When to Suspect CLIPPERS and SLIPPERS in New-Onset Epilepsy with Multimodality Imaging

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Purpose

To educate diagnostic radiologists of the common imaging manifestations associated with CLIPPERS and SLIPPERS

- **CLIPPERS**: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
- **SLIPPERS**: supratentorial lymphocytic inflammation with parenchymal perivascular enhancement responsive to steroids

Methods

A literature review was conducted to assess imaging, clinical presentation, laboratory workup, and pathology of SLIPPERS/CLIPPERS. A case with suspected SLIPPERS was included below:

- 19F with new onset focal seizures + progressive right-sided weakness, aphasia and negative LP
- MRI with multiple supratentorial enhancing lesions (*Figure 1*)
- Biopsy: multifocal perivascular, mixed B-cell/T-cell and histiocytic inflammation
- Initially considered idiopathic demyelinating disease -> Rituxan, Botox, anti-epileptics, multiple courses of steroids without significant improvement
- Multiple multidisciplinary conferences and outside institution evaluation consistent with SLIPPERS

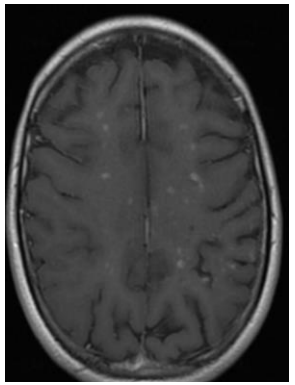


Figure 1: T1 C+ axial image with numerous punctate enhancing lesions within the supratentorial white matter

Results

Clinical presentations of CLIPPERS & SLIPPERS varied, including seizures, focal neurological deficits such as visual field defects and ataxia, and cognitive impairment. Histopathological analysis typically included perivascular CD4-predominant T-cell or lymphohistiocytic infiltrate.

MRI was the primary imaging modality used for diagnosis, though both CLIPPERS & SLIPPERS exhibited overlapping features with other neuropathologies. Notably, a single case report suggested that CLIPPERS lesions may demonstrate high glucose uptake on FDG-PET, highlighting its potential role in treatment monitoring.

Across multiple cases, the diagnostic workup was extensive, involving multimodal imaging, comprehensive autoimmune and infectious panels, invasive procedures such as lumbar puncture and stereotactic biopsy, and many requiring multidisciplinary discussions.

References

1.Tobin et al. Diagnostic criteria for chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS).Brain (2017).
2.Mashriqi et al. 18-FDG Brain PET/MRI in Chronic Lymphocytic Inflammation with Pontine Perivacular Enhancement Responsive to Steroids. Clinical Nuclear Medicine (2024).
3.Horowitz et al. [18F] FDG Brain PET findings in CLIPPERS at diagnosis and therapeutic follow up. European Journal of Nuclear Medicine and Molecular Imaging (2022).

Discussion & Conclusion

- Little extant literature describes imaging characteristics that are sensitive and/or specific to CLIPPERS or SLIPPERS
- MRI remains the predominant modality for evaluation with common findings described in **Table 1**
- Unfortunately, these imaging characteristics are neither sensitive nor specific for either CLIPPERS/SLIPPERS
  - Multiple pathologies appear similar on MRI imaging including, but not limited to;
    - CNS Lymphoma
    - Sarcoidosis
    - Multiple Sclerosis
    - CNS Vasculitis
    - Infectious Encephalitis
  - Each of these pathologies maintains unique clinical history, labs, and pathology
- Nuclear medicine scans such as FDG-fused PET/MRI have shown promise in evaluating treatment response more so than initial diagnosis
  - Depicted in Figures 2 and 3, FDG-fused PET/MRI have been described as beneficial in evaluating early relapses and assessing response at the metabolic level, often before structural MRI changes
- The gold standard of diagnosis remains biopsy
  - There remains much to understand regarding definitive, less invasive diagnostics
- Ultimately, once a thorough clinical workup has been completed with atypical, unexplainable MRI findings, CLIPPERS/SLIPPERS is an entity that requires a high index of suspicion as an interpreting radiologist and may facilitate prompt therapy

MRI Feature	Typical Findings in CLIPPERS[1]	Contrast with Non-CLIPPERS
Enhancing lesion size	≤ 3 mm, punctate nodules	> 3 mm, irregular or large lesions
Enhancing pattern	Homogenous gadolinium enhancement; no ring enhancement	Heterogeneous or ring enhancement common
Enhancement distribution	Predominantly in pons and cerebellum; may extend to midbrain, medulla, subcortical white matter, hemispheres	Often asymmetric and not limited to pontocerebellar region
T2 signal pattern	T2 hyperintensity mirrors enhancement; homogenous	T2 abnormalities exceed size of enhancement; heterogeneous
Mass effect	Absent	Often present
Response to steroids	Marked radiological and clinical improvement	Partial or no radiological improvement
Spinal cord involvement	Punctate gadolinium enhancing lesions with corresponding T2 lesions in 10/17 cases	Less frequent and less specific findings; non-enhancing T2 lesions present

Table 1: *Comparing and contrasting typical findings associated with CLIPPERS*

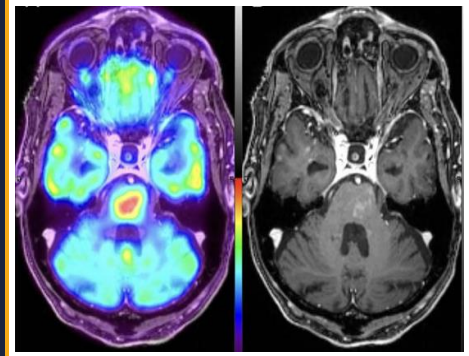


Figure 2 *(Mashriqi et al.) : PET—MRI (left) of tbe brain at the level of the pons notable for intense uptake within the pons. MRI T1 C+ (right) with nonspecific enhancing lesion in the pons.*

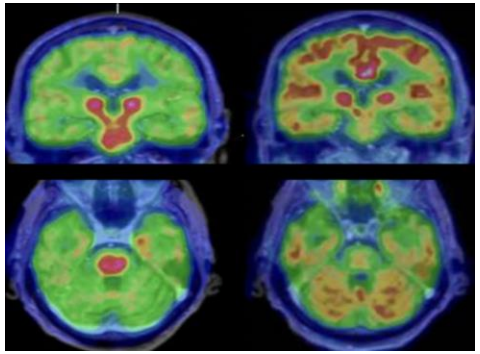


Figure 3 *(Horowitz et al): multiple reformats of PET—MRI taken at onset of symptoms (left) and at follow up (right) in a patient with suspected CLIPPERS with less uptake in the pons, white matter tracts, and basal ganglia.*

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