CENTRAL DIABETES INSIPIDUS DUE TO LANGERHANS' CELL HISTIOCYTOSIS IN AN ADOLECENT NIGERIAN GIRL

Onyiriuka AN¹, Iduoriyekumwen NJ².

¹Endocrine and Metabolic Unit, Department of Child Health, University of Benin Teaching Hospital, PMB 1111, Benin City, Nigeria, ²Nephrology Unit, Department of Child Health, University of Benin Teaching Hospital, PMB 1111, Benin City, Nigeria.

ABSTRACT

Central diabetes insipidus (CDI) is rare and that due to Langerhans' cell histiocytosis (LCH) is even rarer. We report on an 11-year-and-4-month old post-menarcheal Nigerian girl who presented with pain in the left thigh for 8 weeks, extending to the left hip joint after 4 weeks, polyuria, polydipsia, nocturia for 3 weeks and fever for 2 weeks. She had a urine osmolality of 64mOsm/kg and a serum osmolality of 301mOsm/kg, representing urine-to-plasma osmolality ratio of 0.2. Following vasopressin administration, 3.5-fold elevation of urine osmolality level over the baseline was observed. The urine was hyposthenuric, with a urine specific gravity of 1.000 (the same as for distilled water). Pelvic and left thigh radiograph revealed left acetabular fracture with left femoral head protrusion and underlying left hemipelvis osteopenia. Histology result of a biopsy specimen of joint capsule showed evidence of chronic inflammation. A diagnosis of central diabetes insipidus, presumably due to Langerhans' cell histiocytosis (LCH) was made. She was treated with fluid and electrolyte replacement and vasopressin injections. Later she was discharged on desmopressin. Non-availability proper diagnostic tools such as brain imaging and immunohistochemistry staining were challenges that we had to face when managing this patient.

Running title: Central diabetes insipidus and Langerhans' cell histiocytosis.

Keywords: Central diabetes insipidus, polyuria, Langerhans' cell histiocytosis,

INTRODUCTION

Central diabetes insipidus (CDI) is a rare disorder of water metabolism due to deficiency of arginine vasopressin (AVP) (1, 2). The clinical manifestation of CDI is influenced by the age, aetiology and the associated other organ dysfunctions (3). Polyuria is characteristic and overt polyuria is seen when 80-90% of the posterior pituitary AVP secretion is lost (4, 5).

Data regarding CDI in the paediatric population are scarce, both in developed and in developing countries. The report of a 20-year-retrospective study in two large referral hospitals in the United Kingdom showed that 2 hospitals when combined, received an

average of 3 children with CDI per year (6). Over a period of 8 years, only one case of diabetes insipidus was seen at the University College Hospital, Ibadan, Nigeria (7). Two separate retrospective studies, which reviewed paediatric endocrine disorders seen over a period of 7 years in Port Harcourt and 10 years in Benin City did not reveal any case of diabetes insipidus, illustrating the rare nature of this clinical entity (8, 9). In Nigeria, only one case report of paediatric CDI exist in the literature (10).

In the paediatric population, acquired CDI is mostly associated with underlying systemic disorders and Langerhans' cell histiocytosis (LCH) is probably the commonest cause of CDI

in children (11). Although acute leukaemia is another cause, CDI in acute leukaemia is extremely rare (1). In two separate studies that reviewed children over a period of 17 years each for the causes of CDI, found no case of CDI due to leukaemia, reflecting the rarity of this association (1, 12).

LCH is a rare disease mostly seen in children with a wide variability in the clinical manifestations and the outcomes (13). The hallmark of LCH is the uncontrolled monoclonal proliferation of abnormal Langerhans cells, which leads to chronic inflammation and granuloma formation, resulting local infiltration and organ destruction (14, 15). The

aetiopathogenesis of this pathological process is poorly understood (16). However, with the discovery of the association of the mutually exclusive activating somatic BRAF V 600E and MAP2K1 genes mutations that occur in about 75% of cases (17-19), there has been a reasonable interest related to the neoplastic nature of the origin of this disease.

