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CLIPPERS Spectrum Disorder: A Rare Pediatric Neuroinflammatory Condition

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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 al[1] 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,

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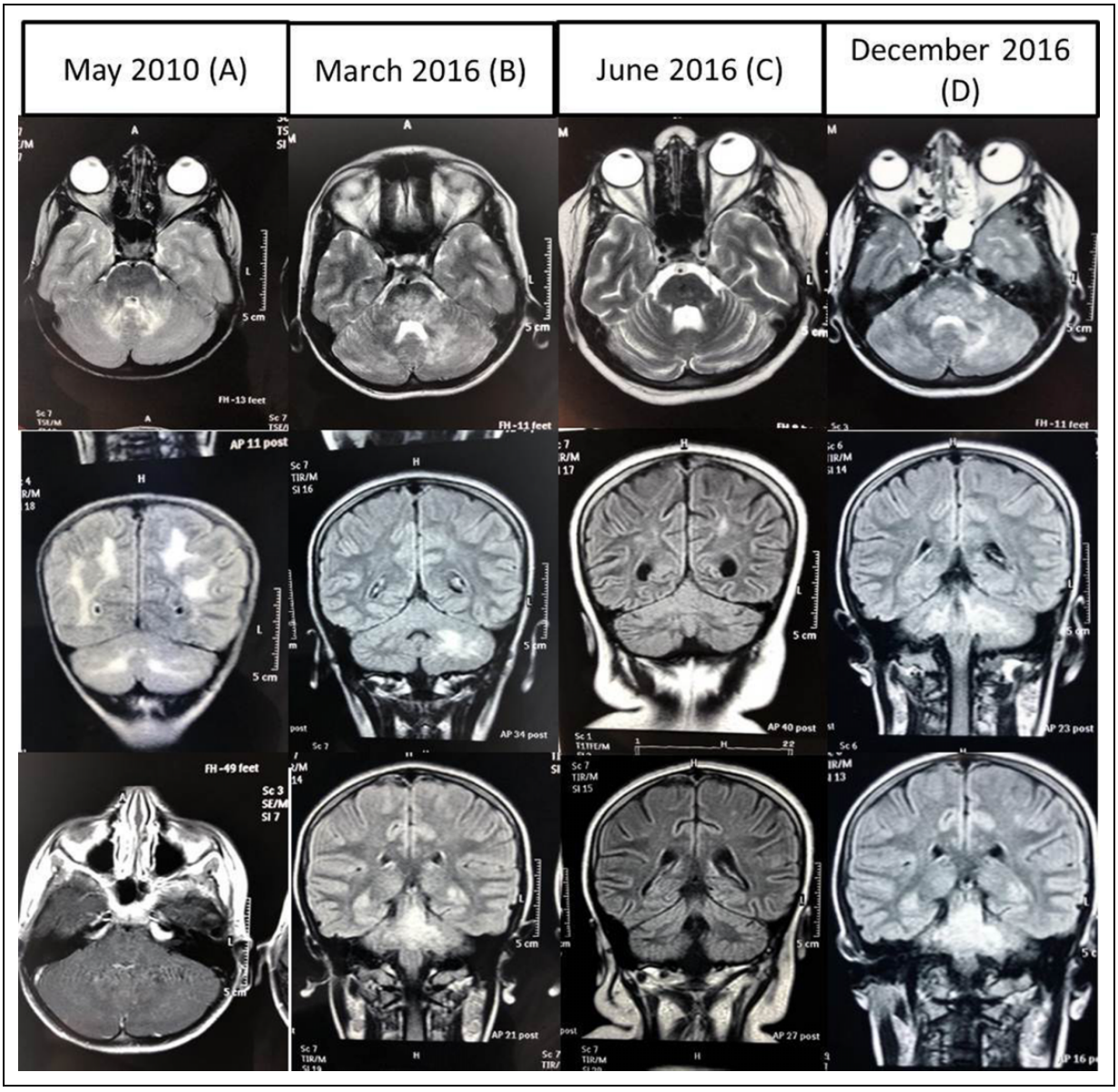

