

Clinical features and molecular analysis of arginine-vasopressin neurophysin II gene in long-term follow-up patients with idiopathic central *diabetes insipidus*

Apresentação clínica e análise molecular do gene da arginina-vasopressina neurofisiina II de pacientes com diabetes insípido central idiopático com longo seguimento

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ABSTRACT

Introduction: Central *diabetes insipidus* (DI) characterized by polyuria, polydipsia and inability to concentrate urine, has different etiologies including genetic, autoimmune, post-traumatic, among other causes. Autosomal dominant central DI presents the clinical feature of a progressive decline of arginine-vasopressin (AVP) secretion. **Objective:** In this study, we characterized the clinical features and sequenced the *AVP-NP/II* gene of seven long-term follow-up patients with idiopathic central DI in an attempt to determine whether a genetic cause would be involved. **Methods:** The diagnosis of central DI was established by fluid deprivation test and hypertonic saline infusion. For molecular analysis, genomic DNA was extracted and the *AVP-NP/II* gene was amplified by polymerase chain reaction and sequenced. **Results:** Sequencing analysis revealed a homozygous guanine insertion in the intron 2 (IVS2 +28 InsG) of the *AVP-NP/II* gene in four patients, which represents an alternative gene assembly. No mutation in the code region of the *AVP-NP/II* gene was found. **Conclusions:** The homozygous guanine insertion in intron 2 (IVS2 +28 InsG) is unlikely to contribute to the *AVP-NP/II* gene modulation in DI. In addition, the etiology of idiopathic central DI in children may not be apparent even after long-term follow-up, and requires continuous etiological surveillance. Arq Bras Endocrinol Metab. 2010;54(3):269-73

Keywords

Central *diabetes insipidus*; *AVP-NP/II* gene; PCR; sequencing; mutation

RESUMO

Introdução: O diabetes insípido (DI) central, caracterizado por poliúria, polidipsia e inabilidade em concentrar a urina, apresenta diferentes etiologias, incluindo causas genética, autoimune, pós-traumática, entre outras. O DI central autossômico dominante apresenta a característica clínica de falência progressiva da secreção da arginina-vasopressina (AVP). **Objetivo:** No presente estudo, caracterizou-se a apresentação clínica e sequenciou-se o gene *AVP-NP/II* de sete pacientes com DI central idiopático seguidos de longa data na tentativa de determinar se uma causa genética estava envolvida na etiologia. **Métodos:** O diagnóstico do DI central foi estabelecido por meio do teste de jejum hídrico e infusão de salina hipertônica. Para a realização da análise molecular, o DNA genômico foi extraído e o gene *AVP-NP/II* foi amplificado pela reação em cadeia da polimerase e, posteriormente, sequenciado. **Resultados:** A análise do sequenciamento do gene *AVP-NP/II* revelou uma inserção em homozigose de uma guanina no íntron 2 (IVS2 +28 InsG) em quatro pacientes, correspondendo a um arranjo alternativo do gene. Nenhuma mutação da região codificadora do gene *AVP-NP/II* foi encontrada. **Conclusões:** A inserção em homozigose de uma guanina no íntron 2 (IVS2 +28 InsG) provavelmente não contribui na modulação do gene *AVP-NP/II* no DI. Adicionalmente, a etiologia do DI central idiopático em crianças pode não se tornar evidente mesmo após um longo período de seguimento, necessitando de contínua vigilância da etiologia. Arq Bras Endocrinol Metab. 2010;54(3):269-73

Descritores

Diabetes insípido central; gene *AVP-NP/II*; PCR; sequenciamento; mutação

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INTRODUCTION

Central *diabetes insipidus* (DI) is a heterogeneous disease characterized by polyuria and polydipsia and failure to concentrate urine leading to a consequent excretion of large volumes of dilute urine. It is caused by a deficient secretion of arginine-vasopressin (AVP) by the neurohypophysis (1).

