CLIPPERS Spectrum Disorder: A Rare Pediatric Neuroinflammatory Condition

Tarishi Nemani, MD1, Anaita Udwadia-Hegde, MD, MRCPCH1, Purva Keni Karnavat, DNB1, Ritu Kashikar, DNB, DMRD2, and Shridhar Epari, MD3

Abstract
CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) is a recently described, rare neuroinflammatory disorder diagnosed by clinical symptoms involving the brain stem with a distinct pattern on neuroimaging and a perivascular T-lymphocyte infiltrate on brain biopsy. It is a condition usually described in adults in the fourth to fifth decade. We report a case of 13-year-old Indian boy who presented with recurrent episodes of ataxia and diplopia with onset at 7 years of age. He was investigated extensively to rule out infective, neoplastic, autoimmune, and demyelinating conditions over a span of 6 years. The diagnosis of CLIPPERS was entertained on the basis of clinico-radio-pathological correlation. Treatment with steroids and steroid-sparing agents, particularly methotrexate, seems to provide a promising outcome. With very few cases in literature so far, reporting of a larger case series with pediatric onset may expand it to CLIPPERS spectrum disorder.

Keywords
Pediatric CLIPPERS, Neuro-inflammatory, Ataxia, Methotrexate

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CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) is a recently described, rare inflammatory disorder of the central nervous system. This condition was first described by Pittock et al1 in 2010 as clinically and radiologically distinct pontine-predominant encephalomyelitis. It is diagnosed by clinical symptoms involving the brain stem with a distinct pattern of magnetic resonance imaging (MRI) changes characterized by punctate and curvilinear gadolinium enhancement “peppering” the brain stem (mainly the pons) and a perivascular T-lymphocyte infiltrate on brain biopsy.1,2 It is reported to be a steroid-dependent condition with a relapsing, remitting course requiring glucocorticoid therapy along with long-term immunosuppression.1,3

Here, we report a 13-year-old boy with CLIPPERS to raise awareness about this rare condition, enabling early diagnosis and treatment. To our knowledge, this would be the first pediatric case from India.

Case Report
A 13-year-old male child was referred to us for complaints of recurring episodes of ataxia and diplopia for last 6 years. He was born of nonconsanguineous marriage with normal birth history and normal development and was asymptomatic till 6.5 years of age. He presented in a private hospital, with complaints of intermittent fever associated with vomiting and giddiness for a period of 1 month. This was followed by medial deviation of both eyes. On examination, he had bilateral sixth cranial nerve palsy with papilledema and unequal pupils; rest of his central nervous system examination was normal. Lumbar puncture showed 30 cells with 90% lymphocytes and normal protein, sugar, and lactate. Magnetic resonance imaging of the brain (Figure 1A) suggested altered signal intensities, punctate, curvilinear enhancement, and perivascular T-lymphocytic infiltrate on the brain stem on MRI T1 axial and FLAIR images. The differential diagnoses entertained were acute disseminated encephalomyelitis, multiple sclerosis, and an immune-mediated process. The patient received a tapering course of methylprednisolone, with gradual improvement in the clinical symptoms and neuroimaging features. He was started on methotrexate as a steroid-sparing agent. The patient has gone on to have two relapses during the follow-up period. The patient is on 15 mg methotrexate weekly and has been asymptomatic since the last relapse.

1 Department of Pediatric Neurology, Jaslok Hospital and Research Centre, Mumbai, India
2 Department of Radiology, Jaslok Hospital and Research Centre, Mumbai, India
3 Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India

Corresponding Author:
Anaita Udwadia-Hegde, MD, MRCPCH, 106, Doctor House, Opp Jaslok Hospital, Peddar Road, Mumbai 400 026, India.
Email: anaitahedegde@gmail.com

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hyperintense on T2 in subcortical and deep white matter over parieto-occipital and bilateral cerebellar region. A probable diagnosis of acute disseminated encephalomyelitis was made, and he was treated with intravenous methylprednisolone followed by tapering doses of oral steroids over 1 month. Improvement was noted within a month, total recovery without sequelae, and the child was asymptomatic for next 6 years.

