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Abdul Salam

Shifa International Hospital, islamabad

Farah Sana

Shifa International Hospital, islamabad

Rashed Nazir

Shifa International Hospital, Islamabad, pakistan

M. Azhar Saeed

Shifa International Hospital

Yasir Iqbal

Shifa International Hospital

See next page for additional authors

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Authors

Abdul Salam, Farah Sana, Rashed Nazir, M. Azhar Saeed, Yasir Iqbal, and Arsalan Ahmad

CLIPPERS (CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIVASCULAR ENHANCEMENT RESPONSIVE TO STEROIDS)–CASE REPORT WITH NEUROIMAGING

Abdul Salam¹, Farah Sana², Rashed Nazir², M. Azhar Saeed¹, Yasir Iqbal³ and Arsalan Ahmad¹

¹ Division of Neurology, Shifa International Hospital, Shifa Tameer-e-Millat University, H-8/4, Islamabad.

² Department of Radiology, Shifa International Hospital, Shifa Tameer-e-Millat University, H-8/4, Islamabad.

³ Department of Pediatrics/Pediatric Hematology/Oncology, Shifa International Hospital, Shifa Tameer-e-Millat University, H-8/4, Islamabad.

Correspondence to: Prof Arsalan Ahmad MBBS, MD (Neurology), Professor of Neurology & Consultant Neurologist, Shifa College of Medicine & Shifa International Hospital, Shifa Tameer-e-Millat University, H-8/4, Islamabad. Email: arsalanahmad65@gmail.com,

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ABSTRACT

Background: CLIPPERS syndrome (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) is an inflammatory disease process primarily involving the pons and adjacent structures. Clinically, the patient may present with cerebellar signs such as dysarthria, gait ataxia and with cranial nerve palsies. It shows good response to steroids / immunosuppressive therapy. Pathologically, there is infiltration of T lymphocytes into the perivascular spaces of brainstem. The disease follows a relapsing and a remitting course and the earlier the treatment is started with high dose steroids and the more prolonged it is, the better the clinical outcome will be.

INTRODUCTION

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described chronic inflammatory central nervous system disorder responsive to immunosuppressive therapy⁽¹⁻³⁾. The disorder was first described in 2010 by Pittock et al and characterized as a T-lymphocyte predominant pontine encephalomyelitis that is responsive to immunosuppression with steroids⁽⁴⁾. In the authors' case series of 8 patients, neuroimaging showed punctuate pattern of patchy gadolinium enhancement 'peppering' the pons, brainstem, cerebellum and spinal cord. All patients showed clinical and radiological improvement when started on corticosteroids but the condition often worsened after corticosteroid tapering and required additional immunosuppressive agents for effective treatment. We report here a rare case of CLIPPERS in a 16 years old boy who was initially treated for meningoencephalitis with no improvement. He was considered to have CLIPPERS as he had characteristic MRI findings consistent with this diagnosis and he had a very good initial response to immunosuppressive therapy.

CASE PRESENTATION

A 16 years old boy presented in Neurology outpatient clinic with complaints of fever, vomiting and headache for 1 month. Fever was high grade at the start of his illness but subsequently it changed to low grade in the range of 99-101 OF. However fever was persistent since the start of his illness. Vomiting was persistent initially but later on it

reduced in severity but nausea was persistent since the start of illness. Headache was continuous and it involved the both sides of head, moderate to severe in intensity and pressing in nature. He had generalized tonic clonic seizure at the start of illness which adequately responded to anti-epileptic drugs. There was associated difficulty in speech and walking as well. Past medical history was significant for headache for last 1 year. Headache was on and off, most commonly in bitemporal regions, sometimes occipital. It was mild to moderate in intensity, usually 2-6 hours in duration. Headache was not associated with nausea, vomiting, photophobia or phonophobia and used to get relieved by simple pain killers. There was no past history of seizures. There was no history of alcohol abuse / smoking, any history of international travelling, or family history of neurological disease, hypertension or diabetes mellitus. Patient was single, studying in 10th grade. He was admitted in two tertiary care hospitals before presenting to us. During his previous admissions, he received ceftriaxone 2 g IV BD and acyclovir 10mg/kg IV TDS, each for 14 days. On examination, he was a young male of average height and thin built, sitting in the wheel-chair with obvious distress on his face. His pulse was 82 beats/ minute; blood pressure was 100/60 mm of Hg. His temperature was 37°C and respiratory rate was 18 breaths/ minute. He was awake, oriented in time, place and person and was responding to commands appropriately. His speech was dysarthric. His neurological examination revealed power of 5/5 in both upper limbs, 4/5 in both lower limbs proximally and 3/5 distally. Deep tendon reflexes were symmetrical and were 2+ with bilateral down going plantars. Sensory examination

