CASE REPORT

Central diabetes insipidus: beware of Langerhans cell histiocytosis!

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disorder, characterised by a monoclonal proliferation of aberrant histiocytes that accumulate in and infiltrate into different organs. When the hypothalamic-pituitary axis is involved, central diabetes insipidus (CDI) can be its first manifestation. Three cases of LCH with central diabetes insipidus were retrospectively analyzed:

Case 1 is a 41-year old female presenting with polyuria and polydipsia. Diabetes insipidus was diagnosed and treated with desmopressin. MRI pituitary showed hypophysitis. Subsequently, she developed bone lesions and a biopsy demonstrated LCH.

Case 2 is a 51-year old female presenting in 2009 with polyuria and polydipsia. Diabetes insipidus was diagnosed and treated with desmopressin. MRI pituitary revealed hypophysitis. LCH was suspected because of known pulmonary histiocytosis. Coexisting bone lesions were biopsied and confirmed LCH.

Case 3 is a 44-year old female presenting with diabetes insipidus. She was treated with desmopressin as well. MRI of the pituitary gland showed impressive thickening of the infundibulum. A few months later, she developed skin lesions and a biopsy revealed LCH.

Conclusively, LCH is a rare, elusive and probably underdiagnosed disease with a broad disease spectrum. Due to infiltration of the hypothalamic-pituitary axis, CDI can be the first manifestation, even before LCH is diagnosed. Therefore, LCH should be considered in the diagnostic workup of CDI.

KEY WORDS

Diabetes insipidus, hypothalamic-pituitary axis, Langerhans cell histiocytosis

What was known on this topic?
Langerhans cell histiocytosis is a rare and still partly elusive disease with a very broad disease spectrum ranging from isolated and indolent symptoms to multisystem and life-threatening conditions. Nevertheless, systemic treatment can be curative.

What does this add?
This article adds that central diabetes insipidus can be the first manifestation of Langerhans cell histiocytosis (LCH), even long before LCH is diagnosed. Therefore, LCH should be considered in the CDI diagnostic workup.

INTRODUCTION

Diabetes insipidus (DI) is a disorder of water balance in the kidneys, characterized by a failure to concentrate urine, causing polyuria (i.e. > 2 l/m²/24h) and subsequently polydipsia. DI is subdivided into central and nephrogenic DI. Central diabetes insipidus (CDI) arises from destruction or degeneration of magnocellular neurons in the paraventricular and supraoptic nuclei, which are responsible for producing vasopressin. If more than 80% of these cell bodies are damaged, polyuria occurs because of vasopressin deficiency. In contrast, nephrogenic DI is the result of an impaired kidney response to vasopressin. The broad differential diagnosis of CDI makes it challenging to determine its underlying aetiology (*table 1*).[1] One cause of CDI is Langerhans cell histiocytosis (LCH), which can appear with variable presentation. We demonstrate this by describing three different patients with LCH.

Table 1. *Differential diagnosis of central diabetes insipidus*

Germinoma/craniopharyngioma
Langerhans cell histiocytosis
Local inflammatory disease
Autoimmune disease
Vascular diseases
Postoperative trauma or accidents
Sarcoidosis
Metastases
Cerebral and cranial malformations
Genetic defects in vasopressin synthesis

SUBJECTS AND METHODS

Three cases of LCH with CDI were retrospectively analysed in the outpatient clinic of the University Hospital in Brussels from 1996 until 2017. Patient characteristics, clinical presentation, diagnosis and treatment were compared (*table 2*).