At 12 years, he returned with complaints of medial deviation of left eye and diplopia. There was no history of fever, vomiting, headache, seizures, or altered sensorium. Magnetic resonance imaging of the brain (Figure 1B) suggested white matter signal changes in bilateral cerebellar hemispheres, cerebellar peduncles, pons, and midbrain. Similar changes were seen in left thalamus, adjacent posterior limb of internal capsule, parahippocampal gyrus, and parietal regions on both sides. Small changes in the left frontoparietal subcortical white matter. Complete blood count and serum biochemistry were normal. Cerebrospinal fluid routine, aquaporin 4, and anti-N-methyl-D-aspartate receptor (NMDAR) antibody were negative. Immunoglobulin E level-1140 (N < 200) was raised (Table 1A). Diagnosis of multiphasic demyelinating encephalomyelitis or probable evolving multiple sclerosis was considered. He was

Figure 1. A, Magnetic resonance imaging (MRI) of the brain suggested altered signal intensities, hyperintense on T2 in subcortical and deep white matter over parieto-occipital and bilateral cerebellar region. B, The MRI of the brain suggested white matter signal changes in bilateral cerebellar hemispheres, cerebellar peduncles, pons, and midbrain. Similar changes in left thalamus, adjacent posterior limb of internal capsule, parahippocampal gyrus, and parietal regions on both sides. Small changes in the left frontoparietal subcortical white matter. C, Significant decrease in hyperintensities as compared to (C), but not totally cleared. D, Reappearance of lesions and patchy involvement of pons, midbrain, cerebellar peduncles, and cerebellum.
again treated with intravenous methylprednisolone, followed by oral steroids tapered over 3 months. Partial improvement was noted in squint. Follow-up MRI brain done 3 months after the episode showed significant improvement but not total clearing of lesions (Figure 1C).

On his subsequent follow-up after 6 months, the child was asymptomatic other than a residual left eye esotropia with no new symptoms. Repeat MRI brain (Figure 1D) showed reappearance of lesions and patchy involvement of pons, midbrain, cerebellar peduncles, and cerebellum. He was referred to a higher center for further management. Here, a differential diagnosis of atypical demyelination, central nervous system lymphoma, autoimmune central nervous system disease was considered, and he was worked up in detail for the same (Table 1B).

After 4 months of rituximab completion (July 2017), he presented with headache, vomiting, giddiness, and an episode of right focal seizure. Repeat cerebrospinal fluid and blood investigations were done (Table 1C). During the course, patient developed hydrocephalus and underwent suboccpital craniectomy and biopsy of left cerebellar lesion which was suggestive of T-cell lymphoma with a differential of CLIPPERS as a possibility. Patient was referred to a premier cancer institute in view of suspected central nervous system T-cell lymphoma. Here, a review of biopsy was done (Figure 2) and malignancy was ruled out and then referred to us.

He presented to us with a history of recurrent ataxia, bilateral persistent esotropia, and diplopia with no other neurological and systemic symptoms. On examination, he was conscious, oriented but emotionally labile with Mini-Mental State Examination-22/30 and normal speech. He had an ataxic gait, with bilateral sixth nerve palsy. On motor examination, power and tone were normal in all limbs, and deep tendon reflexes were uniformly brisk with flexor plantars. Cerebellar signs were present in form of ataxia, dysdiadokokinesia, and dysmetria. His Extended Disability