Figure 1. A, Magnetic resonance imaging (MRI) of the brain suggested altered signal intensities, hyperintense on T2 in subcortical and deep white matter over parieto-occipital and bilateral cerebellar region. B, The MRI of the brain suggested white matter signal changes in bilateral cerebellar hemispheres, 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.

hyperintense on T2 in subcortical and deep white matter over parieto-occipital and bilateral cerebellar regions. 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 with few 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

Table 1. Investigations.

Parameters	March 2016 (A)	December 2016 (B)	July 2017 (C)	September2017 (D)
CBC	Hb = 13.1, TLC = 5200, DLC = P40%L49%, Platelet = 1.26 lac	Hb = 13.8, TLC = 6500, DLC = P57%L33%, Platelet = 1.34lac	Hb = 15.5, TLC = 5200, DLC = P48%L38% Platelet = 2 lac	Hb = 12.8, TLC = 2420 DLC = P30%l64%, Platelet = 2.2lac
Peripheral smear	No abnormal cells	No abnormal cells	No abnormal cells	No abnormal cells
ESR	–	–	–	18
Vitamin B12, homocysteine	–	399, normal	–	Normal
Serum ACE	–	Normal	–	10, negative
Serum ammonia	–	96, normal	55	Normal
TMS and urine metabolites		Normal	–	
ANA &ANCA	–	Normal	–	Normal
ENA panel	–	–	–	Normal
IgA, IgM, IgG	–	–	–	Decreased
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
CSF ACE		–	–	10, negative
CSF & serum AQ4 Ab	Negative	Negative	–	Negative
CSF OCB	–	–	–	Negative
CSF anti-MOG Ab	–	–	–	Negative
CSF anti-NMDA Ab	Negative	Negative	–	Negative
Paraneoplastic Ab	–	Negative	–	Negative
Viral XCyton		–	–	Negative
HBsAg, HIV, HCV		Negative	–	
CT chest		Normal	–	
Bone marrow		Normal	–	
PET scan whole body		Normal	–	

Abbreviations: ACE, angiotencsin 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%

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).

Post this workup, considering an atypical demyelinating disorder, child was treated with intravenous methylprednisolone followed by 4 weekly injections of rituximab from January 2017 to February 2017. However, follow-up after 3 months showed no significant clinical improvement. Repeat MRI brain (May 2017) showed no change in lesions.

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 hydrocephalous and underwent suboccipital 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

