Diagnosing CNS Vasculitis and IBrainD

Clinical assessment including:

- Focal neurological deficits
  - Sensory deficits
  - Motor deficits
  - Cranial nerve palsy
  - Movement abnormality

- Diffuse neurological deficits
  - Neurocognitive deficits
  - Behavior/mood changes
  - Worsening school performance
  - Memory problems
  - Signs of increased intracranial pressure (ICP), such as headaches, vomiting, visual distortions etc
  - Encephalopathy (such as altered level of consciousness)

- Psychiatric symptoms
  - Hallucinations
  - Distortions

- Seizures (confirm with electroencephalography)
  - Focal
  - Generalized
  - Status epilepticus

- Headaches

- Visual deficits

- Detailed clinical examination of all systems to exclude
  - Underlying systemic inflammatory disease
  - Infections
  - Malignancies
  - Other mimics of CNS vasculitis
Some of the tools used to assess the child’s overall clinical status are:

- Glasgow Coma Scale (GCS)
- Pediatric Stroke Outcome Measure (PSOM)

**Laboratory tests:**

- **Inflammatory Markers**
  - Erythrocyte Sedimentation Rate (ESR)
  - C-reactive protein (CRP)
  - Complement C3 and C4
  - von Willebrand Factor (vWF) antigen
  - Albumin

- **Complete Blood Count (CBC)**

- **Autoantibody testing**
  - Immunoglobulin G (IgG)
  - Antinuclear Antibody (ANA)
  - Extractable nuclear antigen (ENA)
    - Anti-Ribonucleoprotein (Anti-RNP) antibody
    - Anti-Smith (Anti-Sm) antibody
    - Anti-Sjögren’s Syndrome A (Anti-SS-A/Ro) antibody
    - Anti-Sjögren’s syndrome B (Anti-SS-B/La) antibody
  - Anti-double stranded DNA (Anti-dsDNA) antibody
  - Antineutrophil Cytoplasmic Antibody (ANCA)
    - Cytoplasmic ANCA (c-ANCA)
    - Perinuclear ANCA (p-ANCA)
    - Myeloperoxidase (MPO)
    - Proteinase 3 (PR3)
  - Anticardiolipin (aCL)/ Antiphospholipid (aPL) antibody
  - Rheumatoid Factor (RF)
  - Thyroid Peroxidase antibodies (TPO)
  - Anti-Aquaporin-4 (Anti-AQP4) antibody

- **Coagulation**
  - INR/PTT
  - D-dimer
  - Lupus Anticoagulant (LAC)

- **Infectious work-up for bacterial, fungal, and viral infections (in serum and in CSF)**
- Lumbar puncture and cerebrospinal fluid analysis
  - CSF protein count
  - CSF cell count
  - Glucose
  - Opening pressure on lumbar puncture
  - Oligoclonal banding
  - Neuronal antibodies (when applicable)
    - Anti-N-methyl D-aspartate receptor (Anti-NMDAR) antibody
    - Anti-Leucine-rich, Glioma-Inactivated 1 (Anti-LGI1) antibody
    - Anti-AMPA Receptor antibody

- Urinalysis (including protein, hematuria and microscopy)

**Neuroimaging and angiography:**

**Parenchymal Imaging**

MRI (magnetic resonance imaging) is crucial in the diagnosis of CNS vasculitis. Computed tomography (CT) is a sensitive method if diagnosing an acute hemorrhage.

The following MRI modalities should be used to detect lesions in suspected CNS vasculitis children:

- T1
- T2
- Fluid-attenuated inversion recovery (FLAIR)
- Gadolinium enhancement (for lesion enhancement and vessel wall enhancement)
- Diffusion-Weighted Imaging (DWI)

FLAIR is the best modality for visualization of inflammatory lesions; it is also helpful in confirming suspicion of abnormality on T2-weighted images. FLAIR also increases sensitivity to periventricular/subcortical and acute lesions.

MRI with gadolinium enhancement is more sensitive in detecting lesions caused by active CNS vasculitis and other inflammatory brain diseases; it demonstrates vessel-wall enhancement and thickening in children with active CNS vasculitis.
Vascular Imaging

Magnetic Resonance Angiography (MRA):

- Localization and characterization of cerebral vascular lesions
- Gadolinium enhancement strongly suggested for vessel wall imaging (thickening and enhancement)
- Less sensitive than conventional angiography

Conventional angiography (CA):

- Considered gold standard for cerebral vascular imaging
- Should be performed in children with negative MRA and high suspicion

Brain biopsy:

Brain biopsy is mandatory to confirm the diagnosis of small-vessel CNS vasculitis. It is highly recommended to perform a brain biopsy before starting long-term steroid therapy (within 10 days after starting steroids).

Brain biopsy specimen requirements:

- Whole thickness biopsy with all 3 layers (leptomeninges, gray matter cortex, subcortical white matter).
- Lesional biopsy is preferred if lesion identified on MRI is accessible, if not available a non-lesional biopsy is performed. Non-lesional biopsies are taken from the non-dominant parieto-frontal lobe.
- Preferred staining by neuropathologist usually includes hematoxylin and eosin. Immunohistochemical test and metabolic work-up based on history and neuropathology laboratory.
- Brain biopsy tissue should be cultured (bacterial, fungal and viral cultures).

No diagnostic criteria are available for the definite diagnosis of CNS vasculitis on brain biopsy. However the following items indicate an underlying inflammatory process. Ongoing research is taking place to develop a scoring system.

- Lymphocytic infiltrate around the walls of parenchymal, leptomeningeal, or dural vessels
- Structural change in vessel wall (signs of necrosis)
- Neuronophagia
- Parenchymal edema
- Biopsy should not contain substantial evidence for systemic vasculitides or secondary CNS vasculitis