Although rare, familial inherited forms account for some cases of central DI (2-4). Genetic causes of central DI are usually due to gene mutations that encode AVP and its intracellular binding protein, neurophysin-II (*AVP-NP11* gene) and include autosomal dominant (2) and recessive forms (5). The *AVP-NP11* gene is located on chromosome 20 and contains three exons: exon 1 encodes the signal peptide, AVP peptide and the amino-terminal region of neurophysin-II; exon 2 encodes the central region of neurophysin-II; and exon 3 encodes the carboxy-terminal region of neurophysin-II and co-peptin, a glycoprotein (6). Most of the mutations causing autosomal dominant central DI have been described in the gene portion encoding neurophysin-II (2,7,8), leading to an improper folding and dimerization of neurophysin-II which accumulates in the endoplasmic reticulum (3,9,10). The onset of vasopressin deficiency in autosomal dominant familial central neurohypophyseal DI (adFNDI) usually becomes gradually apparent during the first decade of life, and is associated with a progressive degeneration of vasopressin-producing magnocellular neurons in the supra-optic and paraventricular nuclei of the hypothalamus (2,8,11). The neuron degeneration is probably due to a cytotoxic effect of the retained vasopressin-neurophysin-II in the magnocellular neurons (3,9,12). In addition, the dimerization between the wild type and the mutant precursors may occur, leading to a dominant negative mechanism that may contribute to the pathogenesis of adFNDI (13).

The destruction or degeneration of vasopressinergic neurons can be due to different acquired etiologies such as intrasellar tumors, granulomatous disease, trauma, inflammatory and vascular disease (1). Nevertheless, central DI is still considered idiopathic in 15% to 50% of patients (14-16) and its etiology should be pursued, especially in those patients with other anterior pituitary deficiencies and pituitary stalk thickening (17). Therefore, periodic clinical, laboratorial and imaging evaluations by magnetic resonance imaging (MRI) are required during the follow-up of patients with idiopathic central DI in order to rule out associ-

ated anterior pituitary deficiencies or cerebral diseases (17,18). However, even after long-term follow-up, the etiology of the so-called idiopathic central DI remains not established in many patients (19). In the present study we aimed to evaluate the clinical presentation and the molecular analysis of the *AVP-NP11* gene in patients with idiopathic central DI with onset of symptoms during childhood.

PATIENTS AND METHODS

We studied seven patients (5 male, 2 female) with idiopathic central DI after obtaining informed consent and the approval of the University Hospital Ethics Committee. The diagnosis of central DI was based on the fluid deprivation test (20) or on hypertonic saline infusion (21). Anterior pituitary function was evaluated at baseline or stimulated pituitary hormone measurements using standard previously published immunoassays (22).

Central nervous system MRI was performed in all but one patient who was lost to follow-up in 1995, before the technique was available at the hospital.

Molecular analysis

Genomic DNA was extracted from peripheral blood samples using a QIAmp kit (Qiagen Inc., Valencia, CA, USA), and the *AVP-NP11* gene was amplified by polymerase chain reaction (PCR) using specific primers. For exon 1, the sense TGG CGG CCG CGT CTC GCC TCC ACG GGA ACA and antisense GCT ATG GCT GCC CTG AGA TGG CCC ACA GTG primers, were used; for exons 2 and 3 and their intronic region, the sense TCG CTG CGT TCC CCT CCA ACC CCT CGA CTC and antisense CCT CTC TCC CCT TCC CTC TTC CCG CCA GAG primers, were used. The PCR reaction was carried out with 10% DMSO, using the hot start method followed by forty cycles of amplification (exon 1: 1 minute at 95°C, 1 minute at 66°C and 1 minute at 72°C; exons 2 and 3: 1 minute at 95°C, 1 minute at 60°C and 1 minute at 72°C). PCR products were visualized in 1% agarose gel followed by automated sequencing (ABI 377; Applied Biosystems). DNA sequencing was compared to data described by Bahnsen and cols. (23) (GenBank access number X62890).