was normal. Finger nose and heel knee shin tests were impaired on both sides. There was horizontal nystagmus on both sides. He was unable to walk due to severe ataxia. There was no neck rigidity and Kernig sign was absent. The respiratory system, cardiovascular system, and abdomen were all normal. Laboratory investigations showed a raised WBC count of 13000/ mm³ with a platelets count of 116000. ESR was 11mm/1st hr. LFTs were normal. Serum sodium was 140 mEq/L, serum potassium was 3.6 mEq/L, serum creatinine was 0.6 mg/ dl, serum calcium was 10.03 mg/dl, and serum albumin was 4.62 mg/dl. His blood sugar was 101 mg/dl. ANA and HIV antibodies were negative. His serum angiotensin converting enzyme (ACE) level was slightly raised (68U/l). His CSF analysis demonstrated 25 leukocytes/ μ l (90% lymphocytes and 10% polymorphs), glucose was normal (69 mg/dl) and protein was 59 mg/dl. CSF cytology was negative for malignancy. An initial CT (Fig 1) showed subtle non specific hypodensity in bilateral cerebellar peduncle. The MRI revealed extensive

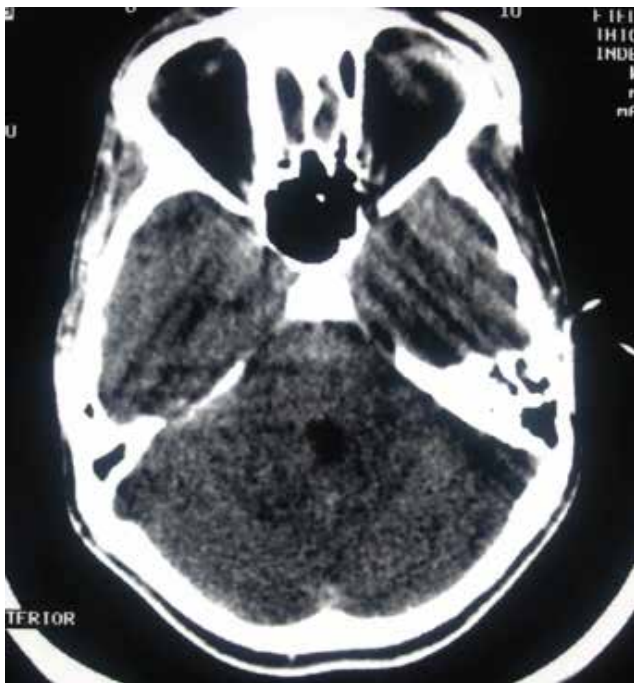


FIGURE 1: Axial unenhanced CT head showing subtle hypodensity in bilateral cerebellar peduncle

T2 / FLAIR hyperintensity in the brainstem and cerebellar hemispheres with symmetric punctiform gadolinium enhancement “peppering” the pons and extending into the cerebellum (figure 2). These MRI features were unique and extensive search of literature suggested that the imaging findings were consistent with CLIPPERS. Therefore, a probable diagnosis of CLIPPERS was made. He was started on intravenous methylprednisone 1 gram daily for 5 days. After 5 days he was put on oral prednisone 1mg/ kg and oral azathioprine 50 mg/day which was slowly increased to a dose of 100mg/day. Follow up visit after 2 weeks showed a

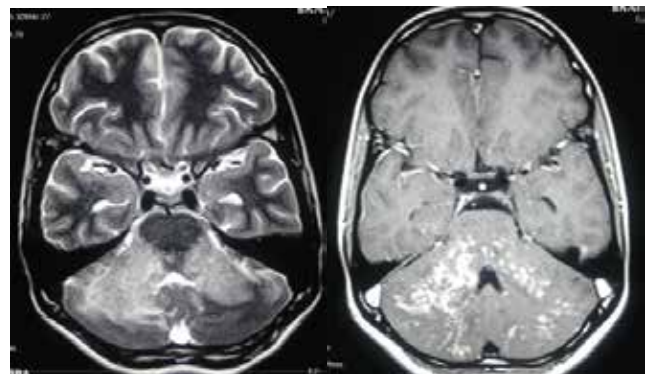


FIGURE 2: Pre-treatment MRI A) T2W axial demonstrates the characteristic hyperintense signal within cerebellar peduncles extending into pons. Fig 2 B) axial post contrast T1W image shows enhancing punctate lesions peppering the cerebellum and pons.

favourable initial response. There was no fever, headache, nausea or vomiting. However, he still had bilateral mild cerebellar dysfunction. After 2 weeks oral prednisone was slowly tapered off to 20 mg daily and during that period patient had 3 episodes of generalized tonic clonic seizures. He was again given intravenous methylprednisolone 1 gram daily for 3 days followed by oral prednisone 1mg/ kg. Oral azathioprine was slowly tapered off and he was put on oral methotrexate 5mg/week with a plan to slowly increase the dose of this medication if it worked for this patient. A follow up post contrast MRI was done after 3 months which revealed remarkable improvement with resolution of punctiform gadolinium enhancement and edema in brainstem and cerebellar hemispheres (figure 3).

