Autoimmune central *diabetes insipidus* in a patient with ureaplasma urealyticum infection and review on new triggers of immune response

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SUMMARY

Diabetes insipidus is a disease in which large volumes of dilute urine (polyuria) are excreted due to vasopressin (AVP) deficiency [central *diabetes insipidus* (CDI)] or to AVP resistance (nephrogenic *diabetes insipidus*). In the majority of patients, the occurrence of CDI is related to the destruction or degeneration of neurons of the hypothalamic supraoptic and paraventricular nuclei. The most common and well recognized causes include local inflammatory or autoimmune diseases, vascular disorders, Langerhans cell histiocytosis (LCH), sarcoidosis, tumors such as germinoma/craniopharyngioma or metastases, traumatic brain injuries, intracranial surgery, and midline cerebral and cranial malformations. Here we have the opportunity to describe an unusual case of female patient who developed autoimmune CDI following ureaplasma urealyticum infection and to review the literature on this uncommon feature. Moreover, we also discussed the potential mechanisms by which ureaplasma urealyticum might favor the development of autoimmune CDI. Arch Endocrinol Metab. 2015;59(6):554-8

INTRODUCTION

Diabetes insipidus (DI) is a disabling and rather often severe disease in which large volumes of dilute urine (polyuria) are excreted due to posterior pituitary and antidiuretic hormone vasopressin (AVP) deficiency [central *diabetes insipidus* (CDI)], or to peripheral AVP resistance (nephrogenic *diabetes insipidus*). DI is accompanied by reactive polydipsia and very high risk of dehydration (1). The destruction or degeneration of neurons, originating in the hypothalamic supraoptic and paraventricular nuclei, produce the disease in the majority of patients. The main and well recognized causes of CDI (Table 1) include local inflammatory or autoimmune diseases, vascular disorders, Langerhans cell histiocytosis (LCH), sarcoidosis, germinoma/craniopharyngioma, metastases, trauma resulting from surgery or accidents, and midline cerebral, as well as cranial malformations (2). In rare cases, the underlying cause can be a genetic defect in AVP synthesis that could be inherited as autosomal dominant, autosomal recessive or X-linked recessive traits (1). Although CDI has been reported to be idiopathic in 30–50% of cases, the identification of antibodies against AVP-secreting neurons (3,4), as well as the use of more modern imaging techniques, have made the true idiopathic form an uncommon finding (2). Indeed, more recently, it has been noted that some patients in the acute phase develop lymphocytic infundibuloneurohypophysitis (LINH), suggesting that an autoimmune mechanism is involved in the development of the disease (5).

Here we first describe an unusual case of female patient, who developed autoimmune CDI and reactive arthritis, following ureaplasma urealyticum (UU) infection, and we took this opportunity to review the current literature concerning this type of DI. We finally discussed the potential mechanisms by which UU might have favored the development of CDI in this specific case.

Table 1. Causes of *diabetes insipidus*

Central	Nephrogenic
Surgery	***Drugs***
Transcranial NCH	Lithium
Transsphenoidal NCH	Ofloxacin
Cranial trauma/Brain injury	Demeclocycline
Primary tumors	Amphotericin B
Hypothalamic tumor	Aminoglycosides
Craniopharyngioma	Cisplatin
Meningioma	Cidofovir
Dysgerminoma	Foscarnet
Glioma	Didanosine
Haematologic disorders	Ifosfamide
Lymphoma	***Obstructive***
Leukemia	Sarcoma
Pituitary metastases	***Vascular***
Breast	Sickle cell disease and trait
Lung	Acute tubular necrosis
Prostate	***Metabolic***
NET	Severe hypercalcemia
Infections	Severe hypokalemia
Tuberculosis (meningitis)	***Infiltrative diseases***
Viral infections (meningitis)	Amyloidosis
Intracranial abscess	Sjögren's syndrome
Toxoplasmosis	***Granulomatous diseases***
Granulomatous diseases	Sarcoidosis
Tuberculosis (mass effect)	***Genetic***
Sarcoidosis	
Histiocytosis	
Inflammatory	
Systemic lupus erythematosus	
Scleroderma	
Wegener's disease	
Vascular	
Aneurysm	
Hypoxic encephalopathy	
Sheehan's syndrome	
Chemicals	
Snake venom	
Tetrodotoxin	
Autoimmune and idiopathic	
Genetic	

NCH: neurosurgery; NET: neuroendocrine tumors.

