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Clippers - A Rare Treatable Neuro Inflammatory Disorder of Brainstem: A Case Report and Review

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Abstract: ***Aim: To bring attention to uncommon such treatable neuroinflammatory condition. Introduction: CLIPPERS (Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids) is a rare immune mediated inflammatory central nervous system (CNS) disorder, prominently involving the brainstem and in particular the pons. It is characterized by Perivascular and T cell-predominant inflammatory cell infiltration in affected CNS lesions and responsive to steroids. Case Report: We are reporting case of 18 year old female who presented with two months history of gradually progressive disequilibrium, diplopia, dysarthria, nystagmus, right lower motor neuron palsy with decrease taste sensation. Patient was investigated and treated accordingly and clinical improvement was seen 5 days after the initiation of the therapy. Conclusion: CLIPPERS is a newly described pontine-centric inflammatory disorder with distinct clinical and radiological features which is completely curable with steroids. All physicians should be aware of such treatable neuro inflammatory condition. Clinical Significance: This highlights the fact that as CLIPPERS is treatable, in whom the cause of their clinical features could not be recognised may help in improving the outcome considerably in these cases.***

Keywords: Chronic Lymphocytic Inflammation, Steroids, CLIPPERS

1. Background

Chronic lymphocytic inflammation with Pontine Perivascular Enhancement responsive to steroids (CLIPPERS) represents a rare central nervous system (CNS) inflammatory disorder involving predominantly the pons.

The disorder was first described in 2010 by Pittock and colleagues as a distinct form of brainstem encephalitis centered on the pons, characterized by a predominant T cell pathology, and responsive to Immunosuppressant with Glucocorticosteroid (GCS) [(1)]. All patients had clinical symptoms related to brainstem involvement, particularly gait ataxia and diplopia. Other symptoms included dysarthria, altered sensation and paraesthesias of the face, dizziness, nystagmus, spastic paraparesis, sensory loss and pseudobulbar affect.

More striking was a characteristic pattern of magnetic resonance imaging (MRI) changes, consisting of 'punctate and curvilinear' perivascular gadolinium enhancement 'peppering' the pons as well as additional parts of the rhombencephalon, such as the brachium pontis, the medulla, the midbrain and/or the cerebellum.

Pittock et al. [(1)] and subsequently also other study groups carried out extensive laboratory, CSF, imaging and pathological surveys to carefully exclude an abundance of alternative causes for the condition. Evidence of specific inflammatory, demyelinating, infectious, neoplastic, paraneoplastic or vasculitic disorders could not be noted. Importantly, four patients underwent brain biopsy, which demonstrated predominantly T cell infiltration in the hindbrain white matter, largely but not wholly perivascular in distribution, accompanied by a moderate number of histiocytes and activated microglia. All patients had a favourable initial clinical response to high dose GCS administration, reflected by clinical and concomitant radiological improvement.

However, the patients routinely worsened following GCS taper and required chronic GCS or other immunosuppressive treatment as maintenance therapy. In consideration of the T cell predominant, perivascular inflammatory pathology in affected CNS tissue, the clinicoradiologial response to immunosuppressive therapies, and no explicit evidence for other underlying disease etiologies, CLIPPERS has been proposed to be an immune mediated, inflammatory process of unknown etiology. We report a patient with features consistent with this syndrome.

2. Case Description

An 18-year-old right handed female, student without any comorbidities was admitted to Female Medicine Ward in Dhiraj Hospital with chief complaints of gradually progressive disequilibrium, tinnitus and hyperacusis since last two months. She had also complains of diplopia, right side facial numbness and decrease taste sensation were added to her symptoms from 2 weeks prior to admission.

She had no history of seizures, blurring or loss of vision, deviation of angle of mouth, slurring of speech, fever, trauma or any preceding history of diarrhea, nausea or vomiting. There was no history of similar complaints, hypertension, diabetes, ischemic heart disease, stroke, tuberculosis or blood transfusion in the past. Family history was not remarkable. Personal history, patient is vegetarian, with normal appetite, adequate sleep, and no bowel and bladder incontinence, without any addiction.