### Table 1. Investigations.

| Parameters                          | March 2016 (A) | December 2016 (B) | July 2017 (C) | September 2017 (D) |
|-------------------------------------|---------------|------------------|--------------|-------------------|
| CBC                                 | Hb = 13.1, TLC = 5200, DLC = P40%L49%, Platelet = 1.26 lac | Hb = 13.8, TLC = 6500, DLC = P57%L33%, Platelet = 1.34 lac | Hb = 15.5, TLC = 5200, DLC = P48%L38%, Platelet = 2 lac | Hb = 12.8, TLC = 2420, DLC = P30%L64%, Platelet = 2.2 lac |
| Peripheral smear                    | No abnormal cells | No abnormal cells | No abnormal cells | No abnormal cells |
| ESR                                 | –              | –                | –             | 18                |
| Vitamin B12, homocysteine           | –              | 399, normal      | –             | 10, normal        |
| Serum ACE                           | –              | Normal           | –             | Normal            |
| Serum ammonia                       | –              | 96, normal       | 55            | Normal            |
| TMS and urine metabolites          | Normal         | –                | Normal        | Normal            |
| ANA & ANCA                          | Normal         | –                | Normal        | Decreased         |
| ENA panel                           | –              | –                | –             | Normal            |
| IgA, IgM, IgG                       | –              | –                | –             | Normal            |
| IgE                                 | >1140 (N-200) | –                | –             | 305, increased    |
| CSF                                 | Normal         | Cells = nil, protein = 55, sugar = 63 | Cells = nil, plenty RBCS, protein = 22, sugar = 69 | Cells = 30 (P20%, L80%), protein = 115, sugar = 51 |
| CSF lactate                         | –              | 12.6             | –             | 1.4               |
| CSF cytospin                        | –              | –                | Negative      | Negative          |
| CSF ACE                             | –              | –                | –             | 10, negative      |
| CSF & serum AQ4 Ab                  | Negative       | Negative         | –             | Negative          |
| CSF OCB                             | –              | –                | Negative      | Negative          |
| CSF anti-MOG Ab                     | Negative       | –                | Negative      | Negative          |
| CSF anti-NMDA Ab                    | Negative       | –                | Negative      | Negative          |
| Paraneoplastic Ab                   | –              | Negative         | –             | Negative          |
| Viral XCyton                        | –              | –                | Negative      | Negative          |
| HBsAg, HIV, HCV                     | Negative       | –                | –             | –                 |
| CT chest                            | Normal         | –                | Normal        | Normal            |
| Bone marrow                         | Normal         | –                | –             | –                 |
| PET scan whole body                 | Normal         | –                | Normal        | –                 |

Abbreviations: ACE, angiotensin converting enzyme; ANA, anti nuclear antibody; ANCA, Antineutrophil cytoplasmic antibody; CBC, complete blood count; CSF, cerebrospinal fluid; CT, computed tomography; DLC, differential leukocyte count; ENA, extractable nuclear antigen panel; ESR, erythrocyte sedimentation rate; Hb, Haemoglobin; HBsAg, Hepatitis B surface antigen; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; IgA, IgM, IgG; Immunoglobulins(IgA, IgM, IgG); IgE, immunoglobulin E; MOG, Myelin Oligodendrocyte Glycoprotein; NMDA, N-methyl-D-aspartate; OCB, oligoclonal bands; PET, positron emission tomography; TLC, total leukocyte count; TMS, tandem mass spectroscopy; RBCS, red blood cells.

P30%- polymorphs 30% and L64%- lymphocytes are 64%
Status Scale score was 5.5. Other systemic examination was normal. Repeat MRI brain with contrast (Figure 3A) suggested punctate T2 hyperintense lesions in pons, bilateral cerebellar hemispheres, brachium pontis, ventral medulla, midbrain extending cranially into thalamus, and posterior limbs of internal capsule. Extensive confluent lesions were also present posteriorly in parieto-occipital region and focal lesions anteriorly in frontal lobes with few showing nodular enhancement with involvement of corpus callosum.

Differential diagnosis of steroid-sensitive autoimmune disease, demyelinating disease, neurosarcoidosis, central nervous system infection, paraneoplastic syndromes, central nervous system lymphoma, and CLIPPERS syndrome was included. He was investigated in detail (Table 1D) for the same. The biopsy sample was reevaluated by hematopathologist and neuropathologist, who performed further tests such as immunohistochemistry and T-cell receptor gene rearrangement.