The annual incidence of LCH is 2.6 to 5.4 cases per million children in the general population with peak age incidence of 1-3 years (14, 20, 21). The report of the British Paediatric Surveillance Unit and the French National Studies revealed incidence rates of 4.12 and 4.6 per million children, respectively (22, 23). The incidence of LCH seems higher in people of northern European descent than in people of African or Asian descent (24).

The disease may resolve spontaneously or progress, compromising the function of vital organs leading to death (25). It is estimated that 50% of children with LCH will develop CDI (5). LCH accounted for 15% and 16.6% of cases of acquired CDI in Italy and in India respectively (1, 26). A higher frequency of CDI (as high as 50%) has been reported in children with a multisystem type of LCH (27). In children with LCH, the onset of CDI may be either before, concurrently with or subsequent to the development of extracranial sites (28).

In LCH, Osseous involvement is typically seen in the flat bones, with lesions of the skull, pelvis and ribs accounting for more than 50% of cases. About 30% of lesions are found in the long bones, with the femur being the most commonly affected, followed by humerus and the tibia (29). The radiologic appearance of the bone lesion depends on the site of involvement and the phase of the disease (29, 30). LCH-induced CDI is almost always a multisystem disease, with lesions in bone (68%), skin (57%), lung (39%) and lymph nodes (18%) (31).

The presumptive diagnosis of LCH is based on the demonstration of granuloma consisting of pale histiocytic cells with unfolded nuclei, eosinophils and multinucleated giant cells in biopsy specimens. The definitive diagnosis is usually based on a positive staining of the cells from the lesion with CD1a and/or Langerin (CD207). A protein that is expressed in Birbeck granules, cytoplasmic organelles typically found in Langerhans cells (15, 32, 33). However, in a recent review by Badalian-Very et al has stated that the demonstration of Birbeck granules by electron microscopy is no longer required for diagnosis due to the remarkable similarity of the histopathological features that are present regardless of the site of the lesion (15, 32).

Although there is a reasonable amount of understanding about LCH, there is a paucity of literature regarding this disease, particularly from the developing countries. Our intention of reporting this case report is to improve the awareness of this rare disease entity among medical community and to highlight the challenges encountered in managing this condition in a resource poor setting.

CASE REPORT

An 11-year-and-4-month old Nigerian girl presented with left thigh pain for 8 weeks, polydipsia and polyuria for 21 days, and left hip pain for 21 days, and fever for 18 days. About 4 weeks prior to this presentation, she was feeling thirsty and her usual daily intake of about 2 liters per day gradually increased up to about 10 liters. This was also associated with nocturia and while she was in the hospital, she was passing up 28 liters of urine per day.

She also had a dull pain in both left thigh and hip pain, which later it became localized to the left hip joint. Gradually her pain got progressively worse until she could no longer walk. The pain was aggravated by movement and relieved by rest and it was throbbing in nature. She did not give a history of antecedent trauma or neurosurgery and there was

no history suggestive of sickle cell disease or autoimmune disorder. There was an associated high-grade fever.

She achieved menarche at the age of 11 years (4 months before her presentation and has had 3 menstrual periods). She did not give a history of ingestion of nephrotoxic substances, constipation or abdominal pain. She did not have a history of psychiatric illness, fluctuation of symptoms or visual problems. The patient's father was working as a police officer and the mother was a petty trader.

Physical examination revealed an ill-looking adolescent girl with moderate pallor and discrete lymph nodes in both axillae. Her anthropometry showed a weight of 48kg (80th percentile), a height of 150cm (60th percentile) and a BMI of 21.3kg/m² (85th percentile). Otoscopic examination was normal. Her left thigh was swollen and warm with tenderness. Left hip joint movements were painful. However, right lower limb and right hip joint were normal. She had hepatomegaly.

