International Journal of Contemporary Pediatrics
Nirmal SR et al. Int J Contemp Pediatr. 2019 May;6(3):1386-1390
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20192050

Case Report

Langerhans cell histiocytosis presenting as isolated central diabetes insipidus in a 2-year-old child: a rare manifestation of rare disease

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Received: 24 January 2019
Accepted: 08 March 2019

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ABSTRACT

Central diabetes insipidus, though uncommon in children, has varied causes, the commonest ones being genetic mutations, infiltrative disorders, infections. Isolated central diabetes insipidus is not one of the often encountered conditions in the pediatric practice. Here we report a case of 2 ½ years old female child who presented to us following history of polyuria for 2 months, who was confirmed to have central diabetes insipidus which was later evaluated to be secondary to Langerhans cell histiocytosis. Magnetic resonance imaging (MRI) and histopathological studies further helped in confirmation of the diagnosis. Langerhans cell histiocytosis is a rare, multifarious, and underdiagnosed hematologic disease in which isolated diabetes insipidus can be the sole presenting feature before other manifestations. Hence, this diagnosis could strongly be considered in the work up of central diabetes insipidus in children.

Keywords: Children, Central diabetes insipidus, Langerhans cell histiocytosis

INTRODUCTION

Central diabetes insipidus (CDI) presents commonly secondary to infections like meningitis, post trauma or any neurosurgical intervention and this wide differential diagnosis substantiates the need for proper workup of this condition.[1] Langerhans cell histiocytosis (LCH) is also an uncommon condition in children with a slight male preponderance.[1] It can affect almost any organ and present with varied clinical manifestations.[2] LCH may be associated with CDI during the course of the disease, however presenting as isolated Diabetes Insipidus (DI) as an inaugural manifestation is quite rare.[2] A focused work up along with magnetic resonance imaging (MRI) modality with classical findings justify the involvement of the hypothalamic-pituitary axis leading to the aforesaid presentation.[3] This supplemented with histopathological evidence will help to confirm the diagnosis. Hence, authors report this case with such an isolated presentation, which was evaluated and diagnosed at our tertiary care center.

CASE REPORT

A 2 ½ years old female, first order child to non-consanguineous parents was brought with polyuria, polydipsia and weight loss for 2 months. On examination she was moderately nourished, hydration was normal, heart rate-108/minute, respiratory rate-28/min, blood pressure-96/62 mm Hg. Systemic examination was normal. On investigation random blood sugar, urea, creatinine, serum electrolytes, arterial blood gas analysis were normal. On further investigation urine osmolality was 85 mosm/L and serum osmolality of 292 mosm/L. Since urine osmolality was much lower than serum

osmolality, DI was suspected and hence water deprivation test was done. Urine osmolality remarkably improved to 825 mosm/L after giving Vasopressin which confirmed the diagnosis of CDI (Table 1). MRI brain was done to investigate the cause of central diabetes insipidus, which showed homogenous enhancement of pituitary gland with loss of T1 hyperintensity of posterior pituitary with thickening of the infundibulum (4 mm) (Figure1).

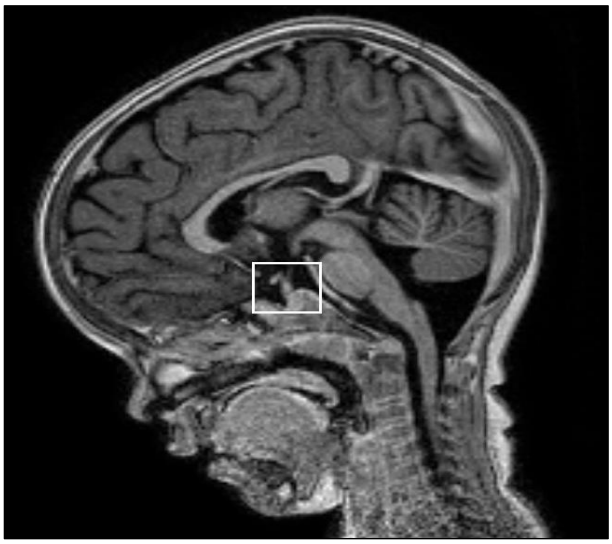

Figure 1: MRI brain showing thickening of pituitary stalk (white box).

T1 iso to hyperintense and T2 hyperintense soft tissue lesions in the greater wing of left sphenoid bone, posterolateral wall of left orbit and left temporal bone (Figure 2) with no abnormal enhancement of the underlying temporal bone was present.