RESULTS

Case histories

Case 1: In 2009, a 41-year-old woman presented with polyuria and polydipsia. A water deprivation test confirmed the diagnosis of CDI, and magnetic resonance imaging (MRI) of the pituitary gland showed hypophysitis. Desmopressin treatment was started. In 2014, she developed skeletal pain and a fever. Positron emission tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose and computed tomography (18-FDG PET/CT) showed various bone lesions. Histological examination of lesional tissue at the right acromion showed positive CD1a and protein S100 staining; polymerase chain reaction (PCR) demonstrated a proto-oncogene BRAF^{V600E} mutation matching the diagnosis of LCH. In the meantime, the patient also developed hypogonadotropic hypogonadism. Systemic treatment with vinblastine and prednisone was initiated, although suspended after six weeks because of toxicity. In 2015, new bone lesions were identified by 18-FDG PET/CT. Treatment with dabrafenib and trametinib was started until last follow-up, resulting in a complete remission of the skeletal lesions and recovery of the menstrual cycle. Desmopressin treatment has been continued because CDI persists.

Case 2: A 51-year-old woman with known pulmonary histiocytosis since 2004 developed polyuria and polydipsia in 2008. CDI was confirmed through a positive water deprivation test, and MRI of the pituitary gland demonstrated hypophysitis. Desmopressin treatment relieved her symptoms. A diagnostic technetium bone scintigraphy revealed lesions at the mandibula and skull. LCH was confirmed upon histological examination of the mandibular lesion expressing CD1a and protein S100 antigens. At the time, mutational analysis was not routinely performed to diagnose LCH. Therefore, we do not have any mutational data of the lesional tissue. The bone lesions were resected and although systemic treatment was repeatedly proposed because of multisystemic disease, the patient declined this.

Case 3: A 44-year-old woman presented in 1996 with polyuria and polydipsia. A water deprivation test confirmed the diagnosis of CDI, and MRI of the pituitary gland showed an impressive thickening of the infundibulum. Simultaneously, coexisting hypogonadotropic hypogonadism and central hypothyroidism were diagnosed. Desmopressin treatment and substitution therapy with levothyroxine and an oral contraceptive pill achieved good results. A few months later, she developed skin lesions. Underlying LCH was identified through electron microscopy and histological examination of a skin biopsy, showing typical Birbeck granules and protein S100 positivity, respectively. No mutational data are available for this case either. Corticosteroids and azathioprine treatment caused the lesions to disappear. Nevertheless, it was necessary to continue treatment for CDI and anterior pituitary function loss.
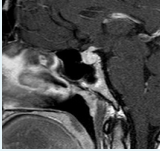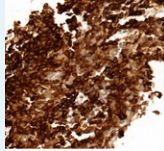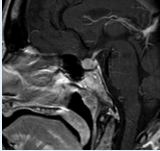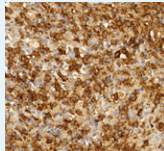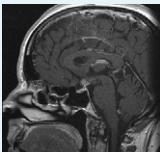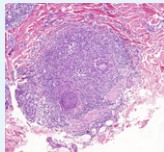
DISCUSSION

The above-described three patients demonstrate the highly variable presentation of LCH, in which the common denominator is the development of CDI.

LCH is a rare disease and can occur at any age, although it is more frequently seen in children with a male predominance.[2] Its incidence is approximately five cases per million children and about one or two cases per million adults.[3] General clinical presentation of LCH can be highly variable depending on which organ is infiltrated, and the disease spectrum ranges from isolated skin or skeletal lesions to multisystem involvement and sometimes life-threatening conditions such as acute lymphoblastic leukaemia.[4] A four-part LCH classification has been established by the Histiocyte Society (*table 3*).[5]

The origin, development and regulation of LCH is complex and unravelling the molecular mechanisms that govern these processes are important for accurate diagnosis and treatment. LCH is characterized by a specific histopathological lesion containing clonal Langerhans-type cells, which can be recognized by their expression of CD1a, S100 protein, langerin (CD207) and Birbeck

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Table 2. *Case history: patient characteristics, clinical presentation, diagnosis and treatment*