Her full blood count results are as follows: WBC 8,200 cells/ml, lymphocytes 2100 cells/ml, granulocytes 5,300 cells/ml, RBC 2.49 x 10⁶/ml, Hb 5.6g/dl, haematocrit 19%, and platelet 274000 cells/ml. Peripheral blood smear was in keeping with mixed anaemia. Her haemoglobin electrophoresis was normal and her urinalysis showed no proteinuria. Pelvic and left thigh radiograph revealed left acetabular fracture (pathological fracture) with left femoral head protrusion and underlying left hemipelvis osteopenia. Biopsy of left hip joint capsule report showed evidence of chronic inflammatory lesion composed of neutrophils, lymphocytes and macrophages within a fibrous stroma with numerous thin-walled blood vessels. These histological findings were in keeping with acute-on-chronic sinusitis. The other laboratory findings are summarized in Table 1.

Table 1: Laboratory findings

Parameter	Result	Comments
Serum sodium	138mmol/L	High normal range
Serum potassium	3.4mmol/L	Normokalaemia
Serum chloride	104mmol/L	Normochloridaemia
Serum bicarbonate	20mmol/L	Within normal limits
Total calcium	2.3mmol/L	Normocalcaemia
Serum phosphate	1.4mmol/L	Normophosphataemia
Urea	2.2mmol/L	Within normal limits
Serum creatinine	54.5umol/L	Within normal limits
Fasting blood glucose	3.8mmol/L	Normoglycaemia
Random blood glucose	5.2mmol/L	Normoglycaemia
Urine glucose	Nil	No glycosuria
Urine specific gravity	1.000	SG of distilled water (hypoosthenuria)
Urine osmolality	64mOsm/kg	Maximally diluted urine
Plasma osmolality	310mOsm/kg	Elevated
Urine/plasma osmolality	0.2	<1 suggest CDI
Haematocrit	19%	Anaemia
Chest radiograph	No infiltrates	Normal
Urine culture	No growth	sterile

Based on urine osmolality studies (Table 2), histological and radiological findings, diagnosis of cranial diabetes insipidus secondary to Langerhans' cell histiocytosis was made. The patient was managed with careful attention to fluid therapy. She had significant anaemia, requiring a blood transfusion. The paediatric oncology unit was invited to assist in proper risk stratification, an appropriate treatment plan and long-term follow up after discharge from hospital admission. The orthopaedic surgery team was also invited to assist with the collection of biopsy specimen for confirmation of the diagnosis of LCH. Currently, she is being followed up in the paediatric endocrine and metabolic clinic of our hospital to identify long-term complications.

DISCUSSION

With the typical history of polyuria, polydipsia and nocturia, the supportive biochemical parameters and the characteristic urinary response to vasopressin, the diagnosis of cranial diabetes insipidus was straight forward in this patient. The patient also displayed an adequate amount of clinical, radiological and histological characteristic to confirm that the cause

of cranial diabetes insipidus as LCH. However, it is not so straight forward and it is presumptive in most of the paediatric patients.

The diagnosis of diabetes insipidus is confirmed by the typical laboratory findings, such as elevated serum osmolality (301mOsm/kg), very low urine osmolality (64mOsm/kg) and hyposthenuria (urine specific gravity 1.000). Response to vasopressin administration distinguished CDI from NDI. Following the administration of vasopressin, an elevation of urine osmolality greater than two-fold is diagnostic of CDI, whereas the urine osmolality does not increase significantly in NDI (5). After administration of vasopressin, 3.5-fold elevation of urine osmolality from baseline confirmed the diagnosis of cranial diabetes insipidus in our patient.

Diabetes mellitus, nephrogenic diabetes insipidus and primary polydipsia are considered as the main differential diagnoses that need to be considered in a patient suspected of cranial DI. The positive history of nocturia and thirst, waking her up at night to drink water in conjunction with a negative history of psychiatric illness, made the diagnosis primary polydipsia unlikely. Serum hyperosmolality in the presence of polyuria, as well as the results of the vasopressin response test, negated the diagnosis of primary polydipsia (34). The presence of normoglycaemia and the absence of glycosuria excluded the diagnosis of diabetes mellitus.