Histologically, fragments of cerebellar folia showed dense band-like lymphoplasmacytic cell-rich leptomeningeal infiltrate (Figure 2A and C), extending into the subjacent parenchyma along the blood vessels with foci of perivascular aggregation (Figure 4B and D). No vasculitis and/or necrosis was seen. The gradient of the inflammatory infiltrate was decreasing from the pial surface to the white matter parenchyma (Figure 2A and B). Additionally, tiny specks of dystrophic calcification were also noted in the cerebellar white matter. On immunohistochemistry, CD3 (Figure 4A and B) and CD7-positive (Figure 4C) T-lymphoid cells were the predominant cellular component with conspicuous admixture by CD163-positive histiocytes (Figure 4D). The T-lymphoid cells showed marked CD4 preponderance over CD8 (Figure 4E and F), unlike the post/viral-related lymphocytic infiltrate, which is CD8 preponderant. Molecular evaluation for T-cell receptor gene rearrangement, evaluated by capillary electrophoresis (Figure 5), did not reveal presence of any clonal T-lymphoid cells, excluding the possibility of T-cell lymphoma. In keeping with all these features, the histomorphology was suggestive of polyclonal CD4 preponderant T-lymphoid cell inflammatory lesion ruling out malignancy.

Clinical features suggesting brain stem dysfunction along with MRI of the brain showing gadolinium-enhancing punctate lesions peppering pons and cerebellum and histopathology showing polyclonal T-cell infiltration along with exclusion of infective, neoplastic, autoimmune, demyelinating conditions child was diagnosed with CLIPPERS.

He was treated with intravascular methylprednisolone (30 mg/kg/d) for 5 days followed by slow tapering of oral steroids. Methotrexate treatment was initiated at 10 mg/m²/wk. He has been symptom-free for 6 months. His repeat MRI of the brain...
on tapering steroids and methotrexate shows considerable improvement (Figure 3B).

Discussion

CLIPPERs is a relatively newly reported demyelination entity identified and defined by Pittock et al in 2010. Literature has reported till date 2 large case series. The age range is from 13 to 86 years; however, it is a condition largely described in adults in the fourth to fifth decade. Very few cases of CLIPPERs have been reported in pediatric age group. There is no male or female predilection. Time to diagnose is usually variable as the persistence of pons and midbrain involvement with characteristic “peppering” sign on MRI are the main diagnostic features.

This condition is insidious in onset with progressive brain stem, cranial nerves, spinal cord, and cerebellar involvement. A long-term follow-up study by Taieb et al found the clinical course to be relapsing-remitting without treatment. There is progressive clinical deterioration with each relapse leaving residual neurological sequelae depending on severity. Since there are only few reported cases in literature, the pathogenesis of CLIPPERs and its preponderance to pons and adjacent structures are not well understood. The clinicoradiological response to glucocorticoids and the perivascular T-cell infiltrate in affected central nervous system lesions suggest an autoimmune or an inflammatory process.

To our knowledge, ours would be the first pediatric case to be reported from India with onset of symptoms at 7 years of age presenting with ataxia and bilateral esotropia. These are known to be the most common symptoms along with dysarthria and/or altered facial sensation. Other features could be spastic quadriparesis or paraparesis, sphincter dysfunction, cognitive deficits, and headache and fatigue. Emotional lability (involuntary crying or laughing) was also present in our patient; it is now being reported that pseudobulbar affect may be an additional feature.

Neuroimaging

CLIPPERs is predominantly a condition diagnosed by MRI findings described as punctate or nodular enhancing lesions peppering the pons with variable extension into the white matter of cerebellar hemispheres. The extension of lesions to
supratentorial regions, basal ganglia, thalamus, corpus callosum, cerebral white matter, and caudally into medulla and cervico thoracic cord has also been well reported.\textsuperscript{1,10,13,15-17} The lesions have characteristic pattern of decreasing intensity with increasing distance from pons.\textsuperscript{4,9}

Our patient had punctate T2 hyperintense lesions in pons, bilateral cerebellar hemispheres, brachium pontis, ventral medulla, midbrain extending cranially into thalamus, and posterior limbs of internal capsule. Our patient also had extensive confluent lesions posteriorly in parieto-occipital region and focal lesions anteriorly in frontal lobes with few showing nodular enhancement with involvement of corpus callosum. This involvement is quite rare for CLIPPERS.\textsuperscript{3,4,9} From the few long-term follow-up reports, it is also known that patients may later develop pontocerebellar and cerebral atrophy.\textsuperscript{3,4,9}

