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Autosomal Dominant Familial Neurohypophyseal Diabetes Insipidus in Three Generations

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Abstract **Original Research Article**

Familial neurohypophysial diabetes insipidus (FNDI), an autosomal dominant disorder, comes in many forms that are differentiated by the inheritance pattern and the underlying genetic lesion. The disease is caused by mutations in the vasopressin-neurophysin 2- copeptin protein (AVP-NPII), in wolframin (WFS1) or in proprotein convertase subtilisin/kexin type 1 (PCSK1) genes. ***Materials and methods:*** In this study, we report a case of familial neurohypophyseal DI in three generations; followed in unit of the endocrinology, diabetology, metabolic diseases and nutrition department of the Mohammed VI University Hospital of Marrakesh. ***Results*:** This was a 45-year-old patient who had been suffering from polyuro-polydipsia syndrome since the age of 12, with daily urine volumes ranging from 8.0 to 15.0 litres, but had not seen a doctor. The patient was born without complications and had normal puberty. In the family history, three other members of the patient's family have also had polypolypolydispic syndrome since adolescence, covering three generations, including the patient's mother, her younger sister and daughter. A water restriction test was performed but the patient did not tolerate it. We completed with the minirin test with a good clinical response: urine concentrated with a volume of 500ml, and urinary osmolarity at H4 of 276.13 (Fig 2). As presented in (Fig 3), cranial MRI revealed a hypersignal region in the posterior pituitary lobe. Serum cortisol, thyroid function, and estrogen were all in the normal range The growth hormone (GH), insulin-like growth factor (IGF)-1 levels and the genetic testing were not performed due to limited financial resources. After treatment with oral desmopressin 60 ug two times daily was started, the symptoms of polydipsia and polyuria were satisfactorily controlled. She currently drinks about 1.5 L of water per day and she has a urine volume of 1.5 L per day. Her sister's daily water/diuresis intake is 3.0 L/2.0 L, due to the effects of the medication. ***Conclusion:*** Familial neurohypophyseal ID is a rare hereditary disease that has a negative impact on the patient's quality of life. The majority of cases are inherited in an autosomal dominant pattern, which is why screening and appropriate management are necessary.

Keywords: autosomal dominant disorder, growth hormone (GH), diabetology, polypolypolydispic syndrome.

INTRODUCTION

Familial neurohypophysial diabetes insipidus (FNDI), an autosomal dominant disorder, comes in many forms that are differentiated by the inheritance pattern and the underlying genetic lesion. The disease is caused by mutations in the vasopressin-neurophysin 2-copeptin protein (AVP-NPII), in wolframin (WFS1) or in proprotein convertase subtilisin/kexin type 1 (PCSK1) genes [1]. Clinically, FNDI is characterized by polyuria (>50 mL/kg), compensatory polydipsia and increased thirst (water intake of up to 20 L/day) and failure to concentrate urine. Usually, symptoms manifest at an age of several months to several years (typically between 1 and 6 years of age), with a gradual onset due to the progressive destruction of vasopressinergic neurons [2, 3].

The severity of polyuria may vary considerably between different families and even among siblings carrying the same mutation. Desmopressin (DDAVP) administration represented the standard treatment. The frequency of FNDI is currently unknown, although autosomal dominant forms account approximately between 3.5 and 8%, with a similar prevalence among males and females, in series of patients with central diabetes insipidus (DI) [4, 5].

The AVP gene, located on the short arm of chromosome 20 (20p13), consists of three exons and encodes for the preprovasopressin precursor (prepro-AVP) that consists of the 19- amino acid signal peptide (exon 1), the 9-amino acid arginine vasopressin (AVP) peptide (exon 1), the 93-amino acid carrier protein neurophysin 2 (NPII) (exon 1, 2, 3) and the 39-amino acid copeptin (exon 3) [6]. AVP is a posterior pituitary hormone, produced in the supraoptic nucleus and paraventricular nucleus of the hypothalamus. It plays a pivotal role in water balance by promoting reabsorption of free water through the V2 receptor in kidney and its synthesis and secretion is regulated by plasma osmolality (or serum Na) in physiological conditions [7]. When AVP-NPII is inadequately produced or it is not perfectly functioning, a condition called DI occurs. Most autosomal dominantly inherited cases of neurohypophyseal diabetes insipidus are due to AVP mutations located in the NPII moiety or in the signal peptide whereas few mutations are located directly in the AVP moiety [8]. Currently, 87 disease-causing mutations in AVP gene have been reported in The Human Gene Mutation Database (HGMD) including mainly missense mutations and rarer deletions, small indels and splice site mutations [9].