LCH is the commonest systemic disease associated with cranial diabetes insipidus in paediatric age group (11). Although LCH can occur at any age, it commonly reported in age 1-3 years (14). However, there are case reports of LCH outside this peak age group. One Centre in India has reported a series of 69 patients with ages ranging from 2 months to 12 years (35) and there have been reported cases presenting even in adolescence (27). Our patient presented at a later stage and she was 11 years at the time of the diagnosis. There are conflicting reports concerning sex predilection. Some reports indicate a male preponderance (27, 34) and others indicate a female preponderance (1, 3) reflecting a broad and protean spectrum of presentation in paediatric LCH.

The bone is the most frequently affected tissue in paediatric LCH, being encountered in 75-80% of cases (23). A report from India has demon-

Table 2: Vasopressin response test

Time	Urine osmolality (mOsm/kg)	Comments
0 hour (Basal)	111	Dilute, hypo-osmolar urine
2 hours after vasopressin	381	3.5-fold increase over baseline
4 hours after vasopressin	346	3-fold increase over baseline

nstrated that bone pain and fever as symptoms in 65.2% and 43.5% of paediatric patients with LCH (35). Paediatric CDI is usually associated with decreased bone mineral density, which is manifesting as osteopaenia (30, 36). The diminished AVP and the resultant decreased effect on postaglandins and bone production are thought to be the reason for the observed osteopaenia (37). Our patient also presented with bone pain and fever and left thigh pain was his earliest complaint. She had bony involvement in femur and pelvis with a pathological fracture at presentation, reflecting a reduction in bone mineral density.

Bone marrow involvement is more common in young children and five (26.3%) of the 19 cases in the series studied by Kumar et al, had bone marrow involvement (38). Axillary lymph node enlargement has been observed in 48.5% of cases (14). The involvement of the bone marrow, lymph node and the posterior pituitary gland is suggestive of a high-risk multisystem disease (15), which is associated with long-term complications (39). The presence of anaemia (haemoglobin concentration < 10g/dl) is indicative of the bone marrow, which was present in our patient (25). Our patient also had evidence of posterior pituitary involvement and axillary lymphadenopathy, suggesting high-risk multi-system disease.

The confirmation of the CDI is done with urine osmolality measurements. It is expected to be greater than 750mOsm/kg, following vasopressin administration. In our patient, the urine osmolality was less than 750mOsm/kg after vasopressin administration. However, a 3.5-fold elevation above the baseline was observed in our patient. A similar finding has been previously reported in a Nigerian child with CDI (8) and also in a case series of 10 children with CDI by Wong et al. in Hong Kong (40). The diagnosis of LCH is usually presumptive in the majority of the

patients. It was based on clinical manifestations (bone pain, fever, features consistent CDI and anaemia), radiological findings (femoral head protrusion, pelvic osteopaenia, a pathological fracture in acetabulum) and the laboratory findings in our patient.

In a resource poor setting, the management of a patient with CDI is a challenge. In order to exclude the presence of brain tumours such as germinomas and central nervous system malformations, magnetic resonance imaging (MRI) scan is an essential investigation in the management of such patients. Lack of brain imaging facilities was a challenge and it has been a challenge even for the previously reported cases in Nigeria (7-9). Immunohistochemistry is another important aspect of diagnosis of LCH in patients with CDI. The non-availability of this was a limitation that we had to face and also in similar resource-poor settings such as in India (3). Non-availability of desmopressin for the treatment of CDI was another challenge that we had to face.

In conclusion, acquired CDI due to a systemic disease, such LCH can occur in post-menarcheal age group and should be suspected in adolescents presenting with polyuria.