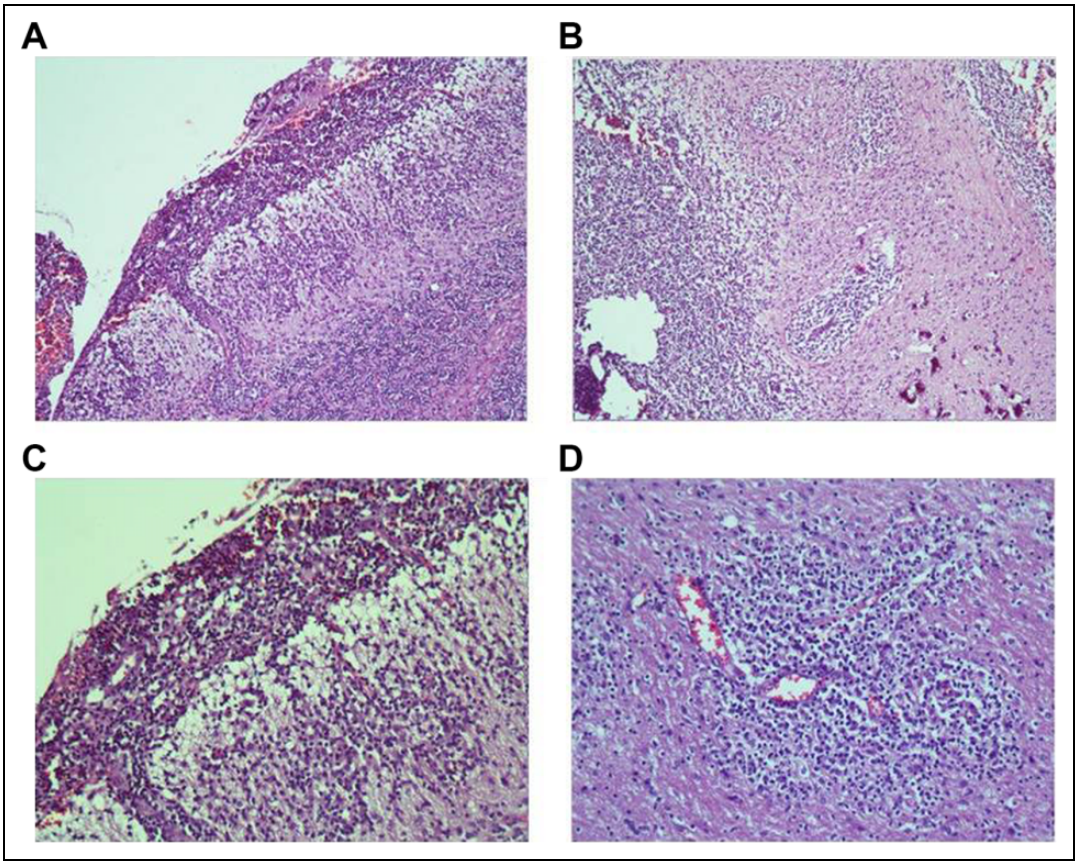

Figure 2. Histopathology representative photomicrographs show inflammatory cell infiltrate involving the leptomeningeal surface (A: ×40, C: ×100; HE) with secondary infiltration into the parenchyma along the thin-walled capillary-sized blood vessels (B: ×40; D: ×100; HE). HE, Hematoxylin and Eosin Stain.

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 hematoncologist 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/m^2/wk. He has been symptom-free for 6 months. His repeat MRI of the brain