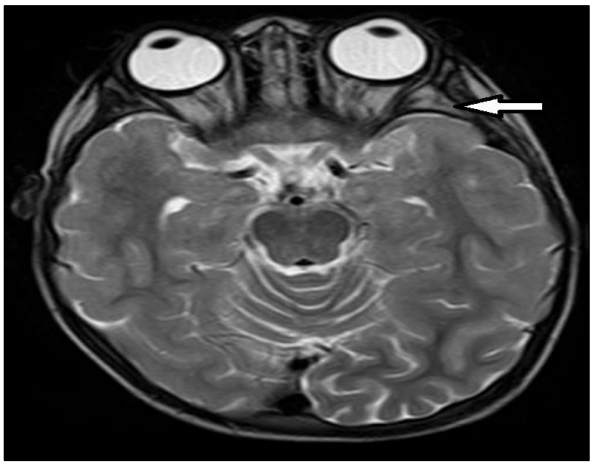

Figure 2: MRI brain with soft tissue lesion in the left temporal bone (white arrow).

These findings gave high suspicion towards LCH following which skeletal screening was done and showed a lytic- expansile soft tissue lesion (4.0 x 3.5 cm) of the right iliac bone (Figure 3).

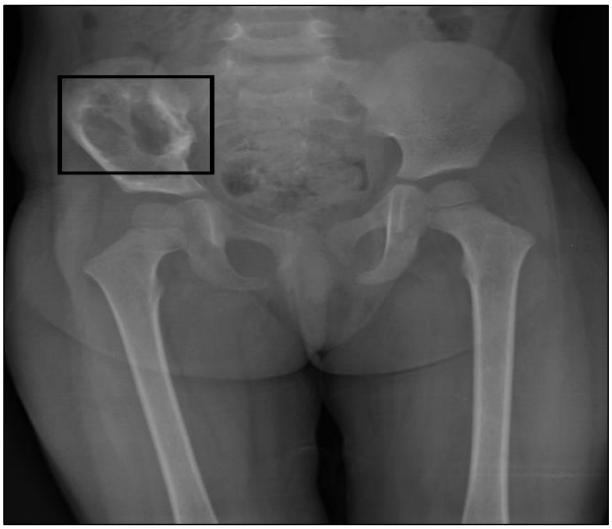

Figure 3: X-ray bilateral pelvis showing lytic lesion in the right iliac bone (black box).

Biopsy was taken from this site and sent for histopathological analysis (Figure 4, 5 and 6) which confirmed the diagnosis of LCH in this child. Hence child was planned for chemotherapy.

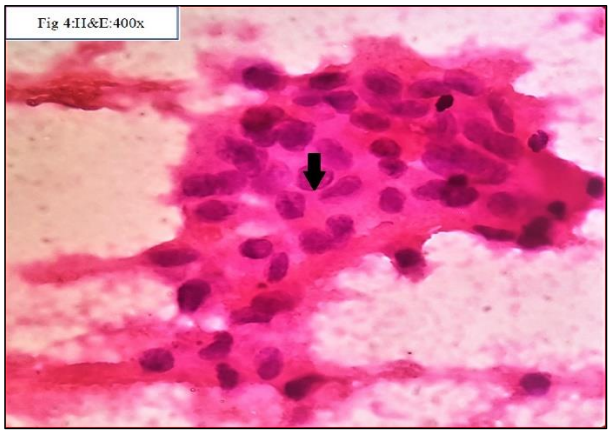

Figure 4: Clusters of histiocytes with nuclear grooving (arrow pointing) with indistinct cytoplasm.

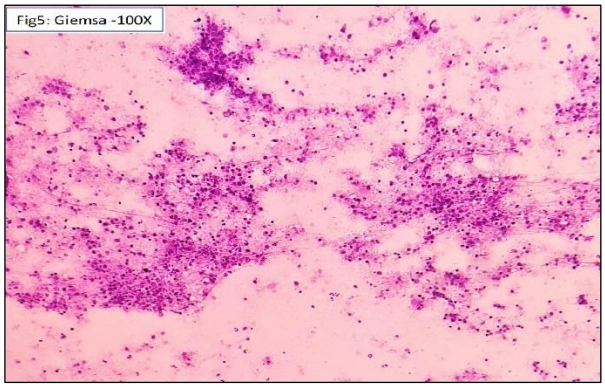

Figure 5: Cellular smear with necrotic background.