REFERENCES

1. Maghnie M, Cosi G, Genovese E, Manca-Bitti ML, Cohen A, Zecca S, et al. Central diabetes insipidus in children and young adults. *New England Journal of Medicine* 2000; 343: 998-1007.
2. Mishra G, Chandrashekhar SR. Management of diabetes insipidus in children. *Indian Journal of Endocrinology and Metabolism* 2011; 15(Suppl 3): S180-S187.
3. Di Lorgi N, Napoli F, Allergri AEM, Olivieri I, Bertelli E, Gallizia A, et al. Diabetes insipidus – Diagnosis and management. *Hormone Research in Paediatrics* 2012; 77: 69-84.
4. Fenske W, Allolio B. Clinical review: current state and future perspectives in the diagnosis of diabetes insipidus: A clinical review. *Journal of Clinical Endocrinology and Metabolism* 2012; 97: 3426-3437.
5. Green RP, Majzoub JA, Muglia LJ. Disorders of water balance. In: Brook CGD, Clayton PE, Brown RS eds. *Brook's Clinical Pediatric Endocrinology*, 5th edition. Oxford, Blackwell Publishing Ltd, 2005:367-395.
6. Charmandari E, Brook CG. 20 years of experience in idiopathic central diabetes insipidus. *Lancet* 1999; 353: 2212-2213.
7. Jarret OO, Ogunbosi BO, Ayoola OO. Paediatric endocrine disorders at the University College Hospital, Ibadan: 2002-2009. *Annals of Ibadan Postgraduate Medicine* 2013; 11(2): 96-101.
8. Anochie IC, Opara PI, Inimgba N. Pattern of endocrine diseases in children at the University of Port Harcourt Teaching Hospital. *Port Harcourt Medical Journal* 2009; 3: 145-152.
9. Onyiriuka AN, Kouyate M. Paediatric endocrine disorders as seen at the University of Benin Teaching Hospital over a ten-year period. *Nigerian Journal of Paediatrics* 2014; 41(2): 316-320.
10. Okpere AN, Anochie K, Yarhere I. Central diabetes insipidus in a Nigerian child: A case report. *Nigerian Journal of Paediatrics* 2014; 41(2): 147-150.
11. Prosch H, Gross N, Prayer D, Waldhauser F, Steiner M, Minkov M, Gardner H. Central diabetes insipidus as presenting symptom of Langerhans cell histiocytosis. *Pediatric Blood and Cancer* 2004; 43(5): 594-599.
12. Hunter JD, Calikoglu AS. Etiological and clinical characteristics of central diabetes insipidus in children: experience from a single center. *International Journal of Pediatric Endocrinology* 2016; 3: 1186-1190.
13. Delprat C, Arico M. Blood spotlight on Langerhans cell histiocytosis. *Blood* 2014; 124(6): 867-872.
14. Wietzman S, Egeler RM. Langerhans cell histiocytosis: Update for the pediatrician. *Current Opinion Pediatrics* 2008; 20: 23-29.
15. Schmidt S, Eich G, Geoffery A, Hanquinet S, Waibel P, Wolf R, et al. Extracerebral Langerhans cell histiocytosis in children. *RadioGraphics* 2008; 28: 707-726.
16. Grana N. Langerhans cell histiocytosis. *Cancer Control* 2014; 21(4): 328-334.
17. Badalian-Very G, Vergilio JA, Deger BA, MacConaill LE, Brandner B, Calicchio MC, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* 2010; 116(11): 1919-1923.