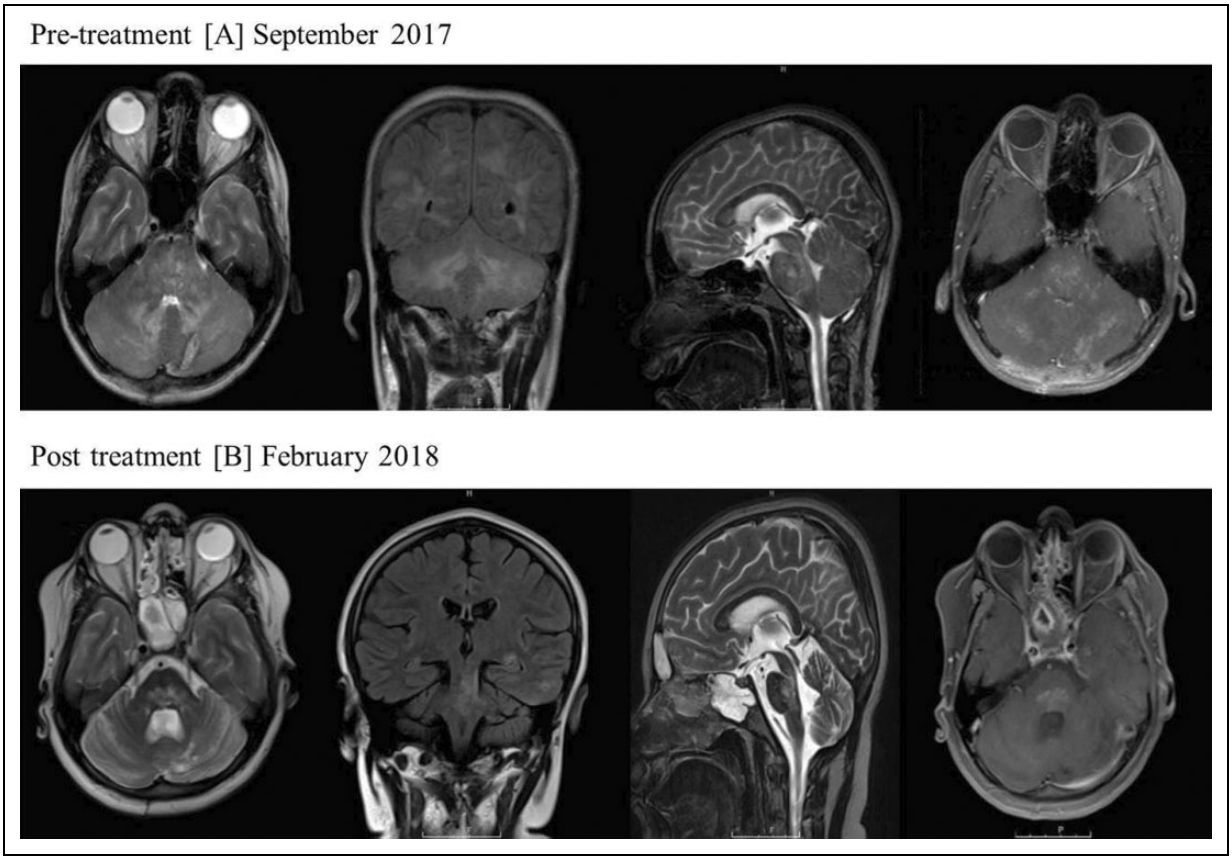

Figure 3. A, It suggested punctate T2 hyperintense lesions in pons, bilateral cerebellar hemispheres, brachium pontis, ventral medulla, midbrain extending cranially into thalamus, and posterior limbs of internal capsule. Extensive confluent lesions were also present posteriorly in parieto-occipital region and focal anteriorly in frontal lobes with few showing nodular enhancement with involvement of corpus callosum. B, Considerable improvement as compared to (A).

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.[3,4] 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.[3,5-8] 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.[4] A long-term follow-up study by Taieb et al[3] 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.[3,4] 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.[1]

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.[1,4,9] Other features could be spastic quadriparesis or paraparesis,[1,9-12] sphincter dysfunction, cognitive deficits,[9,13] and headache and fatigue.[1,9,14] 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.[1,9,14]

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.[9] The extension of lesions to

