Central Diabetes Insipidus and Autoimmunity: Relationship between the Occurrence of Antibodies to Arginine Vasopressin-Secreting Cells and Clinical, Immunological, and Radiological Features in a Large Cohort of Patients with Central Diabetes Insipidus of Known and Unknown Etiology

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Central diabetes insipidus (CDI) is a rare hypothalamus-pituitary disease due to the deficiency of arginine vasopressin (AVP) synthesis from the hypothalamus and/or secretion from the neurohypophysis. The etiology of CDI is unknown in over one third of cases, classified as idiopathic CDI. The aim of this study was 2-fold: 1) to evaluate the occurrence of circulating autoantibodies to AVP-secreting cells (AVPcAb), and 2) to correlate it to clinical (sex, age of disease onset, disease duration, and degree), immunological (clinical history of autoimmune diseases and presence of organ-specific autoantibodies), and radiological features (neurohypophyseal bright spot, pituitary stalk thickening, and empty sella) in a large cohort of patients with apparently idiopathic CDI or CDI of known etiology. To this purpose, 150 patients with CDI were studied: 64 idiopathic, 6 familial, 12 associated to granulomatous diseases, and 68 secondary to cranial trauma, tumor, or surgery. AVPcAb were measured by an indirect immunofluorescence method. AVPcAb were found in 23.3% of CDI patients: 21 idiopathic (32.8%); and 14 nonidiopathic (16.3%; χ² = 13.1; P < 0.001). AVPcAb were independently associated with age less than 30 yr at disease onset (P = 0.001) in patients with idiopathic CDI and with history of autoimmune diseases (P = 0.006 and P = 0.02, respectively) and radiological evidence of pituitary stalk thickening (P = 0.02 and P = 0.003, respectively) in both idiopathic and nonidiopathic CDI. The likelihood of autoimmunity in one patient with apparently idiopathic CDI with age of disease onset less than 30 yr was 53%, it increased to 91% when history of autoimmune diseases was associated and to 99% when pituitary stalk thickening was further associated. In conclusion, autoimmunity is associated with one third of patients with apparently idiopathic CDI, which should therefore be classified as autoimmune CDI. Autoimmune CDI is highly likely in young patients with a clinical history of autoimmune diseases and radiological evidence of pituitary stalk thickening. Conversely, autoimmunity probably represents an epiphenomenon in patients with nonidiopathic CDI. (J Clin Endocrinol Metab 88: 1629–1636, 2003)

Central diabetes insipidus (CDI) is a rare hypothalamus-pituitary disease due to the deficiency of arginine vasopressin (AVP) synthesis from the hypothalamus and/or secretion from the neurohypophysis (1, 2). It is mainly characterized by a polyuria-polydipsia syndrome (1, 2), although it was also found to be associated with skeletal damage and cardiac dysfunction (3, 4). The etiology of CDI includes a familial form and forms secondary to cranial trauma, tumor, surgery, or neurohypophyseal granulomatous diseases (1, 2, 5, 6). However, the etiology of CDI remains unknown in over one third of cases, classified as idiopathic CDI (1, 2, 5, 6).

Autoimmunity has been found to be the cause of several endocrine diseases previously classified as idiopathic disease. These immunoendocrine diseases are usually defined by deficiency of a specific hormone and the presence of circulating autoantibodies to the hormone-producing cells (7). CDI has been associated in a proportion of cases with autoantibodies to AVP-secreting cells (AVPcAb) (8, 9). On the other hand, besides the absence of the physiological neurohypophyseal hyperintense signal or bright spot, which is feature of CDI regardless of etiology (10), various morphological abnormalities of the hypothalamus-pituitary region were found at radiological examination in CDI patients of different etiologies (11). However, no specific clinical, immunological, and/or radiological pattern has been unequivocally associated with autoimmunity in patients with CDI.

The aim of the current study was 2-fold: 1) to evaluate the presence of circulating AVPcAb in a large series of patients with CDI of unknown etiology (apparently idiopathic CDI)
in comparison with patients with CDI of known etiology (or nonidiopathic CDI) to estimate the prevalence of autoimmune CDI in this category of patients, and 2) to correlate AVPcAb to clinical, immunological, and radiological features of these patients in attempt to identify a specific pattern associated with autoimmunity in patients with CDI.

**Subjects and Methods**

**Subjects**

One hundred fifty patients (52 males and 98 females, aged 10–60 yr) with a diagnosis of CDI admitted to our departments during the last 15 yr entered the study after their informed consent had been obtained, and the study protocol had been approved by the local ethical committee. Among the 150 patients, 6 had familial CDI, 12 had CDI associated with granulomatous disease (histiocytosis X in 9 cases and sarcoidosis in 3 cases), and 68 had CDI secondary to cranial trauma (4 cases), tumor (12 cases), or surgery (52 cases); the remaining 64, in whom no etiology had been found, were diagnosed as idiopathic CDI. These patients with apparently idiopathic CDI were tested for the possible presence of autoimmune CDI. Therefore, the prevalence of AVPcAb was evaluated in this category of patients and compared with that in patients with non-idiopathic CDI.