On examination at presentation, she was afebrile, pulse rate was 80 beats/ min, regular, blood pressure was 118/70 mmHg and respiratory rate was 18/min abdomino thoracic type with a normal BMI. There was no sign of pallor, icterus, cyanosis, clubbing, lymphadenopathy or edema. No abnormality was detected in respiratory, cardiovascular and per abdominal system examination either. On central nervous system examination, patient's higher mental functions, speech and cranial nerve examination was normal. Nutrition was normal.

On initial neurological examination, she showed bilateral six nerve palsy, right peripheral facial palsy and decrease in

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light touch and pin prick sensation in the right side of his face (in V3 territory). In cerebellar examination she had bilateral limb and gait ataxia, more on right side. Other sensory and motor examinations had no significant finding.

Lab investigations were in normal limits (Table 1). No evidence of papilloedema on fundus examination. Cerebrospinal fluid (CSF) examination demonstrated a raised protein level (64mg/dl, normal <25 mg/dl) with normal glucose and cell count. A cranial MRI showed focal T2 and FLAIR hyperintensity involving Pons which Extends into right middle cerebellar peduncle. Mildly hypointense on T1 and shows patchy moderate post contrast enhancement on T1W1 post contrast images (Image 1 and 2).

Based on the assumption of an immune-mediated subacute encephalomyelitis, methylprednisolone intravenously was administered 1gr/day over 5 days, followed by oral steroid administration (prednisolone, 60 mg/day) and azathioprine 50 mg/day. An almost immediate improvement was seen in the patient's clinical condition. Patient was alert and able to follow commands within several days. She was discharged on request on oral steroids with other supportive medications with advice to follow up.

3. Discussion

CLIPPERS manifests characteristically in a subacute manner and presents usually with a varying symptomatology related to brainstem, cranial nerve and/or cerebellar involvement, frequently including gait ataxia, dysarthria, diplopia and/or altered facial sensation. Clinical manifestations may be heterogeneous, multifaceted and variable in individual cases, but comprise essentially the following.

Commonly prominent symptoms related to multilocular brainstem including cranial nerve and cerebellar involvement, which may present in various combinations or rarely in isolation (e.g. ataxia, dysarthria, oculomotor abnormalities, tingling of the face, vertigo) [1, 3, 5-9, 9-15] ; And Possible additional features such as:

Symptoms referable to long tract affections and/or a spinal cord syndrome (e.g. pyramidal tract signs, spasticity, para/tetraparesis, altered limb superficial and deep sensation, sphincteric dysfunction) [1, 3, 4, 7, 12, 14, 15] ;
Pseudobulbar affect (pathological crying and laughter) [1, 3, 9] ;

Cognitive dysfunctions (e.g. mnestic deficits, dysexecutive syndrome) [3, 6, 9] ;

Presumably also Headache [3, 16] and abnormal fatigue [1, 3, 5, 9, 16].

Meningism, alterations of quantitative consciousness, significant systemic symptoms (such as fever, night sweating, weight loss, lymphadenopathy) and symptoms related to connective tissue diseases, rheumatic disorders or Behcet's disease (such as arthritis, uveitis, sicca syndrome, oral and/or genital ulcera, pathergia) are generally not a feature of CLIPPERS patients.

There are obviously considerable differences regarding the age at onset of CLIPPERS, ranging from 9 to 46 years. In larger series, the mean age at onset was 52·4 years (range 16–46 years) [1], 28·4 years (range 12–65 years) [3] and 46·5 years (range 9–64 years) [2], respectively. The disorder affects both genders. A minor male preponderance may be assumed considering the hitherto reported cases. Initial symptoms usually evolve subacutely over several weeks. The clinical course without specific treatment seems to be relapsing–remitting in nature [2].

Clinical features of CLIPPERS.

