Case Report

CNS Histiocytosis- Rare Disease with An Unusual Manifestation

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Abstract

CNS histiocytosis is a rare and debilitating disease with multiple presentations. We here present a rare case of histiocytosis in a 4 year old child manifesting with diplopia as the sole neurological symptom. The patient had only saccadic abnormalities on examination and lesions in tectal pons and cerebellum. Initially considering the possibility of demyelinating disorder, steroids were given with partial resolution of signs but no improvement in signs or MRI imaging. Biopsy gave the diagnosis. The diagnosis of CNS histiocytosis should be considered even in patients with few symptoms and actively evaluated for.

Introduction

Histiocytosis encompasses a group of disorders characterized by uncontrolled clonal proliferation of histiocytes. Prevalence of histiocytosis is 1-2/ 2,00,000 with most cases presenting with skin, lungs and bone disease. CNS involvement is very rare but can be potentially devastating[1].

Histiocytosis commonly presents in the age group of 5 -15 years. Focal granulomatous lesions may present as lesions of craniofacial bone and skull base. Hypothalamic pituitary axis is the commonest intracranial site involved, diabetes insipidus being the most common initial symptom.[2,3]

The other clinical features include (i) bone pains (ii) headache (iii) ataxia (iv) psychomotor retardation. Radiological abnormalities reported are increased T2 weighted signal in basal ganglia, pons and dentate nucleus of cerebellum, thickening of the pituitary stalk, absence of the pituitary bright spot and hypothalamic lesions. Histopathologic studies demonstrated these lesions being dominated by Langerhan cells. We hereby report an unusual case in a younger child.

Case report

Four year old girl presented with an acute onset of diplopia since one week. On clinical examination, abnormalities of slow ocular saccades and diplopia which was present in both horizontal and vertical direction were seen. There were no evidence of any other cranial nerve

palsies. Rest of the neurological examination-cognition, motor and sensory, cerebellar systems assessment was normal. There were no meningeal signs.

MRI Brain revealed patchy enhancing ill-defined lesions in T2/ Flair sequences in tectal pons and medial cerebellum. (Fig 1a,b)

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Low Grade Glioma or demyelinating disorder were considered. MR Spectroscopy showed decreased NAA with increased choline peaks. Blood, CSF and Neurophysiological (VEP) work up was done which was normal except CSF hypo-glycorrhachia (CSF sugar-32). Whole body PET CT was normal.

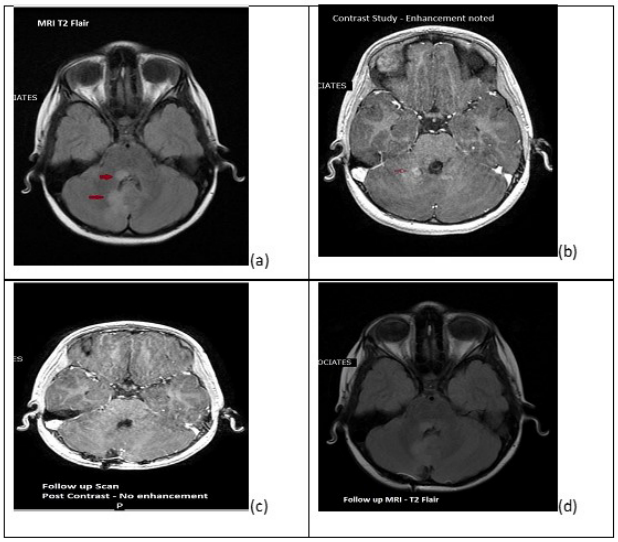

Fig 1 : MRI images: (a)T2 sequence showing right tectal pons and medial cerebellum hyperintensities, (b)post contrast images showing enhancement in the corresponding locations, (c) follow up post contrast image showing no enhancement, (d)T2 Flair sequence on follow up showing hyperintensities in the same locations as in the earlier image.

She received IV methylprednisolone 250 mg for a period of 3 days followed by tapering oral steroids for four weeks. This led to transient symptomatic improvement with persistent isolated diplopia not affecting her academic abilities.

Two months later, MRI brain was repeated, which showed no change in the lesion. (Fig 1c, 1d) The patient underwent a biopsy from the lesion, which showed sparse lymphohistiocytic infiltration in the leptomeninges. The lymphocytes in leptomeninges and cerebellar white matter were stained by LCA and CD3. Distinct demyelinated areas were not seen. The histiocytes showed scattered MIB-1 labelling. Deeper sections did not reveal any neoplastic glial cells. The biopsy was interpreted as most of the MIB-1 staining cells are histiocytes. BRAF mutation test which is specific for Erdheim Chester(Non Langerhans Histiocytosis) was unavailable.

Histopathology and immunohistochemistry findings, along with patient's age, fluctuating clinical course and MRI findings were all favouring a diagnosis of CNS Histiocytosis with an atypical presentation. Chemotherapy was considered but was deferred as parents did not give consent considering young age of the patient and possible side effects

During the last one year our patient remained clinically stable and is able to carry on her daily activities. There is no evidence of disease progression on repeat MRI. She did not receive any chemotherapeutic agent in this span of one year.