Case Age and gender	Medical history	Presentation CDI	MRI imaging	Initial treatment	Biopsy: LCH	Other manifestations	Treatment	Follow-up
#1 41 F	Obesity, laparoscopic gastric banding, hip prosthesis left, eczema	2009: Polyuria and polydipsia	Hypophysitis MRI: Diffuse enlargement of pituitary (i.e. > 3 mm)	Desmopressin intranasally	2014: Acromion right IHC: CD1a+, S100+ PCR: BRAF^{V600E}+ CD1a highlighting lesional cells (magnification 400x)	2014: hypo-gonadotropic hypogonadism; diffuse bone lesions: right shoulder, left clavicle, left hip, L2 2015: Bone lesions at both knees, left shoulder, sacroiliac joint	2014: Vinblastine/ prednisone[§] 2015: Dabrafenib 150 mg 2x/d and trametinib 2mg 1x/d[‡]	2016: CR of bone lesions 2017: Recovery of menstrual cycle, CDI persists
#2 51 F	Hysterectomy, pneumo-thorax right treated with talcage, pulmonary LCH, nicotine dependence	2008: Polyuria and polydipsia	Hypophysitis MRI: Diffuse enlargement of pituitary (i.e. > 3 mm)	Desmopressin intranasally	2004: Lung (no data) 2010: Mandibule IHC: CD1a+, S100+ PCR: No mutation data[¶] CD1a highlighting lesional cells (magnification 400)	2004: Pulmonary cysts 2010: Mandibular cyst + 1 skull lesion 2014: 2 skull lesions 2017: Relapse pneumothorax	2004: Smoking cessation[†] 2010: Surgical cyst resection	Lost to follow-up
#3 44 F	None	1996: Polyuria and polydipsia	MRI: Impressive thickening of infundibulum (> 3mm)	Desmopressin intranasally	1996: Skin IHC: S100 +, no CD1a data[¥] EM: Birbeck granules PCR: no mutation data[¶] H&E: Skin infiltrate	1996: Skin lesions, thy-rotropic and gonadotropic insufficiency	1996: Corticoids, azathio-prine 50 mg, Levothyroxine and gestodene/ ethinyl-estradiol	CR of skin lesions, persisting CDI, hypo-thyroidism and secondary amenorrhea

IHC: immunohistochemistry; PCR: polymerase chain reaction; EM: electron microscopy; H&E: hematoxylin and eosin stain; CR: complete remission
[§] At the time, vinblastine/prednisone was administered, based on established protocols for multisystem LCH in children. It was suspended because of neurotoxicity. Vinblastine is currently known to be less effective and has higher toxicity rates in adults.
[‡] Dabrafenib (BRAF inhibitor), trametinib (MEK inhibitor). Combination therapy with trametinib instead of dabrafenib monotherapy was chosen to eliminate the incidence of known BRAF inhibitor-induced palmoplantar hyperkeratosis and secondary skin malignancies at higher dosages.
[¶] These cases date from before determination of recurrent mutations in LCH. Since these biopsies are no longer accessible; post hoc mutation analysis was not possible.
[†] After smoking cessation, pulmonary lesions remained stable and did not affect pulmonary function tests. No systemic treatment was administered at the time.
[¥] CD1a data and biopsy no longer available.

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Table 3. *Langerhans cell histiocytosis classification according to the Histiocyte society*

Subtype	Description
LCH – SS	A single organ is affected; no lung or risk organ involved.
LCH lung	Lung involvement but no risk organ.
LCH – MS – RO⁻	Multiple systems affected but no lung or risk organ involved.
LCH – MS – RO⁺	Multiple systems affected and at least one risk organ involved.