- Symptoms/signs referable to brainstem, cranial nerve and/ or cerebellar dysfunctions
- Ataxia (gait ataxia, stance ataxia, truncal ataxia, limb ataxia)
- Dysarthria
- Dysphagia
- Dysgeusia
- Diplopia/oculomotor abnormalities (oculomotor palsies, gaze palsy, internuclear ophthalmoplegia, one and a half syndrome, disturbances of saccadic eye and slow eye pursuit)
- Nystagmus (spontaneous, gaze evoked, upbeat, downbeat, rotational nystagmus)
- Altered sensation or tingling of the face (facial tingling, par/ dysaesthesias, hyperesthesia), altered sensation of the scalp, palate or tongue
- Facial nerve palsy
- Vertigo, hyperacusis, hearing impairment, tinnitus
- Hoarse voice
- Tongue weakness
- Hiccup, Nausea
- Symptoms/signs referable to long tract affections and/or spinal cord syndrome Paraparesis, tetraparesis, hemiparesis, paresis of a single extremity
- Spasticity, long tract motor signs (extensor plantar response, hyperreflexia)
- Altered sensation/sensory loss of extremities (bilateral, unilateral; hemihypaesthesia, tetrahypaesthesia, hypoesthesia in single limbs)
- Decreased vibration sense
- Neurogenic bladder (urine retention/incontinence)
- Cognitive dysfunction

Management

Diagnosis of CLIPPERS is based on clinical, radiological, laboratory and CSF investigations and, if necessary, brain biopsy. Extensive investigations are mandatory to exclude alternative conditions that may mimic CLIPPERS syndrome. To date, validated diagnostic criteria for CLIPPERS are not available.

Due to the varied clinical presentation and the potential for diagnostic confusion, Simon *et al.* [3] has highlighted core features of CLIPPERS including clinical, radiological, GCS response and histopathological criteria. Evidence of an inflammatory CNS disorder matching the core features I–III and exclusion of alternative causes by extensive noninvasive diagnostic procedures may allow a highly probable diagnosis of CLIPPERS. In this constellation, avoidance of brain biopsy – which would enable evaluation of the

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histopathological criteria (IV) – may be justified. Such a noninvasive approach in 'typical cases' was already suggested by Pittock *et al.* [(1),] who treated 50% of patients without biopsy.

In some cases, however, which clinically and radiologically seemed to be compatible with CLIPPERS, other underlying conditions were detected only by biopsy [e.g. primary CNS lymphoma (PCNSL) [(21)], lymphomatoid granulomatosis that evolved into fatal B cell lymphoma of the CNS [(22)] ; lowgrade glioma [(13)], potentially primary angiitis of CNS (PACNS) [(23)].

Performance of a biopsy, usually a brainstem or cerebellar lesion biopsy from areas that are specifically involved radiologically, should therefore be recommended in cases which exhibit one or more of the following attributes:

- Alternative etiologies remain a distinct possibility despite rigorous investigations,
- Uncommon, atypical clinical or MRI findings are noticed (e.g. signs of systemic disease; MRI disclosing dominant brainstem mass effects or necroses)
- Resistance to GCS treatment is evident. In these cases, brain biopsy may finally add the definitive support for a similar pattern of CNS perivascular lymphocytic inflammation as in the originally described CLIPPERS patients and exclude other diagnoses.

Core features of CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) (adapted from Simon et al. [(3)]).

a) Clinical

- Subacute progressive ataxia and diplopia
- A range of other clinical features referable to brainstem pathology plus cognitive and spinal Features occur in some patients

b) Radiological

- Numerous punctate or nodular enhancing lesions bilaterally within at least two of the three following anatomical locations: pons, brachium pontis, cerebellum
- Individual radiological lesions are small but may coalesce to form larger lesions (mass effect may suggest an alternative diagnosis)
- Lesions may occur in the spinal cord, basal ganglia or cerebral white matter but should be decreasing density with increasing distance from the pons/hindbrain
- Absence of the following radiological features:
  - Restricted diffusion on diffusion weighted imaging
  - Marked hyperintensity on T2weighted images
  - Abnormal cerebral angiography

c) Glucocorticosteroid responsiveness

Prompt and significant clinical and radiological response to glucorticosteroids

d) Histopathological

- White matter perivascular lymphohistiocytic infiltrate with or without parenchymal extension
- Infiltrate contains predominantly CD3 and CD4 lymphocytes
- Absence of the following histopathological characteristics:
  - Monoclonal or atypical lymphocyte population
  - Necrotizing granulomas or giant cells
  - Histological features of vasculitis

(MS: multiple sclerosis; ADEM: acute disseminated encephalomyelitis; NMO: neuromyelitis optica; CNS: central nervous system.)