MATERIALS AND METHODS

In this study, we report a case of familial neurohypophyseal DI in three generations; followed in unit of the endocrinology, diabetology, metabolic diseases and nutrition department of the Mohammed VI University Hospital of Marrakesh.

CASE REPORT

It's a 45-year-old patient with a history of polyuria and polydipsia since age 12, but had not sought any medical care, as she always had access to water. The patient was born at term without any complications and had a normal pubescence. A total of 3 additional family members spanning three generations, including the patient's mother and younger sister and her daughter, also had teenage onset of polyuria and polydipsia. Daily urine volumes varied from 8.0 to 15.0 liters. The pedigree of the family is presented in (Fig 1).

RESULTS

The patient underwent a water restriction test which did not tolerate supplemented by a minirin test with the urinary osmolarity at H4 at 276.13 (Fig 2), the patient clinically responded to the test: the urine became concentrated and she urinated only 500ml. As presented in (Fig 3), the cranial MRI revealed a high signal region in the posterior lobe of the pituitary gland/ Serum cortisol, thyroid function and estrogen were all within normal ranges. The growth hormone (GH), insulin-like growth factor (IGF)-1 levels and the genetic testing were not performed due to limited financial resources.

After treatment with oral desmopressin 60 ug two times daily was started, the symptoms of polydipsia and polyuria were satisfactorily controlled. Currently he drinks approximately 1.5 L of water daily and has a urine output of 1.5 L per day. Her sister's water intake/diuresis per day are 3.0 L/2.0 L, due to the effects of the medication.

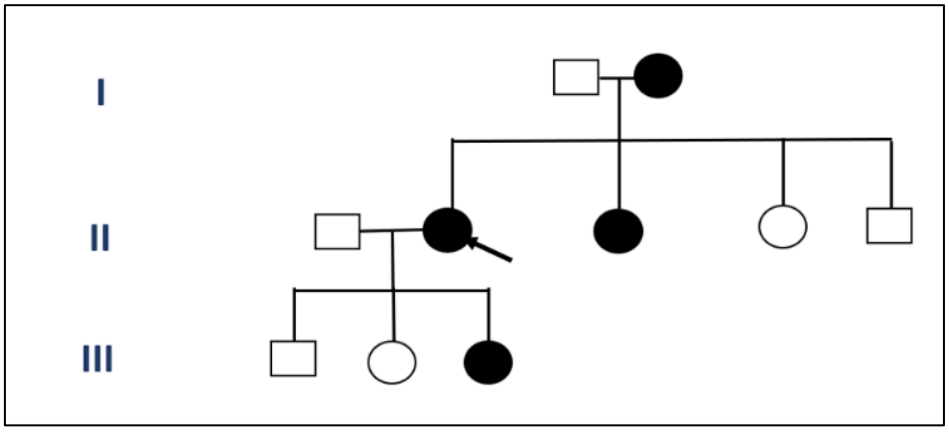

Fig 1: Family pedigree with familial neurophyseal diabetes insipidus in three generations

Duration (hr)	H2	H3	H4
U-Osm (mOsm/kg)	106,97		**276,13**
Calculated S-Osm (mOsm/kg)	291	291	293
Effective S-Osm (mOsm/kg)	290	289	292