In our patient, the T2 hyperintensity extended beyond the extent of T1 postgadolinium enhancement which is atypical for CLIPPERS.\textsuperscript{18} These features were most prominent in the scans when he was young, and the scans at older age show more characteristic neuroimaging findings. Although these atypical features do not fulfill the recently proposed MRI diagnostic criteria,\textsuperscript{2,18} similar imaging findings have been reported in pediatric case series by Sa et al.\textsuperscript{6} Given that

![Figure 4. Immunohistochemical evaluation representative photomicrographs of immunohistochemical evaluation, which shows CD3 (A: ×40; B: ×100) and CD7-positive (C: ×100) T-lymphoid cells admixed with CD163-positive (D: ×100) histiocytes in the leptomeningeal space with involvement of the subjacent parenchyma. The T-lymphoid cells show marked preponderance for CD4 (F: ×100) over CD8 (G: ×100).]
there are so few reports of pediatric-onset CLIPPERS in literature,\(^3,6-8\) we believe these atypical features could either be expanding the spectrum of CLIPPERS or represent differences in early-onset cases as compared to imaging findings in adults. With the evolving clinical and radiological phenotypes, it needs to be seen whether we are looking at a new pediatric-onset inflammatory disorder. Reporting of more cases might help us understand the phenotypic spectrum better.

**Laboratory Investigations**

Along with clinical and radiological features, the diagnosis of CLIPPERS requires exclusion of a long list of differential diagnosis.\(^1,4,9,13,14,17,19\) Extensive laboratory investigations including autoantibodies, paraneoplastic antibodies, and vasculitis markers, to rule out autoimmune encephalitis, paraneoplastic diseases, and central nervous system vasculitis, are required. Serological tests from blood and cerebrospinal fluid were done to exclude infectious etiology and serum angiotensin-converting enzyme levels to rule out neurosarcoi-
dosis. All these tests were negative for our patient. Cerebrospinal fluid examination showed mild pleocytosis with lymphocytic predominance.\(^1,3,4,9,13,14\) It was negative for malignant cells. Cerebrospinal fluid oligoclonal bands were also negative excluding demyelinating disorders; however, there are few reports showing transient presence of oligoclonal bands.\(^1,3,14\) Elevated immunoglobulin E levels were noted in

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**Figure 5.** Electropherograms representing T-cell receptor (TCR)-\(\gamma\) (A and B) and TCR-\(\beta\) (C, E, G and D, F, H representing 3 tubes) in duplicate concentrations (the electropherograms on the left, ie, A, C, E, G representing 50 \(\mu\)g of sample DNA; while those on right, ie, B, D, F, H represent 100 \(\mu\)g of sample DNA), do not reveal any presence of clonal peak, suggesting absence of clonal T-lymphoid cells.
CLIPPERS is a rare inflammatory disorder of the central nervous system predominantly affecting adults; however, it is now being recognized in children as well. The trademark features of pontocerebellar involvement, with “peppering of the pons” on neuroimaging, a relapsing remitting clinical course, steroid responsive picture, and characteristic histopathology should raise the suspicion of CLIPPERS. Although the underlying etiology/precipitant has not yet been identified, treatment with steroids and steroid-sparing agents, particularly methotrexate, seems to provide a promising outcome. Reporting of a larger case series of pediatric CLIPPERS will help us further understand the spectrum more clearly.

**Conclusion**

CLIPPERS is a rare inflammatory disorder of the central nervous system predominantly affecting adults; however, it is now being recognized in children as well. The trademark features of pontocerebellar involvement, with “peppering of the pons” on neuroimaging, a relapsing remitting clinical course, steroid responsive picture, and characteristic histopathology should raise the suspicion of CLIPPERS. Although the underlying etiology/precipitant has not yet been identified, treatment with steroids and steroid-sparing agents, particularly methotrexate, seems to provide a promising outcome. Reporting of a larger case series of pediatric CLIPPERS will help us further understand the spectrum more clearly.

**Author Contributions**

TN and AH contributed to conception and design. TN drafted the manuscript. All authors contributed to acquisition, analysis, and interpretation. AH, PK, RK, and SE critically revised the manuscript. AH gave final approval. AH and SE agree to be accountable for all aspects of work ensuring integrity and accuracy.

**Declaration of Conflicting Interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Ethical Approval**

Consent was taken from parents of the patient (care givers).

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