CASE REPORT

On January 2011, a 45 year-old-female was admitted for arthralgia, swelling and limited movement of hands, feet and knees lasting for 6 months. The patient was experiencing polydipsia, polyuria and nicturia since November 2010. Indeed, she was drinking about 7-8 L of water per day, and urinated every 1-2 hours at night with a daily urinary output of approximately 7 L. Urine specimens were cultured for aerobic bacterial species and examined by polymerase chain reaction-based assays for the presence of chlamydia trachomatis, mycoplasma hominis, ureaplasma parvum and UU. Among these latter, only UU was detected. Elevated serum antibody titer to UU was demonstrated and UU was isolated from the knee synovial fluid as well. Antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin, anti-β_2-glycoprotein-I and anti-phosphatidylserine antibodies, lupus anticoagulant (LAC), human leucocytes antigen (HLA)-B51, HLA-B27, rheumatoid factor test and anticitrulline antibodies, anti-thyroid peroxidase antibody, anti-thyroglobulin antibodies and thyroid-stimulating hormone receptor antibody were negative. Fasting blood glucose was 75 mg/dL, glycated hemoglobin (HbA1c) was 4.9% (reference value: 4.3-5.8%), urinalysis was unremarkable and did not show any evidence of glycosuria, which excluded the possibility of symptomatic *diabetes mellitus*. A further endocrinological assessment showed low level of antidiuretic hormone (AVP; 0.7 pg/mL) and normal levels of anterior pituitary hormones, as well as cortisol, free T3 and T4. The patient underwent the water deprivation test and plasma osmolality was 380 mosm/Kg, at baseline, while urine osmolality was 152 mosm/Kg. After 7 hours of water deprivation, plasma osmolality was 388 mosm/Kg and urine osmolality was 140 mosm/Kg. After the administration of five units of 1-deamino-8-D-arginine vasopressin (DDAVP), urine osmolality raised to 780 mosm/Kg, strongly indicating the presence of CDI. The diagnosis was confirmed by magnetic resonance (MR) imaging, which displayed the absence of classical posterior pituitary lobe hyperintensity in T1. Anti-pituitary antibodies (APAs) resulted negative while anti-hypothalamus antibodies (AHAs) were positive. AHAs and APAs were detected by simple indirect immunofluorescence method on cryostat sections of young baboon hypothalamus and pituitary, respectively, supplied by Biosystem Italia Srl (San Martino Buon Albergo, VR, Italy), as described previously (6). Finally, quantiferon tuberculosis gold test resulted negative and angiotensin-converting enzyme (ACE) was in the normal range. The diagnosis of an autoimmune CDI and reactive arthritis following UU infection was made and the patient started oral desmopressin (100 mcg at bedtime), experiencing a marked relief of polyuria, as well as polydipsia. Finally, the reactive arthritis was treated with doxycycline (100 mg twice daily for 14 days), followed by a single 2 g dose of azithromycin. Complete clinical remission of arthritis was achieved after ten days of tre-

atment. The patients signed an informed consent for the use of the data concerning the case.

