported in 33% of cases (Susac et al., 2003). The widespread white and grey matter involvement appears not to show a distribution pattern along the PVS.

5) Mitochondrial disorders:

Ataxia is the most dominant clinical presentation of a MID with CNS manifestations. Other features of CNS involvement are epilepsy, migraine, stroke-like episodes, ischemic stroke, Parkinsonism, dystonia, optic atrophy, cognitive decline, psychiatric abnormalities and coma (Finsterer, 2004). There are no reports on distribution along the PVS. (fig 28 on page 35).

Disease showing miliary enhancing brain lesions with a distribution pattern suggestive of either with or without PVS involvement.

1) Metastatic disease:

There are, to my knowledge, 12 autopsy confirmed reports on miliary enhancing lesions in metastatic disease, showing distribution along the perivasculr spaces without invading the brain parenchyma. Usually the junction zone between grey and white matter is the preferred site of metastatic carcinomatous cells. In case of hematogenous metastasis, a non-PVS distribution pattern might also be possible. This very rare presentation was most often found in metastatic adenocarcinoma (Ogawa et al., 2007). (fig 29-31).
Images for this section:

![Brain Lesions](image)

**Fig. 0:** Miliary enhancing brain lesions in neurosarcoid, at the level of the centrum semiovale, following the PVS distribution pattern

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Fig. 0: Disease specific finding neurosarcoid; bilateral nVII enhancement

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**Fig. 0:** Disease specific finding neurosarcoid: mediastinal / hilar lymphadenopathy

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Fig. 0: Disease specific finding neurosarcoid: basal leptomeningeal enhancement at the level of the pons and along the cerebellar folia

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**Fig. 0:** CNS angiitis, clustered miliary enhancing brain lesions at the level of the corpus callosum, following the PVS distribution pattern

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Fig. 0: CNS angiitis, clustered miliary enhancing brain lesions at the level of the centrum semiovale, following the PVS distribution pattern

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**Fig. 0:** CNS angiitis, miliary enhancing infratentorial brain lesions, following the PVS distribution pattern

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**Fig. 0:** LYG miliary enhancing brain lesions at the level of the basal ganglia, following the PVS distribution pattern

© - Amsterdam/NL
**Fig. 0:** LYG miliary enhancing brain lesions at the level of the pons, following the PVS distribution pattern

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Fig. 0: ECD miliary enhancing brain lesions at the level of the basal ganglia, following the PVS distribution pattern

© - Amsterdam/NL
**Fig. 0:** ECD miliary enhancing brain lesions at the level of the pons, following the PVS distribution pattern

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**Fig. 0:** ECD disease specific finding; high signal on T2 nucl. Dentatus

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**Fig. 0:** ECD disease specific finding; enhancement nucl. Dentatus.

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**Fig. 0:** ECD disease specific finding; sclerotic metaphyseal bone lesion of the tibia

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**Fig. 0:** Lyme disease disease specific finding; nVII enhancement

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Fig. 0: Vit B12 deficiency; miliary enhancing brain lesions at the level of the centrum semiovale, following the PVS distribution pattern

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**Fig. 0:** Vit B12 deficiency; miliary enhancing brain lesions, following the PVS distribution pattern

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**Fig. 0:** Disease specific finding Vit B12 deficiency; dorsal column involvement

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**Fig. 0:** Disease specific finding Vit B12 deficiency; dorsal column involvement

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Fig. 0: Miliary enhancing brain lesions along the leptomeninges in NeuroTBC (a non-PVS distribution pattern)

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**Fig. 0:** Miliary enhancing lesions in NeuroTBC. Disease specific finding; basal leptomeningeal enhancement and some parenchymal miliary enhancing brain lesions

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**Fig. 0:** Disease specific finding in NeuroTBC; miliary pulmonary nodules

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Fig. 0: Histoplasmosis, miliary enhancing brain lesions mainly along the leptomeninges (a non-PVS distribution pattern)

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Fig. 0: Histoplasmosis, miliary enhancing brain lesions mainly oriented along the leptomeninges (a non-PVS distribution pattern)

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Fig. 0: Disease specific finding in Histoplasmosis; cavitating pulmonary lesion

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Fig. 0: Disease specific finding: wall thickening of the transverse colon.
**Fig. 0:** Disease specific finding Behcet; wall thickening of the small bowel.

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**Fig. 0:** Mitochondrial disorder showing almost confluent, miliary enhancing lesions at the level of the pons

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**Fig. 0:** Miliary enhancing brain lesions in metastatic disease, scattered through the brain parenchyma

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Fig. 0: Disease specific finding metastatic disease; bone metastasis

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Fig. 0: Disease specific finding in metastatic disease; right hilar primary pulmonary mass with accompanying atelectasis.