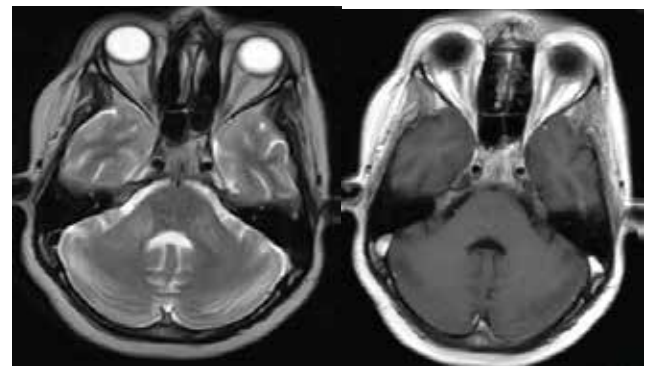


FIGURE 3: Post treatment MR A) T2W axial demonstrates significant interval improvement of edema signal Fig. 3 B) axial post contrast T1 image shows marked resolution of enhancing punctate lesions

As his prednisolone was tapered to 10mg on alternate days, his ataxia worsened, so he was advised Methylprednisolone 1gm I/V on two consecutive days every month. At last follow-up two weeks back he was fit free and had no ataxia and was independent in activities of daily living. His present medications are Tab Levetracetam 500mg PO q 12 hourly, Tab Prednisolone 10mg PO on alternate days, Tab Metho-

trexate 7.5 mg PO weekly, Methyl Prednisolone 1gm I/V on two consecutive days every month as well as calcium supplements

DISCUSSION

In 2010, Pittock et al. reported 8 patients with a clinically, radiologically and pathologically distinct pontine-predominant encephalomyelitis and named it “chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids” (CLIPPERS) (1). It was suggested that CLIPPERS is a definable, treatable inflammatory CNS, brainstem-predominant syndrome. Clinical and radiological findings point to a pontine-centric disorder with variable involvement of adjacent structures. Our patient had fever, headache, seizures, persistent vomiting, dysarthria and ataxia on presentation and initially thought to have meningoencephalitis. He, however, did not respond to treatment for meningoencephalitis and his symptoms were persistent. When we considered the diagnosis of CLIPPERS in this case based on the clinical and radiological features, we put patient on high dose intravenous methylprednisolone followed by oral prednisone and azathioprine. The response was excellent to immunosuppressive therapies initially but when we tried to taper off corticosteroids, patient had a relapse. Giving him monthly pulses of Methyl Prednisolone has been successful over the past 6 months. This finding was also seen in patients described by Pattick et al and therefore prolonged immunosuppressive therapy is necessary for the majority of cases. Other disorders likely to present with these findings were carefully excluded. CSF cytology and hematologic investigations showed no evidence of lymphoma. Vasculitis was not found on magnetic resonance angiography. There was no evidence of demyelination on MRI. The clinical course, negative microbiology workup and improvement with immunosuppressant therapy pointed out that it was not an infectious process. Bickerstaff brainstem encephalitis is also a brainstem-pre-

dominant inflammatory disease. We excluded this diagnosis on the basis of radiological features and absence of peripheral nerve involvement. MRI abnormalities in Bickerstaff brainstem encephalitis include homogenous, non-gadolinium enhancing lesion as against the pepper-like gadolinium enhancement seen in CLIPPERS. The pathogenesis of CLIPPERS is unknown. The presence of perivascular and parenchymal inflammatory cell infiltrate in affected CNS tissue and a clinical response to immunosuppressive therapies suggest that CLIPPERS has an autoimmune or other inflammatory mediated pathogenesis. Pattick et al suggested that biopsy should be considered when an alternative diagnoses is likely and expertise is available for performing brain biopsy. However, if alternative diagnoses are excluded and the clinical and radiological features support the diagnosis of CLIPPERS, brain biopsy is not necessary. We did not perform brain biopsy in our patient because we had excluded other diagnoses and clinical and radiological features were very suggestive of CLIPPERS.

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Author's Contribution:

Abdul Salam: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Farah Sana: Study concept and design, data collection, data analysis, manuscript writing, manuscript review

Rashed Nazer: Data collection, data analysis, manuscript writing, manuscript review

M Azhar Saeed: Study concept and design, data analysis, manuscript writing, manuscript review

Yasir Iqbal: Data collection, data analysis, manuscript writing, manuscript review

Arsalan Ahmed: Study concept and design, Data collection, data analysis, manuscript writing, manuscript review