RESULTS

Clinical and laboratory findings of studied patients are presented in table 1. None of the patients had family

Table 1. Clinical, radiological and laboratory data for patients with central *diabetes insipidus*

| Patient | Age at diagnosis (years)/ Genre | Follow-up (years) | Familial history | Diuresis (mL/kg/d) | Basal serum sodium | Basal pOsm | Basal uOsm | Maximum pOsm post-dehydration | Maximum uOsm post-dehydration | Dehydration duration time (hours) | Minimum pOsm post-desmopressin | Maximum uOsm post-desmopressin | Image (MRI) |
|---------|---------------------------------|-------------------|------------------|--------------------|--------------------|------------|------------|-------------------------------|-------------------------------|-----------------------------------|--------------------------------|--------------------------------|---|
| 1 | 3.6/M | 28 | Present | 250 | 143 | 296 | 72 | 307 | 291 | 6 | 295 | 466 | Normal hypophysis volume Bright spot not present |
| 2 | 3.7/F | 30 | Absent | 320 | 135 | 296 | 64 | – | 84 | 2 | 300 | 600 | N/A |
| 3 | 6/M | 34 | Present | – | 147 | 300 | 298 | – | – | – | – | – | Reduced hypophysis volume Progressive bright spot loss |
| 4 | 7/M | 7 | Absent | 143 | 143 | 289 | 51 | 294 | 50 | 3 | 281 | 180 | Normal hypophysis volume Bright spot not present |
| 5 | 5.8/M | 28 | Absent | 150 | 150 | 286 | 46 | 318 | 52 | 6 | 280 | 502 | Normal hypophysis volume Progressive bright spot loss |
| 6 | 7.5/M | 16 | Absent | 200 | 144 | 291 | 70 | – | – | – | – | – | Normal hypophysis volume mild infundibulum thickness Progressive bright spot loss |
| 7 | 1/F | 10 | Absent | 206 | 127 | 293 | 64 | 294 | 591 | 8 | 290 | 717 | Normal hypophysis volume Bright spot not present |

M: male; F: female; pOsm: plasma osmolality; uOsm: urinary osmolality; MRI: magnetic resonance image.

history of *diabetes insipidus* except patients 1 and 3 who were third-degree cousins but had no other relatives affected. Also, no autoimmune disease was identified in any of the nine patients. Age at onset of polyuria and polydipsia varied from 1 to 7 years of age, and duration of symptoms at diagnosis varied between 2 months and 5 years. Polyuria and polydipsia were the presenting symptoms in all patients, whose urinary volume at diagnosis ranged from 3 to 13.3 L/24h (143 to 320 mL/kg/day). The fluid deprivation test and vasopressin analog responses were consistent with the diagnosis of total central DI in all but one patient that had a response compatible with partial central DI (Patient 6). Growth retardation and bone age delay were observed in patients 1 and 7. Adrenal and thyroid functions and pubertal development were normal in all patients. Patients were followed for 22 years at our out-patient clinic.

No expansive sella turcica lesions were visualized by imaging study in any patient, except patient 6 who showed mild infundibulum thickness and a *pars intermedia* cyst, which disappeared during follow-up. Initial sella turcica MRI studies in six patients resulted in the absence of the posterior pituitary hyperintense signal in three patients and its presence in three patients also; which lost the bright spot of the neurohypophysis in

subsequent MRI during follow-up. Only one patient showed a reduced anterior pituitary.

Sequencing of *AVP-NP11* gene revealed no mutations in exons 1, 2 and 3 in any patients. However, a homozygous insertion of an additional guanine in intron 2 (IVS2 +28 InsG) was found in 4 patients. Due to the latter finding, we also sequenced *AVP-NP11* gene from controls and the same insertion in intron 2 was found in three out of nine controls.

DISCUSSION

In this study we presented seven patients with central DI diagnosed during the infancy with no apparent etiology after long-term follow-up. Molecular analysis of *AVP-NP11* gene showed no mutations in the coding region of this gene.

In the present series the age of onset for symptoms of polyuria and polydipsia was between 1 and 7 years of age, median of 5.8 years, very similar to the median age of 6.4 years reported by Maghnie and cols. (16) in a multi-centric study of pediatric patients with central DI. In our cohort, all patients but one were diagnosed within 6 months after the onset of symptoms. The literature usually describes a more dilated latency between

the onset of symptoms and the diagnosis, with previous reports showing an interval of 4 years (24). The delay of the diagnosis of *diabetes insipidus* in pediatric patients suggests that clinicians may not be aware of the need to investigate the symptoms of polyuria and polydipsia in children.