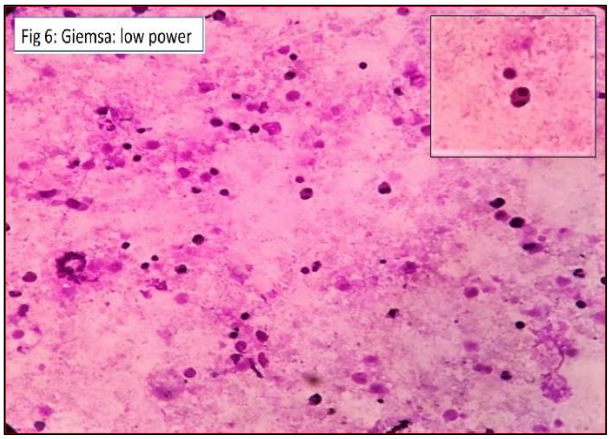

Figure 6: Inflammatory background showing numerous eosinophils.

DISCUSSION

Diabetes insipidus (DI) is a disorder where the kidneys fail to concentrate urine, causing polyuria (i.e. >2 l/m^2/24 hours) and subsequently polydipsia. It is subdivided into central and nephrogenic DI. Destruction or degeneration of magnocellular neurons in the paraventricular and supraoptic nuclei, which are responsible for producing vasopressin leads to CDI.[1]

Etiological diagnosis of CDI in children is straight forward when it occurs following events such as meningitis, neurosurgery, trauma, or following the diagnosis of LCH in contrast to patients with apparently isolated CDI. LCH, dysgerminoma, craniopharyngioma, tuberculosis and sarcoidosis are differential diagnoses to be considered in this setting.[2,3]

LCH itself, is a rare entity with a variable presentation with an incidence of approximately five cases per million children and about one or two cases per million adults.[1]The variable clinical presentation of LCH depends on which organ is infiltrated, with a disease spectrum ranging from isolated skin or skeletal lesions to multisystem involvement and sometimes life-threatening conditions such as acute lymphoblastic leukemia. The common clinical manifestations based on previous Indian study include bone (65%) and skin involvement (55%), followed by fever (43.5%) and lymphadenopathy (30.4%), ear discharge (20%), tachypnoea (18.8%), jaundice (15.9%) and finally proptosis (7%).[4]

Table 1: Water deprivation test.

Times	Body weight (kg)*	Urine volume (cc)*	Urine osmolality (mOsmol/kg)*	Serum sodium (mmol/L)*	Serum osmolality (mOsmol/kg H_20)*	Management
Baseline	9.30	930	85	141	292	-
5 hr	9.20	85	97	140	290	-
6 hr	9.20	65	102	142	293	-
7 hr	9.15	76	92	146	302	-
8 hr	9.10	68	120	147	303	-
9 hr	9.06	88	108	-	-	-
10 hr	8.96	104	114	-	-	-
11 hr	8.90	110	97	-	-	DDAVP* 0.05 cc SC*
12 hr	8.80	96	825	-	-	-

DDAVP; desmopressin, hr; hour, Kg; kilogram, mmol/L; millimoles per liter, mOsmol/kg; millimoles per kilogram; Sc; sub-cutaneous

The prevalence of CDI in patients with LCH ranges from 10-50% with an average of 11% during the natural course of the disease.[1,4] CDI may be an isolated and inaugural manifestation (4%), occur concomitantly with another location (7%), or occur after extra-pituitary involvement (14%).[4] Case reports on LCH with CDI as an initial manifestation or at the same time with other system involvements are limited. [5-8] Our case also falls into this group. CDI was confirmed by the water deprivation test following which MRI was done to find the aetiology.

Radiological manifestations of LCH include thickening of pituitary stalk (PS) more than 3 mm, with loss of physiological hyperintense signal in posterior pituitary on T1W images signifying the loss of ADH storage granules.[9]A lack of posterior pituitary hyperintensity, is considered a hallmark of hypothalamic-posterior pituitary disorders (though not specific) and may signify the early occurrence of occult local tumors.[10] This was also in accordance to our case which had an infundibular thickening of 4mm with homogenous enhancement and loss of T1 hyperintensity in posterior pituitary.T2W hyperintense soft tissue lesions were also found in the greater wing of left sphenoid, posterolateral wall of left orbit and squamous part of left temporal bone.