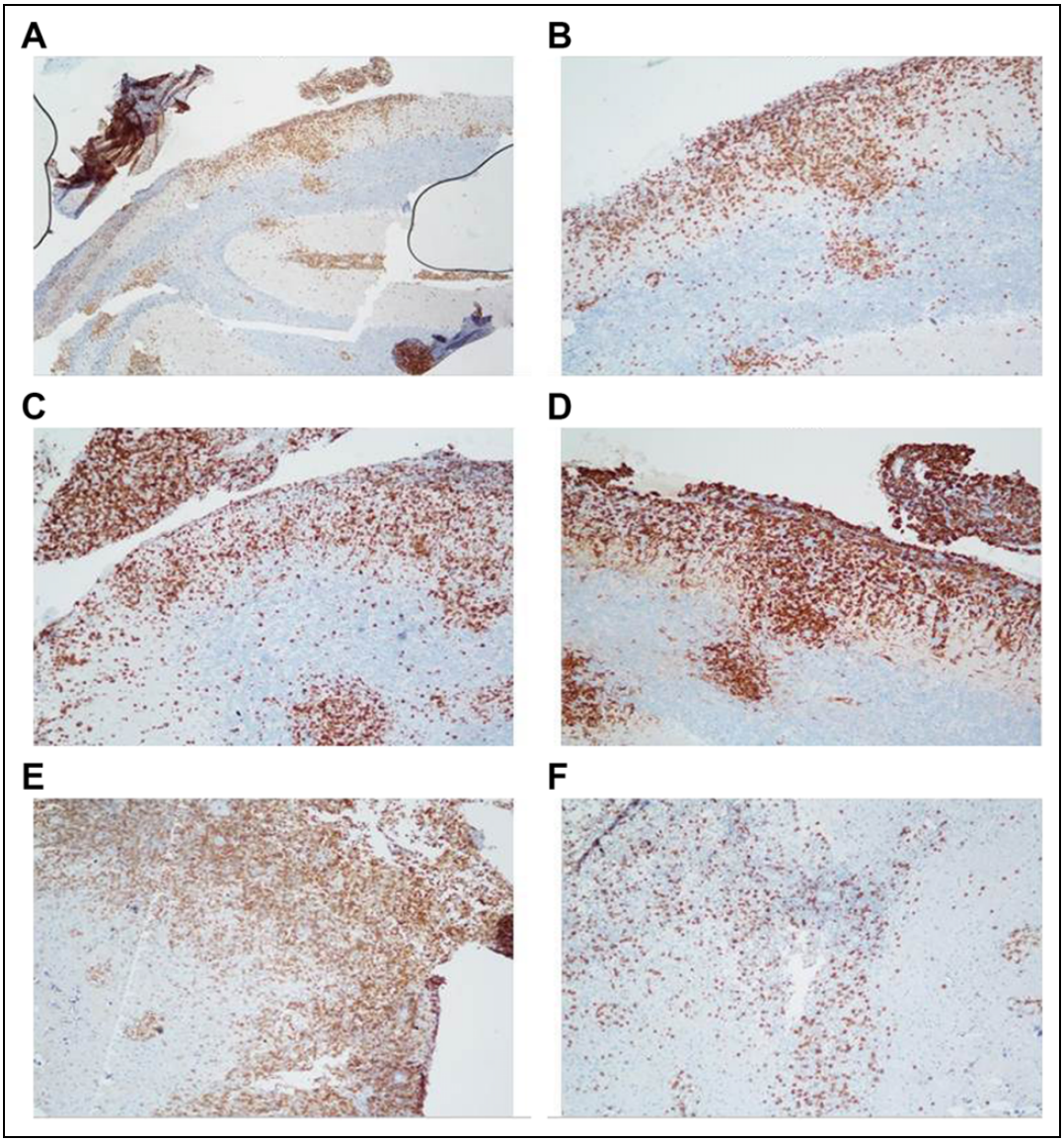

Figure 4. Immunohistochemical evaluation representative photomicrographs of immunohistochemical evaluation, which shows CD3 (A: ×40; B: ×100) and CD7-positive (C: ×100) T-lymphoid cells admixed with CD163-positive (D: ×100) histiocytes in the leptomeningeal space with involvement of the subjacent parenchyma. The T-lymphoid cells show marked preponderance for CD4 (F: ×100) over CD8 (G: ×100).

supratentorial regions, basal ganglia, thalamus, corpus callosum, cerebral white matter, and caudally into medulla and cervico thoracic cord has also been well reported.[1,10,13,15-17] The lesions have characteristic pattern of decreasing intensity with increasing distance from pons.[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. There was no mass effect, presence of which would have suggested an alternative diagnosis. Diffusion-weighted images show no areas of restricted diffusion and MRI spine screening showed no significant abnormality. One of the previous MRI, done after the second episode while on steroids, showed complete resolution of lesions along with clinical improvement, thus showing early steroid responsiveness.[1,3,4,9-15] From the few long-term follow-up reports, it is also known that patients may later develop pontocerebellar and cerebral atrophy.[3,4,9]

In our patient, the T2 hyperintensity extended beyond the extent of T1 postgadolinium enhancement which is atypical for CLIPPERS.[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,[2,18] similar imaging findings have been reported in pediatric case series by Sa et al.[6] Given that