Growth retardation and bone age delay were observed in patients 1 and 7, which are in accordance with the 20% to 35% of patients with idiopathic central DI and short stature previously described (16,24,25).

All seven patients in this series had no clear etiology for the vasopressin deficiency, despite the follow-up of 3 to 34 years. In an attempt to uncover the etiology of the disease in these patients, we carried out molecular analysis of the *AVP-NP11* gene. Although we found no mutation in the *AVP-NP11* gene in this series of DI patients, Rutishauser and cols. (10) previously reported a *de novo* *AVP-NP11* gene mutation in a patient with early onset of central DI and no family history, suggesting that genetic testing may be useful in patients who develop idiopathic DI during childhood.

While no mutation in the coding region was found, we identified a homozygous guanine insertion in intron 2 (IVS2 +28 InsG) in 4 patients. This insertion has also been described by Bahnsen and cols. (23) (GenBank access X62891) with a concomitant mutation in the coding region (Gly57Ser). As the authors performed direct gene sequencing in only one member of the kindred of 6 affected members, we do not know whether the G insertion was also present in their other patients or non-affected individuals, and the authors do not discuss this particular issue. Moreover, an error due to PCR/sequencing technique problems is less likely to account for our findings since the result was found in both, sense and antisense sequences as well as in repeated PCR experiments. Indeed, finding the G insertion in 3 out of 9 controls indicated that this variation might represent an alternative gene assembly that is unlikely to contribute to the *AVP-NP11* gene modulation (26).

The presence of vasopressin-secreting cell autoantibodies in association with pituitary stalk thickening suggests autoimmunity in almost 100% of patients with apparent idiopathic central DI (27). However, circulating human hypothalamus vasopressin-secreting cell autoantibodies have also been reported in patients with different causes of central DI (19,27-29), including Langerhans cell histiocytosis and germinoma; therefore, the presence of these antibodies may not be a reliable marker of autoimmune central DI (29). In the present

study, determination of autoantibodies to vasopressin secreting cells was not available, therefore, we could not rule out an autoimmune cause of central DI, especially in patient 6, who showed pituitary stalk thickness.

Although, pituitary stalk thickening in patients with central DI can be reversible and transient, as reported by De Buyst and cols. (24), the finding of pituitary stalk thickening in patients with central DI strongly indicates the need for long-term follow-up, since organic cause of central DI, such as germinoma and Langerhans cell histiocytosis, has been associated with isolated central DI with pituitary stalk thickening (18,30).

In the present study, brightness signal of the posterior lobe on magnetic resonance T1-weighted images was absent in five patients. The absence of posterior pituitary bright signal has been associated with central DI (31-33). On the other hand, presence of the signal may not indicate normal vasopressin secretion (31). Mahoney and cols. (34) studied the kindred with adFNDI by magnetic resonance imaging and showed the presence of the posterior pituitary hypertensive signal in all affected children, but an absent or barely visible signal in all adult patients but one, suggesting a progressive loss of the posterior pituitary signal in this inherited form of DI. In fact, three out of six patients in the current study presented a normal posterior pituitary signal, which disappeared later during follow-up, indicating progressive development of MRI features, similar to the decrease in AVP secretion (8).

It is important to point out that vascular abnormality should also be considered as a plausible cause of vasopressin deficiency in the present series of patients, since abnormal arterial blood flow affecting posterior pituitary blood supply has been previously described in patients with idiopathic central DI and normal anterior pituitary and pituitary stalk size with absence of posterior pituitary bright signal in the MRI (35).

In conclusion, we found a homozygous guanine insertion in intron 2 (IVS2 +28 InsG) in the *AVP-NP11* gene in DI patients as well as in controls, suggesting an alternative gene assembly that is unlikely to contribute to the *AVP-NP11* gene modulation. In addition, we confirm that the etiology of idiopathic central DI in children may not be apparent even after long-term follow-up, and requires continuous etiological surveillance.

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