DISCUSSION AND UPDATE UPON CURRENT LITERATURE

The identification of antibodies against AVP-secreting cells (AVPc) on the one hand (3), and the advances in imaging techniques on the other (4), have shed light on the pathophysiological aspects of CDI, making the idiopathic form a very uncommon condition. An autoimmune process involving the hypothalamic-neuroendocrine AVPc leading to CDI was initially suggested in the early 1980s by Scherbaum and Bottazzo (7). Subsequently, AVPc autoantibodies were detected in 37% of individuals affected by idiopathic CDI and in 6.3% of those with CDI associated with LCH, at a mean age of 34.9 years (4). Furthermore, Pivonello and cols. reported a relationship between AVPc autoantibodies and clinical, immunological and radiological features in about 23% of a large cohort of individuals with CDI of different etiologies at mean age of 29.2 years (8). All these findings confirm that autoimmune CDI most commonly affects female patients with associated autoimmune diseases. The evidence of pituitary stalk thickening, as well as the absence of classical posterior pituitary lobe hyperintensity in T1 at MR imaging, generally characterizes the radiologic features of these patients. Finally, AVPc autoantibodies have been reported in patients affected by autoimmune polyendocrinopathy (9), while pituitary stalk thickening and CDI have been described in the course of autoimmune polyglandular syndrome (2). The fact that AVPc autoantibodies are recognized in few patients seems to indicate either that they are subject to early disappearance or, possibly, that autoimmune T-cell local damage took place, not, however, necessarily associated with autoantibody formation (4). Indeed, Imura and cols. confirmed the immune-mediated pathogenesis of some cases of CDI using neuroimaging and histological assessment (5). These authors reported that an autoimmune process, affecting the posterior pituitary gland and infundibulum, without anterior pituitary involvement, could cause LINH. Furthermore, hypothalamic-neurohypophyseal autoimmune involvement seems to occur more commonly in children and young adults with idiopathic CDI (4). However, a high frequency of AVPc autoantibodies was observed in patients with LCH characterized by "activated antigen presenting cells" (in particular histiocytes) in the target-affected tissue (10). Patients with LCH and CDI presented radiological and immunological targets similar to those with idiopathic CDI, suggesting that both diseases may have a common pathogenesis. The hypothesis of an important role of autoimmunity in the pathogenesis of CDI is strengthened by the fact that the pituitary gland is susceptible to CD8+ T-cell-mediated autoimmunity, triggered by a cell-specific model autoantigen (11), as well as to the development of autoimmune hypophysitis through the immunization of female SJL/J mice with mouse pituitary extracts (12). Furthermore, LINH has been found associated also with autoimmune inflammatory disease of the pituitary gland, although the exact etiology remains unknown so far. The underlying process of pituitary stalk thickening in idiopathic CDI is not yet completely understood. The term LINH has been introduced to distinguish between children and adolescents with CDI (2), pituitary hormone deficiency, decrease in anterior pituitary size and transient and/or persistent pituitary stalk thickening and adult subjects with similar posterior pituitary findings at MR imaging, but normal size and function of the anterior pituitary (5). Mirocha and cols. reported two different potential pathogenic mechanisms (13). The first one apparently directed against self-antigens and known as "T-helper dominance", whereas the second one directed against non-self-antigens (i.e., post-infection mechanism). Both these mechanisms may favor primary hypophysitits.

However, LINH is considered a disease characterized by lymphocytic infiltration of the posterior lobe of the pituitary gland, resulting in clinically evident CDI. It has been suggested that an immune response, triggered by viral or bacterial infection, could be involved in the development of LINH. However, the viruses or bacteria that may commonly cause this disease have not yet been identified, probably because of the extremely low incidence. Kobayashi and cols. reported a case of CDI following probable type A/H1N1 flu infection (14). In this case, the autoimmune mechanism of LINH was hypothesized associated with novel flu sustained by A/H1N1 virus infection (14). Furthermore, cases of LINH after meningoencephalitis due to the type A flu virus, or herpes simplex virus, were previously reported (15). Hannon and cols. a retrospectively reviewed the databases from the endocrinology units of two tertiary referral centers, in England and Ireland, and identified 39 patients with CDI, who presented other autoimmune diseases, such as Hashimoto's thyroiditis, Graves' disease, type 1