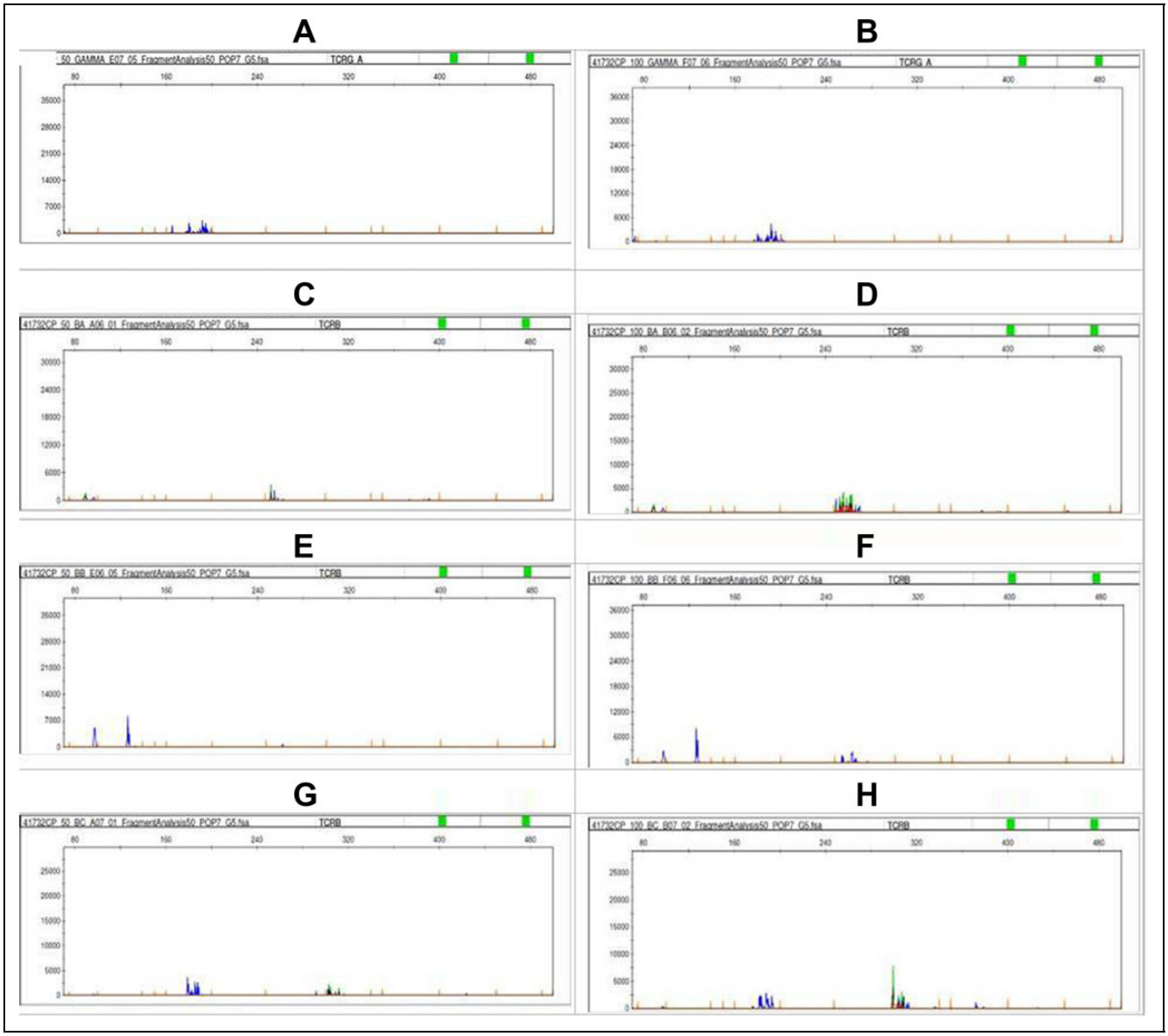

Figure 5. Electropherograms representing T-cell receptor (TCR)-γ (A and B) and TCR-β (C, E, G and D, F, H representing 3 tubes) in duplicate concentrations (the electrograms on the left, ie, A, C, E, G representing 50 μg of sample DNA; while those on right, ie, B, D, F, H represent 100 μg of sample DNA), do not reveal any presence of clonal peak, suggesting absence of clonal T-lymphoid cells.