18. Davies H, Bignell GR, Cox C, Stephen P, Edikens S, Clegg S, et al. Mutations of the BRAF gene in human cancer. *Nature* 2002; **417(6892)**: 949-954.
19. Brown NA, Furtado LV, Betz BL, Kiel MJ, Weigelin HC, Lim MS, et al. High prevalence of somatic MAP2K1 mutation in BRAF V600E negative Langerhans cell histiocytosis. *Blood* 2014; **124(10)**: 1655-1658.
20. Campos MK, Viana MB, de Oliveira BM, Ribeiro DD, de Resende Silva CM. Langerhans cell histiocytosis: a 16-year experience. *Journal of Pediatrics (Rio J)* 2007; **83(1)**: 79-86.
21. Alston RD, Tatevossian RG, McNally KJ, Kesley A, Birch JM, Eden TO. Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1998. *Pediatric Blood and Cancer* 2007; **48**: 555-560.
22. Salotti JA, Nanduri V, Pearce MS, Parker L, Lynn R, Windebank KP. Incidence and clinical features of Langerhans cell histiocytosis in UK and Ireland. *Arch Dis Child* 2009; **94**: 376-380.
23. Guyot-Goubin A, Donadieu J, Barkaoui M, et al. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. *Paediatric Blood Cancer* 2008; **51**: 71-75.
24. Jaffe R, Weiss LM, Facchetti F. Tumours derived from Langerhans cells. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al (eds). *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th edition. Lyon, France, IARC Press; 2008: 358-360.
25. Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. *Hematology Oncology Clinics of North America* 1998; **12**: 247-258.
26. Bajpai A, Kabra M, Menon PS. Central diabetes insipidus: clinical profile and factors indicating organic aetiology in children. *Indian Pediatrics* 2008; **45**: 463-468.
27. Marchand I, Barkaoui MA, Garel C, Polak M, Donadieu J. Central diabetes insipidus as the inaugural manifestation of Langerhans cell histiocytosis: Natural history, and medical evaluation of 26 children and adolescents. *Journal of Clinical Endocrinology and Metabolism* 2011; **96**: E1357-E1360.
28. Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. *Journal of Pediatrics* 1995; **127**: 1-11.
29. Stull MA, Kransdorf MJ, Davancy KO. Langerhans cell histiocytosis of bone. *RadioGraphics* 1992; **12(4)**: 801-823.
30. Buckwalter JA, Brandser E, Robinson RA. The variable presentation and natural history of Langerhans cell histiocytosis. *The Iowa Orthopaedic Journal* 1999; **19**: 99-105.
31. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ. Langerhans cell histiocytosis: diagnosis, natural history, management and outcome. *Cancer* 1999; **85**: 2278-2290.
32. Badalian-Very G, Vergilio JA, Fleming M, Rollins BJ. Pathogenesis of Langerhans cell histiocytosis. *Annual Review of Pathology* 2013; **8**: 1-20.
33. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorder. *American Journal of Surgical Pathology* 2008; **32(4)**: 615-619.
34. Sabio P, Tipton GA, Chan JGM. Diabetes insipidus. *Pediatric Review* 2000; **21**: 122-129.
35. Bansal D, Marwaha RK, Trehan A, Gupta V, Varma N. Langerhans' cell histiocytosis: Experience from a single center. *Indian Pediatrics* 2008; **45**: 685-688.
36. Khung S, Budzik J, Amazallag-Bellenger E, Lambilliotte A, Ares GS, Cotton A, et al. Skeletal involvement in Langerhans cell histiocytosis. *Insights Imaging* 2013; **4**: 569-579.
37. Pivonello R, Colao A, Di Somma C, Faccillio G, Klain M, et al. Impairment of bone status in patients with central diabetes insipidus. *Journal of Clinical Endocrinology and Metabolism* 1998; **83**: 2275-2280.
38. Kumar M, Sachdeva MUS, Naseem S, Ahluwalia J, Das R, Varma N, Marwaha RK. Bone marrow infiltration in Langerhans' cell histiocytosis – An unusual but important determinant for staging and treatment. *International Journal of Hematology Oncology and Stem Cell Research* 2015; **9(4)**: 193-197.
39. Haupt R, Nanduri V, Calevo MG, Bernstrand C, Braier JL, Broadbent V, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society – Late Effects Study Group. *Pediatric Blood and Cancer* 2004; **42(5)**: 438-444.
40. Wong CM, Man SS. Water deprivation test in children with poly-

-uria. *Journal of Pediatric Endocrinology and Metabolism* 2012; **25**: 869-874.