Four different subtypes of LCH are defined by the Histiocyte Society depending on the number and kind of organs (systems) involved. Risk organs (RO) are the spleen, liver or the hematologic system.
LCH = Langerhans cell histiocytosis; SS = single system; MS = multiple systems; RO = risk organs.
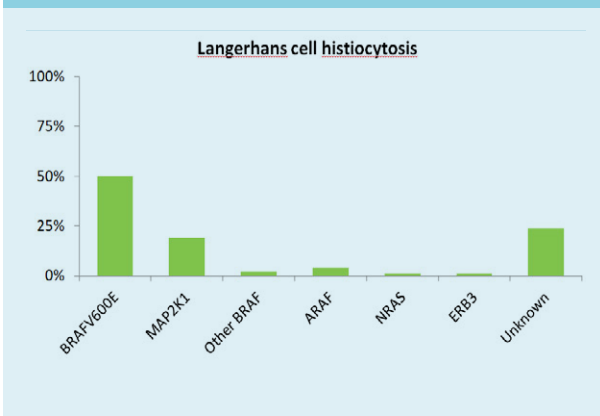
granules.[6,7] Interestingly, based on their gene expression profile these pathological histiocytes do not correspond to epidermal Langerhans cells, but rather originate from myeloid-derived precursor dendritic cells.[8] A 2010 report demonstrated recurrent genetic abnormalities in clonal LCH cells, establishing LCH as a neoplasm.[9]

To date, the two most prevalent mutations are found in either the proto-oncogenes BRAF (BRAF^{V600E}) or MAP2K1.[9,10] These mutations result in a constitutive activation of the mitogen-activated protein kinase (MAPK) pathway causing pathological proliferation and differentiation. However, not all responsible genes have yet been discovered (*figure 1*).[11,12]

The endocrine system can also be affected by LCH, as Langerhans cells can migrate to the lymph nodes and affect the hypothalamic-pituitary axis. This can lead to mostly irreversible CDI with corresponding symptoms of polyuria and polydipsia. In Patient 1 and 3, CDI was the first presenting feature of LCH and in patient 2, CDI developed later in the course of the disease.

Figure 1. *Illustration of the currently known activating kinase alterations in Langerhans cell histiocytosis (LCH). Other mutations in MAPK genes have been reported, in addition to mutations in BRAF or MAP2K1. Thus, alternative mutated genes might contribute to the activation of the MAPK pathway in LCH.[11]*

A positive water deprivation test can confirm the diagnosis of CDI. An MRI, typically shows a lack of the hyper-accentuated signal of the posterior pituitary on sagittal T1-weighted imaging and a thickening of the pituitary stalk.[1] Infiltrative disease of the pituitary gland can lead to thyrotropic, somatotropic or gonadotropic axis failure.[13] The prevalence of CDI in patients with LCH ranges from 10-50% and CDI presents in most cases after the diagnosis of LCH is established.[1,13] In addition, CDI occurs more frequently in patients with BRAF^{V600E}.[14]

Treatment options for LCH differ because of its wide disease spectrum. They range from minimal conservative treatment in single skin or bone disease to intensive combination chemotherapy in multisystem disease. However, vinblastine/prednisone treatment for one year is the standard initial systemic regimen for children.[3] Adults, conversely, are preferably treated with cytarabine (second-line) because of poor overall responses and excessive toxicity of first-line chemotherapy.[15] Targeted therapy with inhibitors of the BRAF/MAPK pathway (i.e. vemurafenib or trametinib, respectively) can be used in patients with corresponding mutations in whom first-line therapy fails; BRAF^{V600E} is associated with more resistant LCH and higher reactivation rates in response to first-line treatment.[14] LCH-induced CDI is treated with desmopressin.[1] LCH prognosis depends on the extent of the disease, and disseminated disease may still have serious and even fatal outcomes.[13]

CONCLUSIONS

Our three patients clearly demonstrate that the diagnosis of LCH can be challenging and is sometimes made after a long clinical history. Occassionally, CDI arises as primary manifestation before LCH is known. Furthermore, although most publications report a male and pediatric predominance, our three cases presented females in their 40s and 50s. LCH is a rare disorder with a broad disease spectrum, and a more comprehensive understanding of the LCH etiopathogenesis may lead to alternative therapeutic interventions in the future.

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ACKNOWLEDGMENTS

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