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 neurosarcoidosis. 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

our patient like a few other cases reports, suggesting an allergic trigger may evolve into a perivascular inflammatory process.[4,11,13]

Neuropathology

The histopathological findings in CLIPPERS is not specific; however, it may help to exclude few important clinic-radiological mimics such as central nervous system T-cell lymphoma, low-grade glioma, and primary central nervous system angitis. The biopsy review in our patients showed perivascular polyclonal CD4 T-cell predominance with no evidence of demyelination, granulomatous inflammation, and vasculitis fulfilling the neuropathological diagnostic criteria.[2] These findings were similar to other cases reported in literature.[1,3,4,6,9]

Pathogenesis

The pathogenesis of CLIPPERS is yet to be known. Presence of perivascular inflammatory infiltrates was explained by Pittock et al[1] and other authors as an immune-mediated process against an auto-antigenic epitope predominantly in pons and adjacent structures. Predominance of CD4 T cells in biopsy and cerebrospinal fluid samples seen in a study by Taieb and colleagues[3] suggested an immune response to exogenous antigen (or environmental allergens). However, some authors believe it to be a primary venous inflammatory central nervous system disorder in view of anatomical arrangement of small intra-axial veins predominantly in brain stem.[3,4]

Treatment

CLIPPERS being a newly described entity there are limited data to define standard treatment guidelines. With only few reported pediatric cases, the clinical course and response to treatment are thought to be similar to adults.[3,8,20] All cases reported in literature so far have shown significant clinical and radiological improvement with glucocorticoids. Literature suggests each relapse to be treated with pulse methylprednisolone followed by a very slow tapering of oral steroids.[3,4,20] A few long-term follow-up studies have described increasing relapse rate on tapering steroids indicating the need for chronic glucocorticoid therapy along with a steroid-sparing agent to limit steroid side effects.[4,3,9,12] Various immunosuppressive agents have been tried as monotherapy and combined therapy such as azathioprine,[11,12,16] cyclophosphamide,[3,9,13] rituximab,[3,15] and methotrexate.[1,4,12-14,19,21] A few reports have shown methotrexate as potentially the most beneficial.[1,8,13,14,21,22] Thus, we started our patient on weekly methotrexate along with glucocorticoids to which he has responded very well. The duration of therapy is still not defined, a few long follow-up reviews suggest duration of immunosuppressive therapy to be 2 to 5 years.[3,12]

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).

References

1. Pittock SJ, Debruyne J, Krecke KN, et al. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain*. 2010;133(9):2626-2634. doi:10.1093/brain/awq164.
2. Tobin WO, Guo Y, Krecke KN, et al. Diagnostic criteria for chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain*. 2017;140(9):2415-2425. doi:10.1093/brain/awx200.
3. Taieb G, Duflos C, Renard D, et al. Long-term outcomes of CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) in a consecutive series of 12 patients. *Arch Neurol*. 2012;69(7):847-855. doi:10.1001/archneurol.2012.12
4. Dudesek A, Rimmele F, Tesar S, et al. CLIPPERS: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. Review of an increasingly recognized entity within the spectrum of inflammatory central nervous system disorders. *Clin Exp Immunol*. 2014;175(3):385-396. doi:10.1111/cei.12204.
5. Salam A, Farah S, Rashed N, Azhar SM, Yasir I, Ahmad A. Clippers (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids)—case report with neuroimaging. *Pak J Neurol Sci*. 2014;9(3):Article 8.