diabetes mellitus and Addison's disease, including vitamin B12 deficiency secondary to Addisonian pernicious anaemia (16). These data were in line with an estimated overall incidence of 28-38% for associated autoimmune endocrine disease in autoimmune CDI, as defined by the presence of AVPc autoantibodies (8-10). Finally, in the present case, there was a temporal association between the UU infection and the onset of polyuria and polydipsia. To our knowledge, this is the first case of autoimmune CDI following UU infection. The pathogenic link remains obscure although an immunologic response to UU antigen may be associated with the generation of AVPc-specific antibodies, suggesting the presence of common antigenic epitopes in their structures, as reported for chlamydia trachomatis and human apolipoprotein B (17). In support of this hypothesis, infection with a pathogen sharing similar structures with autoantigens is one possibility of how pathogens might induce or accelerate autoimmunity. Such 'molecular mimicry', indeed, exists and has been detected between pathogens and autoantigens recognized by antibodies or T cells of patients with a broad variety of autoimmune diseases (18,19). Notably, an association between the infection with campylobacter jejuni and the Guillain Barré syndrome has been described as well (20). Indeed, campylobacter jejuni shares a structural homology of the lipo- oligosaccharide with the peripheral nerve GM1 ganglioside, and could be convincingly reproduced in an animal model (20). However, the best example of post-infectious autoimmunity due to molecular mimicry has been established for streptococcus pyogenes-induced acute rheumatic fever, where the lysoganglioside of the host shares a structural similarity to N-acetyl-b-D-glucosamine, the dominant epitope of the group A streptococcal carbohydrate (21). The occurrence of "molecular mimicry" between trigger and target seems to circumvent peripheral tolerance to the target antigen, resulting in the generation of a high frequency of target antigen--specific T cells, which surpasses a critical threshold for the induction, or the acceleration, of autoimmune diseases. However, besides genetic predisposition and environmental factors, local inflammation seems to play a key role in the transition from autoimmunity to autoimmune overt disease. Indeed, the balance between pro- and anti-inflammatory chemokines and cytokines, which determines the local inflammatory milieu, or the proportion of apoptotic and anti-apoptotic signals influencing the fate of a cell, the ratio between aggressive and regulatory T-lymphocytes might be as important as the absolute number of autoaggressive lymphocytes (22). The case we presently reported represents an example of pathogenetic autoimmune pathway induced by a cross-reactive immune response following UU, and confirms that autoimmune CDI may be included among the potential clinical manifestations of cross-reactive response in individuals exposed to UU infection.

TREATMENT OF CENTRAL *DIABETES INSIPIDUS*

The drug of choice for the treatment of CDI is DDAVP (desmopressin). Given intranasally or currently more often orally, maximum plasma concentration is reached in about 40-55 minutes and its half-life is about 3-5 hours. The intravenous route is only used in case of disabled patients, coma, or other condition contraindicating or impeding the other modalities of treatment. Orally daily dosages may vary from 100 to 1200 μg (once or twice a day). Symptomatic dilution hyponatremia is a potential hazard if desmopressin is administered in excess over a long period. Symptoms of hyponatremia include headache, nausea, vomiting, seizure and, in untreated cases, coma and death. Notably, extrapontine myelinosis may occur in multidrug treated individuals (23). Corticosteroid treatment of LINH gave conflicting results (14). However, starting corticosteroid therapy as soon as possible seems to improve more rapidly the clinical picture of CDI (14). It is advisable to start treatment within 2 months from symptom onset. Indeed, Kajiyama and cols. described a case of a patient with clinical autoimmune CDI associated with systemic lupus erythematosus (SLE) and dermatomyositis (24). After treatment with intravenous cyclophosphamide and concomitant oral prednisone, AVPc antibodies disappeared, CDI improved and vasopressin replacement therapy was completely withdrawn. Finally, TNF-α inhibitors appeared efficient in the treatment of chronic immune-mediated or inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis, psoriasis and/or psoriatic arthritis (25-31). Which may be their potential effectiveness in treating autoimmune CDI, is a question that remains unanswered so far. However, tumor necrosis factor-α inhibitors may represent a new frontier in the treatment of autoimmune CDI associated with systemic autoimmune diseases.

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