However, PS size at presentation is variable and can change over time. 30-50% of patients with a widened PS

usually have multiple hormone defects. Growth hormone deficiency is the most frequent additional deficit, seen in about 42% of cases with CDI and LCH.[10,11]

It is recommended that in LCH patients with pituitary stalk thickening, the search for extracranial lesions (dermatological and bone survey, chest X-ray, ear, nose and throat examination) could reduce the need for intracranial biopsy.[10] Our screening revealed a lytic-expansile soft tissue lesion in the right iliac bone of our case which served as our biopsy site.

The definitive diagnostic test for LCH is by histological examination.[9] Our biopsy report was also consistent with features in evidence of Langerhans cell histiocytosis, hence confirming our diagnosis. However, electron microscopy for Bierbeck granules was not done owing to non-availability though it is not a gold standard diagnostic test at present. Langerin, which is a cell-surface receptor that induces formation of Bierbeck granules is now considered instead.[12]

Depending on the extent of involvement at the time of diagnosis, LCH is classified into single system disease (SS-LCH) and multisystem disease (MS-LCH). Involvement of only one organ or system is seen in SS-LCH. In MS-LCH, two or more organs, or systems are involved with or without risk organs being involved.[13] Those presenting with CDI generally present as MS-LCH. In our case the skeletal system and central nervous system were found to be affected.

Therapy for multifocal skeletal LCH most commonly employed is steroids and vinblastine (VBL), which is a relatively well tolerated and non-toxic combination. Clinical response after the first 6 weeks of treatment is a good marker of further disease evolution. The risk of disease reactivations can be reduced by prolonged treatment for at least 1 year.[13] Second line chemotherapeutic agents include cladribine and cytarabine. Surgical removal of small tumours and radiation may also be employed.

Complications of CDI with LCH

Fifty-six percent of LCH patients with DI will develop anterior pituitary hormone deficiencies within 10 years of DI onset. These patients may present growth deficiency (up to 10% of LCH patients), precocious or delayed puberty, galactorrhea and symptoms of hypothyroidism. Hypothalamus infiltrations (rare), cause changes in behavior, eating, sleep, or thermoregulation disorders. The patient may have headache, vomiting, or blurred vision, or display convulsions and other focal symptoms if meninges or choroid plexus is involved. Craniofacial bone, ear, eye and/or oral lesions (CNS-risk lesions) have a higher occurrence in DI presenting cases.[7,12,14]

Neurodegenerative central nervous system Langerhans cell histiocytosis (ND-CNS-LCH) syndrome remains a progressive and devastating complication seen in 1-3% of LCH with initial subtle neurological deficits that can enhance and develop years after the first LCH symptoms.

DI is usually permanent and requires lifelong Vasopressin.[9] Neurodegenerative complications represent a complex situation and need to be managed by a multidisciplinary team.

Prognosis

The prognosis for LCH varies on the form of the disease (SS-LCH vs. MS-LCH), its location and response to chemotherapy. Unifocal LCH involving bone or an isolated skin lesion, have good prognosis. However, relapses are more with multifocal bone involvement. The likelihood of internal organ involvement increases in cases of extensive skin lesions even many years after the completion of the first-line treatment of the disease. Survivors may experience long-term permanent consequences that include endocrine disorders (DI and growth hormone deficiency), orthopedic problems, visual and hearing loss, loss of teeth, neurological defects (which affect the CNS in up to 30%of cases), and impaired functioning of liver and lungs.[12,13,15]

Hence once diagnosed, prompt follow up and systemic screening for all the above said complications and serial MRI scans are recommended.

CONCLUSION

CDI occurring as an isolated condition is not common in young children and it manifesting as one of the initial presentations of LCH is even rarer. Though LCH has a multi-faceted clinical profile with a male preponderance, there have been upcoming reports in female children as in our case study thus emphasising the importance of suspicion of this condition in both sexes with such presentations. As the treatment parameters, complications and sequelae of LCH presenting as CDI worsen with time, early and prompt suspicion and diagnosis would aid in reducing the morbidity and mortality associated with this condition.

ACKNOWLEDGEMENTS

Authors would like to thank Department of Pathology and Radio-Diagnosis for the images rendered.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Nirmal SR, Krishnakumar R, Nair GG, Chordia SL, Arunagirinathan A. Langerhans cell histiocytosis presenting as isolated central diabetes insipidus in a 2-year-old child: a rare manifestation of rare disease. Int J Contemp Pediatr 2019;6:1386-90.