'Red flags' - Analysis of the above mentioned and other cases yielded some important 'red flags' that should alert physicians to an incorrect diagnosis and raise concern regarding illness other than CLIPPERS:

- No response to treatment with GCS at the beginning or during follow-up. GCS therapy failure seems to be a very strong indicator for an alternative diagnosis and raises the possibility of a tumor or neuronal degeneration[(13, 21, 22)]
- Unusual clinical findings such as fever, marked B symptoms, extra cerebral organ manifestations (such as arthritis, uveitis, sicca syndrome, lymphadenopathy, etc.) and Meningism should lead to increased alertness. Conversely, some findings such as dysarthria and ataxia are so common in CLIPPERS that their absence should be considered a hint that the disorder might be something else.
- MRI findings: although they may be subtle, abnormalities of brainstem are so common in CLIPPERS that their absence is worth noting. Pontine lesions with necrosis may point to a PCNSL [21] and marked mass effects to CNS tumors in general.
- CSF findings: marked pleocytosis (> 60/µl) or malignant cells should prompt reevaluation of the diagnosis

4. Treatment

So far, relatively few patients with CLIPPERS have been reported and it is difficult to recommend general therapeutic proceedings. CLIPPERS, as the term already implies, represents a typically steroid responsive disorder: both clinical and radiological responses can be noted following GCS therapy. With the use of GCS, patients usually show early and marked clinical improvement within days, although in many cases the restitution may remain incomplete. Simultaneously, a reduction or even a clear disappearance of enhancing lesions can be noted as the patients responds to immunosuppressive therapy [(1, 2, 3)].

Despite relatively prompt improvement of the imaging correlates of CLIPPERS, patients may develop brainstem, cerebellar, spinal cord and even cortical atrophy in follow-up MRI studies [(2, 3)]. The initial treatment of choice seems to be a relatively short course of high dose intravenous methylprednisolone (e.g. methylprednisolone 1 g over 5 days), followed by oral GCS. This regimen should also be applied and started as early as possible in case of relapses [(2, 3)].Attempts to withdraw or taper GCS below a particular lower dose limit usually provoke the recurrence of inflammation, accompanied by a relapse of clinical symptoms as well as MRI activity signs. The high risk of relapse during reduction of GCS [(1, 6)] and the chronicity of the disorder account for the reason to establish a maintenance immunosuppressive therapy, usually consisting of an oral GCS combined with a GCS sparing immunosuppressant. This long term therapy with

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immunosuppressive agents seems to be necessary to maintain remission [1, 2, 6, 11, 12]. The following therapeutic substances were used in long term therapy.

Chronic Glucocorticosteroid therapy- Chronic GCS therapy seems to be necessary, as attempts to taper oral GCS below a daily dose of 6–12 mg (prednisone equivalent) [2, 8, 11] leads almost inevitably to neurological relapse. As chronic GCS therapy is limited by GCS side effects, additional GCS sparing agents were commonly used to reduce the daily glucocorticosteroid dose in long-term therapy. It seems noteworthy, however, that some immunosuppressive agents, given alone without sustained GCS therapy, are obviously not capable of maintaining remission and therefore cannot replace GCS completely.

GCS sparing immunosuppressants -Various immunosuppressive agents, given as monotherapy alone or combined with sustained oral GCS, have been used to maintain clinical improvements and prevent further relapses. So far, an independent benefit of GCS sparing therapies could not be substantiated reliably. After complete GCS withdrawal, only methotrexate [1, 9, 16] and potentially rituximab [2] were described to be effective in a few patients.

The following immunmodulatory or immunosuppressive agents have been used for long-term therapy in hitherto published cases; either as monotherapy or as add on therapy. Although at least partial benefits were reported, their GCS independent efficacy could not been proved so far:

- Azathioprine (as add on therapy [8, 11, 14, 15, 35]; as monotherapy in one patient not controlling recurrence[1])
- Methotrexate, weekly oral administration (as add on therapy [1, 5 ,6, 17-15]; as monotherapy [1, 6, 16])
- Cyclophosphamide, intravenous pulses (as add on therapy [2, 6, 9, 25] and as monotherapy [3]: mainly reported to improve the clinical syndrome although presumably not protecting against subsequent relapse)
- Rituximab (antiCD12 monoclonal antibody treatment) (as add on therapy [10] or monotherapy [2] possibly beneficial) [26-28]
- Application in individual cases with undetermined efficacy: mycophenolate mofetil (as add on therapy [3, 15]) mitoxantrone (as add on therapy [1]).