6. Sa M, Green L, Abdel-Mannan O, et al. Is chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) in children the same condition as in adults? *Dev Med Child Neurol*. 2018:1-8. doi:10.1111/dmcn.13997.
7. Mathias S, Hickman D, Lightner D, Smith C, Baumann R. A pediatric case of CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) (P6.265). *Neurology*. 2015;84(14 supplement): P6.265.
8. Veerapandiyan A, Chaudhari A, Deo P, Ming X. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS): a pediatric case report with six year follow-up. *Mult Scler Relat Disord*. 2017;17(July):95-98. doi:10.1016/j.msard.2017.07.012.
9. Simon NG, Parratt JD, Barnett MH, et al. Expanding the clinical, radiological and neuropathological phenotype of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *J Neurol Neurosurg Psychiatry*. 2012;83(1):15-22. doi:10.1136/jnnp-2011-301054.
10. Tohge R, Nagao M, Yagishita A, Matsubara S. A case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) in East Asia. *Intern Med*. 2012;51(9):1115-1119. doi:10.2169/internalmedicine.51.7040.
11. Biotti D, Deschamps R, Shotar E, et al. CLIPPERS: chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *Pract Neurol*. 2011;11(6):349-351. doi:10.1136/practneurol-2011-000043.
12. Wijntjes J, Wouda EJ, Siegert CEH, Karas GB, Vlaar AMM. Need for prolonged immunosupressive therapy in CLIPPERS—a case report. *BMC Neurol*. 2013;13(1):1. doi:10.1186/1471-2377-13-49.
13. Kastrup O, Van De Nes J, Gasser T, Keyvani K. Three cases of CLIPPERS: a serial clinical, laboratory and MRI follow-up study. *J Neurol*. 2011;258(12):2140-2146. doi:10.1007/s00415-011-6071-4.
14. List J, Lesemann A, Wiener E, et al. A new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. *Brain*. 2011;134(8):8-10. doi:10.1093/brain/awr035.
15. Keegan BM, Giannini C, Pittock SJ. Reply: a new case of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) with initial normal magnetic resonance imaging. *Brain*. 2011;134(8):1-2. doi:10.1093/brain/awq391.
16. Gabilondo I, Saiz A, Graus F, Villoslada P. Response to immunotherapy in CLIPPERS syndrome. *J Neurol*. 2011;258(11):2090-2092. doi:10.1007/s00415-011-6068-z.
17. Lee MS. Contrast-enhanced magnetic resonance imaging and perfusion-weighted imaging for monitoring features in severe. *J Neuro-Ophthalmol*. 2011;31(4):392. doi:10.1097/WNO.0b013e318236599e.
18. Tobin WO. Growing the phenotype of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) in children. *Dev Med Child Neurol*. 2018:2018. doi:10.1111/dmcn.14043.
19. Hillesheim PB, Parker JR, Parker JC, Escott E, Berger JR. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids following influenza vaccination. *Brain*. 2012;136(6):681-685. doi:10.5858/arpa.2011-0428-CR.
20. Taieb G, Allou T, Labauge P. Therapeutic approaches in CLIPPERS. *Curr Treat Options Neurol*. 2017;19(5):17. doi:10.1007/s11940-017-0455-4.
21. Sempere AP, Mola S, Martin-Medina P, Bernabeu A, Khabbaz E, Lopez-Celada S. Response to immunotherapy in CLIPPERS: clinical, MRI, and MRS follow-up. *J Neuroimaging*. 2013;23(2):254-255. doi:10.1111/j.1552-6569.2011.00631.x.
22. Reddy SM, Lath R, Swain M, Ranjan A. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS): a case report and review of literature. *Ann Indian Acad Neurol*. 2015;18(3):345-347. doi:10.4103/0972-2327.152085.