Fig 2: Minirin test results of the patient

S-Osm: serum osmolarity; U-Osm, urine osmolarity

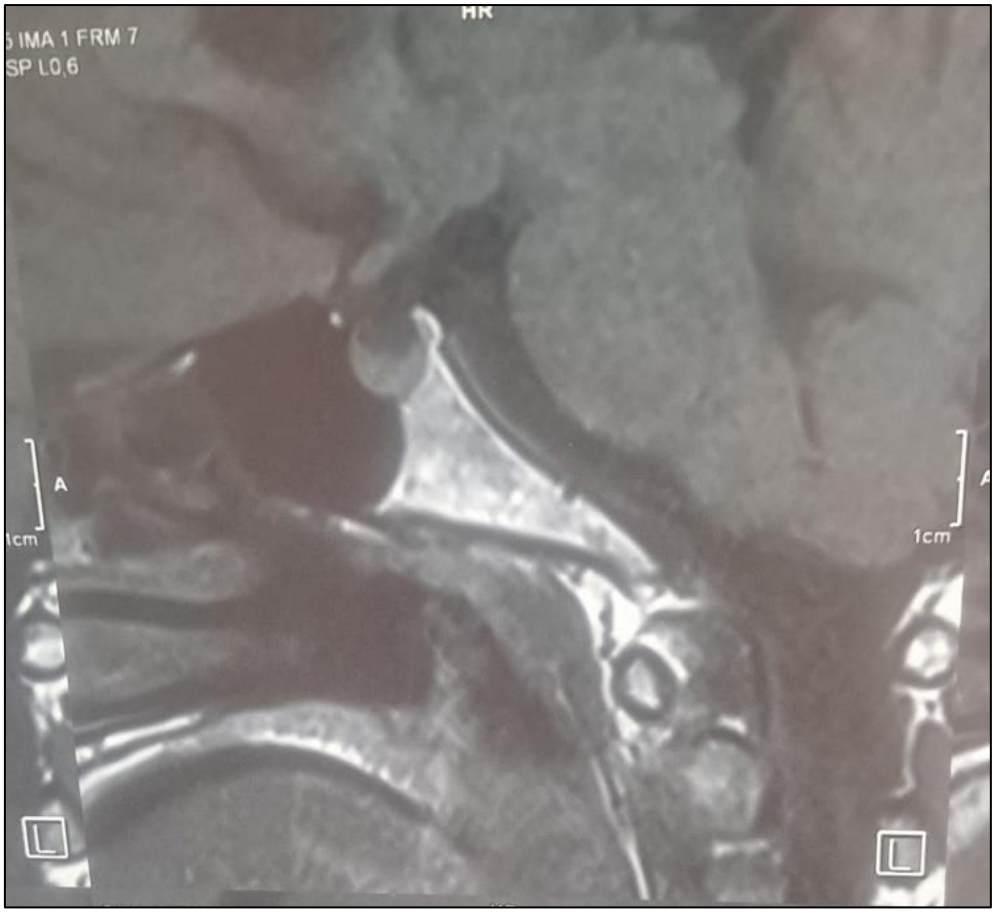

Fig 3: Sagittal hypothalamic-pituitary MRI showing a hypersignal region in the posterior pituitary lobe

DISCUSSION

Familial neurohypophyseal DI is caused by mutations in the AVP-NPII gene, which are usually inherited in an autosomal dominant pattern [10]. The AVP-NPII gene is located on chromosome 20p13 and has three exons, with an open reading frame of 492 bp. Exon 1 encodes a signal peptide, AVP, and the N-terminal portion of NP II; exon 2 encodes the central region of NP II; and exon 3 encodes the C-terminal part of NP II and copeptin, a glycoprotein with an unknown function [11]. The mutations involved in familial neurophyphyseal DI include small deletions, as well as missense and nonsense mutations that affect the signal peptide, the AVP moiety, or the AVP carrier protein, NPII. The majority of these mutations have been found in the region of the gene encoding NPII, an intracellular binding protein for AVP. Only a few mutations have been localized to the signal peptide or the AVP coding sequence, and no mutations have been localized to the glycoprotein moiety. It is assumed that all known autosomal dominant mutations cause defective folding or dimerization of the precursor protein [12, 13]. Since the first AVP-NPII mutation was reported6), 62 different mutations have been identified [14]. In Korea, a splice site mutation within the intron, a missense mutation in exon 2 (+1692C>A), and a deletion mutation of Glu78have been reported [12].

The discovery of novel genetic abnormalities in the AVP let's to further expand the panel of mutations associated with FNDI allowing an early diagnosis and follow-up of patients.

Despite replacement therapy with DDAVP is simple and effective, the identification of specific mutation-FNDI associated may represents a target for future drugs which can avoid protein misfolding.

CONCLUSION

Familial neurohypophyseal ID is a rare hereditary disease that has a negative impact on the patient's quality of life. The majority of cases are inherited in an autosomal dominant pattern, which is why screening and appropriate management are necessary [15].

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