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Conclusion

The purpose of this poster is to guide a clinician and radiologist in their diagnostic workup by providing a review of the wide spectrum of diseases known to show miliary enhancing brain lesions and emphasizing disease specific findings from both a radiological and clinical perspective. The clinician obviously should thoroughly evaluate the patient’s context, including, for example, prior medical history, physical examination, age, gender, laboratory findings, cerebral spinal fluid (CSF) analysis, and maybe less prominent signs suggesting a possible systemic disease like skin alterations, genital scars etc.

First, the radiologist should distinguish whether or not there is a specific distribution pattern of miliary enhancing brain lesions suggestive of involvement within the perivascular space (PVS), also known as Virchow Robin spaces (VRS).

Secondly, once a differential diagnosis has been made, disease specific findings of each differential diagnosis needs to be confirmed or excluded.

Finally, in those patients not considered candidates for an invasive procedure like (brain) biopsy, one could consider the response to immunosuppressive agents in follow up imaging and other clinical modalities, in order to further narrow down the differential diagnosis (fig 1 on page 43).

<table>
<thead>
<tr>
<th>Disease</th>
<th>PVS</th>
<th>Effect on cortico's</th>
<th>Disease Specifics on imaging</th>
<th>Symptom</th>
<th>Age</th>
<th>Gender</th>
<th>CSF</th>
<th>Additional imaging / tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosarcoditis</td>
<td>+</td>
<td>+</td>
<td>nVII palsy</td>
<td>20-40</td>
<td>#&gt;#</td>
<td>Non-specific</td>
<td>CT chest BAL</td>
<td></td>
</tr>
<tr>
<td>Prim. CNS Angiitis</td>
<td>+</td>
<td>+</td>
<td>Throbbing headache, Stroke-like</td>
<td>Average 50, wide range</td>
<td>#&gt;#</td>
<td>Non-specific</td>
<td>DSA</td>
<td></td>
</tr>
</tbody>
</table>

Page 40 of 48
<table>
<thead>
<tr>
<th>Condition</th>
<th>Age at Onset</th>
<th>Symptoms</th>
<th>MRI Findings</th>
<th>Clinical Findings</th>
<th>Additional Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>LYG</td>
<td>+</td>
<td>Weight loss, Night sweat.</td>
<td>Middle Aged</td>
<td>#=&gt;#</td>
<td>PET-CT</td>
</tr>
<tr>
<td>ECD</td>
<td>+</td>
<td>Neuro-endocrine disorders</td>
<td>Elderly (≥50)</td>
<td>#=&gt;#</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Lyme’s disease</td>
<td>+</td>
<td>Annular Rash, nVII palsy</td>
<td>Peak 2-15</td>
<td>#=#</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Vit B12</td>
<td>+</td>
<td>Anemia, Peripheral neuropathy</td>
<td>childhood</td>
<td>#transcobalam</td>
<td>MR spine</td>
</tr>
<tr>
<td>CLIPPERS (n=8)</td>
<td>+</td>
<td>Gait ataxia, Diplopia</td>
<td>16-86</td>
<td>?</td>
<td>PET-CT, DSA</td>
</tr>
<tr>
<td>Neuro TBC</td>
<td>-</td>
<td>Focal neurol. signs</td>
<td>&lt; 30</td>
<td>#=#</td>
<td>PCR, CSF culture + CT Chest</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>-</td>
<td>None, coughing</td>
<td>Young, elderly</td>
<td>#=##</td>
<td>CT Chest</td>
</tr>
<tr>
<td>Behcet</td>
<td>-</td>
<td>Pyramidal signs</td>
<td>10-50</td>
<td>#=&gt;#</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Susac</td>
<td>-</td>
<td>Hearing loss</td>
<td>20-40</td>
<td>#=&gt;#</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>-</td>
<td>Multi-organ</td>
<td>Early</td>
<td>#=#</td>
<td>DNA analysis</td>
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<td></td>
<td>failure</td>
<td>childhood</td>
<td># 5 hydroxy acid</td>
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<tr>
<td>Metastatic / - (n=12)</td>
<td>+/-</td>
<td>+</td>
<td>?</td>
<td></td>
<td></td>
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</tbody>
</table>

Headache; Elderly; Malign. cells; PET-CT

Box 2: Specific findings for diseases known to show miliary enhancing brain lesions.
Fig. 0: Radiological decision tree showing a group of diseases with a distribution pattern suggestive of (perivascular space) PVS involvement distribution pattern and one group without, followed by the distinguishing affects on immunosuppressive drugs. More frequently encountered diseases are listed higher than less frequently encountered diseases.

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Personal Information

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References