Discussion

Review of literature reveals cases of isolated neuro-histiocytosis affecting cerebellum being very rare and are always associated with lesions in other deep gray matter structures like basal ganglia, pituitary gland or calvarial deposits commonly in the orbitofrontal regions.

In cases of brainstem involvement, the pons and midbrain are likely to get involved apart from cerebellum, presenting radiologically as midbrain atrophy and hyperintensities in pons. Most of the cases in literature presented clinically with ataxia, dysarthria, dysmetria, behavioural disturbances along with other constitutional symptoms.

In our patient there was a paucity of clinical symptoms as well as MRI findings. Her symptoms could not be explained based on MRI findings alone. This suggests that the associated pathology is patchy and not interrupting the fibers grossly.

Review of histopathological studies done in Histiocytosis shows that the presence of classical CD1a+ cells is highly variable, it might dominate in some cases, whereas another series demonstrated an absence of CD1a+ cells and histiocytes, presence of inflammation with collection of CD8+ lymphocytes along with neuronal degeneration and extensive demyelination. These studies are consistent with findings in our case demonstrating absence of CD1a+ cells, but presence of leptomeningeal histiocytes and other features suggestive of histicytosis. Spectroscopy was consistent with neuronal loss and ruled out an infectious lesion[5].

In a study by Nicole Grois et al, where 12 children in the age group of 2-15 years, isolated brainstem involvement was not found in any patient. All cases had Hypothalamic/Pituitary lesions, Basal Ganglia, Cerebellar and pontine lesions and absence of the Pituitary bright spot. Ataxia, cognitive decline and bony pains were presenting symptoms in most of the children, unlike our patient.

In a study by Movement Disorder Society a single case of a 58 year old man who presented with isolated cerebellar involvement and ataxia is reported. A Bone scan was done in this case which showed non specific uptake of tracer in the left calvarial bone and was diagnosed as Erdheim Chester(non Langerhan Histiocyotsis). Our patient did not show any osteolytic bony lesions.

Demyelinating diseases, Neoplasms, CLIPPERS and isolated Neurosarcoid are possible differential diagnosis. Often biopsy is probably the gold in clinching the diagnosis.

Histiocytosis leads to production of cytokines which results in recruitment of proinflammatory cells from circulation to the brain. This can explain the response to steroids in such cases[6].

Gold standard for the diagnosis of CNS histiocytosis is CSF levels of Interferon Alpha, Interleukin 1,6, and S-100 levels[7]. These tests could not be carried out in our patient due to non availability..

Hematologists/ Pediatric Oncologists treat Histiocytosis with chemotherapeutic agents like Vincristine, Vinblastine, Methotrexate, Isotretinoin and newer agents BRAF inhibitor like dabrafenib.[8] Considering the age of the patient, side effects and risk of serious complications arising out of chemotherapy regimens is quite high. Whether aggressive treatment is warranted in cases of isolated neuro-histiocytosis, where the involvement is restricted to a particular region and non-disabling symptoms is a matter of further research.

Conclusions

This case is unique due to isolated involvement of brainstem, disproportionate clinical findings with fluctuating course thus causing a diagnostic dilemma. In such situations, young age of the patient, steroid responsive relapsing course and bilateral brainstem involvement on imaging, a possibility of CNS Histiocytosis should be considered along with other diagnosis. Histopathology and Immunohistochemistry confirm the diagnosis of histiocytosis.

Conflict of Interests: The authors declare that no conflict of interest in this study.

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References

1. Egeler RM, Favara BE Laman JD, Claassen E. Differential in situ cytokine profile of langerhans like cells and T cells in Langerhans cell Histiocytosis, abundant expression of cytokines relevant to disease and treatment. Blood 1999; 94:4195-201.

2. Grois N, Fahrner B, Arceci RJ Henter JI, McClain K, Lassmann H, et al. Central nervous system disease in Langerhans cell histiocytois. J Pediatr. 2010; 156: 873-881.

3. Dunger DB, Broadbent V, Yeoman E, Lightman, SL, Grant DB, Pritchard J et al. The frequency and natural history of diabetes insipidus in children with Langerhans cell Histiocytosis. N Eng J Med. 1989; 321: 1157-1162.

4. Willman CL, Busque L. Griffith BB McClain KL, Duncan MH, Gilliland DG. Langerhans cell histiocytosis(histiocytosis X)- a clonal proliferative disease. N Engl J Med. 1994: 331:154-160.

5. Grois N,Prayer D, Prosch H, Lassmann H CNS LCH Co-operative Group. Neuropathology of CNS disease in Langerhans cell histiocytosis. Brain 2005; 128: 829-838

6. Yu RC, Chu C, Buluwela L Chu AC. Clonal proliferation of Langerhans Cells Histiocytosis. Lancet. 1994;343:767-768.

7. Rosso DA, Ripoli MF, Roy A, Diez RA, Zelazko ME, Braier JL Serum levels of IL-1 receptor antagonist and TNF-alpha are elevated in children with LCH. Journal of Pediatric Hematology/ Oncology. 2003;25: 480-483.

8. Yang Y, Wang D, Cui L, Ma HH, Zhang L, Lian HY, et al. Effectiveness and Safety of Dabrafenib in the Treatment of 20 Chinese Children with BRAFV600E-Mutated Langerhans Cell Histiocytosis. Cancer Res Treat. 2021;53:261-269.