There is some evidence that intravenous immunoglobulin (IVIG) therapy [11] and oral hydroxychloroquine [1] are not effective. Considering the histiocytic components found in CLIPPERS pathology, it was suggested that the use of tumor necrosis factor inhibiting drugs such as infliximab should be explored in the treatment of CLIPPERS [3]. To the best of our knowledge, this therapeutic approach has not been tried so far.

It appears that prompt recognition of the disease and early and vigorous pulse GCS treatment with an ensuing maintenance immune suppression result in the best long-term functional outcome. Prompt pulse GCS treatment of relapses may limit clinical worsening during relapses and permanent neurological sequelae [2, 3].

Regarding maintenance therapy, independent beneficial effects of specific immunosuppressive/modulating agents alone or as add on treatment need to be proved in further studies. Moreover, follow up studies are necessary to determine the duration of a prolonged GCS based maintenance therapy.

5. Conclusion

CLIPPERS is a newly described pontine centric inflammatory disorder with distinct clinical and radiological features. The cardinal feature of the condition is a punctate and/or curvilinear gadolinium Enhancement, ‘peppering’ the pons and adjacent hindbrain structures on MRI. Since 118, the unique MRI features of this condition have attracted the attention of many clinicians, neuroradiologist and pathologists, leading to an increasing number of case reports and small case series.

To date, these comprise more than 50 cases and are accounted to extend the clinical, neuro imaging and pathological phenotypes of the disorder. However, the pathogenesis of CLIPPERS is still unknown, and its nosological position is still to be established. A specific biomarker of the disorder is lacking.

Clinical Significance: CLIPPERS may, in fact, be a newly emerged, ‘truly novel’ disease, speculatively reflecting the immune response to a novel environmental factor. Notwithstanding, physicians should be aware of this condition and relevant differential diagnoses so that the benefits of early diagnosis and GCS based therapy are not lost. Further studies to determine the exact nosological position of the disorder, potential biomarkers, reliable diagnostic criteria’s as well as the optimal form and duration of treatment are necessary.

Table 1: Investigation

	20/7/2019	23/07/2019
Haemoglobin (gm %)	11.6	11.5
Total count (cells/cu.mm)	9200	7800
Differential count (cells/cu.mm) (N/L/M/E)	82/9/4/5	84/7/4/5
Platelet (lacs/cu.mm)	3.49	3.06
RBC (mil/ul)	4.27	4.35
PT INR (control -14)	Test -14- INR -1	
APTT (control -30)	Test -30	
S.urea (mg %)	30	26
S.creatinine (mg%)	0.7	0.6
Total Bilirubin (mg%)	0.9(Direct-0.4, Indirect 0.5)	
SGOT (IU/L)	39	
SGPT (IU/L)	27	
$S.NA^+$ (mmol/lit)	141	142
$S.K^+$ (mmol/lit)	4.5	4.3
$S.CL^-$ (mmol/lit)	103	101
Urine	Albumin – absent Sugar- absent Pus cell- 1-2 cell/ml Epithelial cell – 1-2cell/ml RBC- absent	
ECG	Sinus rhythm, normal axis, no ST – T changes	
HIV/HbSAG/HCV	Negative	
CSF	pH-7.0 sugar – 25mg/dl	

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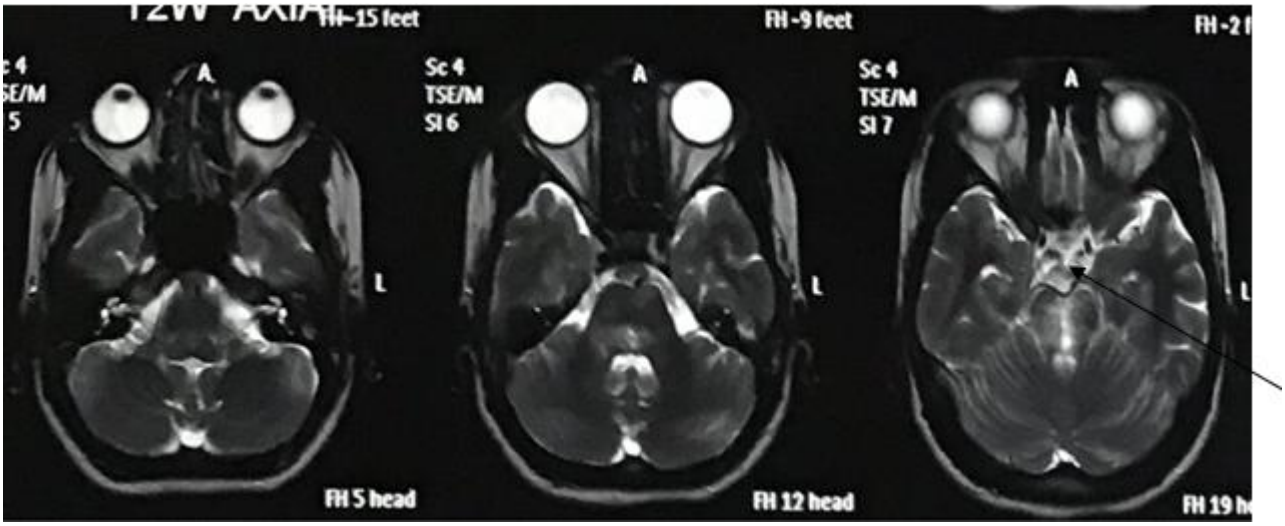
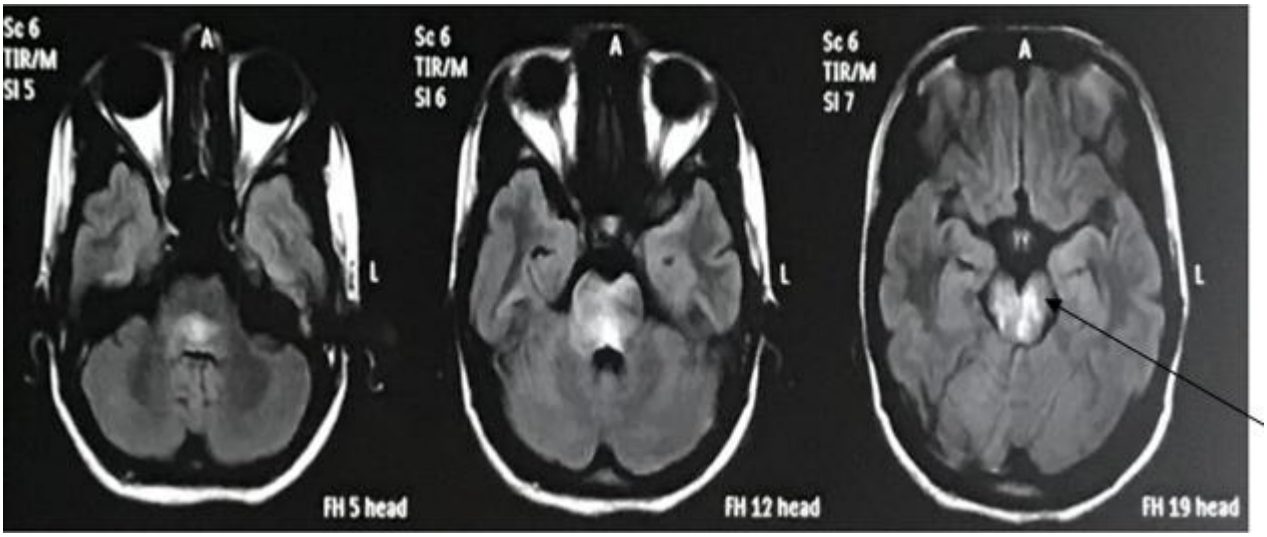
	protein- 64 mg/dl ADA- 09 LDH – 5 u/l
CSF (culture)	No organism detected
USG (abdomen/pelvis)	No abnormality detected
Chest X ray	Within normal limits
MRI brain	Focal T2 and FLAIR hyperintensity

	involving Pons which Extends into right middle cerebellar peduncle. Mildly hypointense on T1 and shows patchy moderate post contrast enhancement on T1W1 post contrast images.



T2W Axial Images of Cranial MRI



T1W and Flair Images of Cranial MRI

Figure 1: Cranial MRI

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