**Diagnostic protocol**

All patients presented with a polydipsia-polyuria syndrome with urinary specific weight below the normal range. The diagnosis of DI was suspected on the basis of clinical syndrome and urinary and plasma osmolality (1, 12). To confirm the diagnosis of CDI, all patients underwent a dehydration test, followed by a desmopressin administration test (1, 12). During the test, plasma and urinary samples were collected hourly, starting at 0800 h, for the determination of plasma and urinary osmolality. Body weight, urinary volume, and cardiovascular parameters were also evaluated at each determination of plasma and urinary osmolality. The procedure was continued until steady state urinary osmolality was achieved (variation in urinary osmolality of <30 mosmol/liter in three consecutive hourly urine samples) or until a decrease in absolute body weight of more than 5% was observed. At the end of the dehydration period, the patients underwent an im administration of 1 μg desmopressin (Minirin, Ferring Pharmaceuticals Ltd., Limhamn, Sweden) with evaluation of urinary osmolality every 30 min for 2 h. An increase of more than 10% in urinary osmolality after desmopressin administration was considered to be diagnostic for CDI (1, 12). An increase in urinary osmolality of more than 50% or between 10–50% after desmopressin injection allowed the diagnosis of complete or partial CDI, respectively (1, 12). In the series of patients included in the current study, 112 (74.7%) had complete CDI, whereas the remaining 38 (25.3%) had partial CDI. In 80 of the 150 patients, the diagnosis of CDI was confirmed by the evaluation of plasma AVP levels after the dehydration test; an absent or subnormal AVP response to the water deprivation test under conditions of plasma osmolality above the normal range were confirmatory of complete or partial CDI, respectively (13). Plasma AVP levels were measured by RIA (14) using a Medical System (Genova, Italy) kit. The normal range of plasma AVP response to the water deprivation test was estimated as the mean ± 2 so of the results obtained when a dehydration test was performed on 40 healthy subjects (mean ± 2 so, 6.8 ± 3.4 pmol/liter; range, 3.9–9.8 pmol/liter). Plasma AVP levels below 3.4 pmol/liter after a dehydration test were considered suggestive of CDI. In patients of the current study the mean plasma osmolality and plasma AVP after dehydration test were, respectively, 295 ± 0.2 mosmol/liter and 2.5 ± 0.04 pmol/liter. In all patients the diagnosis of CDI was further confirmed by the evidence of normalization of water balance without onset of symptoms and signs of water intoxication after 2 d of desmopressin treatment at standard doses (25 μg twice a day, intranasally) (13). In patients who had CDI diagnosis more than 10 yr before the study, the diagnosis were reconfirmed repeating all appropriate diagnostic procedures after 3-d withdrawal of replacement treatment with desmopressin to make the diagnostic procedures homogeneous for all patients according to the recent criteria. At the time of diagnosis, age of disease onset and disease duration were evaluated in each patient on the basis of the start of the polyuria-polydipsia syndrome. In the current series the age of disease onset ranged 10–60 yr, whereas disease duration ranged 1–48 months. The patients’ profiles are shown in Table 1.

**Study protocol**

All patients were submitted to 1) measurement of circulating AVPcAb; 2) accurate anamnesis, to collect clinical data (sex, age of disease onset, and disease duration and degree) and disclose a possible history of autoimmune diseases; 3) measurement of the most common autoantibodies to hormone-secreting cells; 4) magnetic resonance imaging (MRI) of the hypothalamus-pituitary region, to study the neurohypoph-

**TABLE 1a.** Clinical, immunological, and radiological features of patients with CDI of different etiology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Whole CDI series</th>
<th>Idiopathic CDI</th>
<th>Nonidiopathic CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>150</td>
<td>64</td>
<td>86</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>52/98</td>
<td>19/45</td>
<td>33/33</td>
</tr>
<tr>
<td>Age of disease onset (yr)</td>
<td>29.2 ± 2.2</td>
<td>30.3 ± 3.6</td>
<td>29.8 ± 3.0</td>
</tr>
<tr>
<td>Disease duration</td>
<td>5.2 ± 1.3</td>
<td>5.0 ± 1.6</td>
<td>5.3 ± 1.0</td>
</tr>
<tr>
<td>Disease degree (C/P)</td>
<td>112/38</td>
<td>47/17</td>
<td>65/21</td>
</tr>
<tr>
<td>Immunological features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune diseases [n (%)]</td>
<td>26 (17.3%)</td>
<td>21 (32.8%)</td>
<td>15 (17.4%)</td>
</tr>
<tr>
<td>Endocrine autoantibodies [n (%)]</td>
<td>49 (32.7%)</td>
<td>40 (64.9%)</td>
<td>19 (22.1%)</td>
</tr>
<tr>
<td>Radiological features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of bright spot [n [%]]</td>
<td>120 (80%)</td>
<td>50 (78.1%)</td>
<td>70 (81.4%)</td>
</tr>
<tr>
<td>Pituitary stalk thickening [n [%]]</td>
<td>20 (13.3%)</td>
<td>10 (15.6%)</td>
<td>10 (11.6%)</td>
</tr>
<tr>
<td>Empty sella [n [%]]</td>
<td>22 (14.7%)</td>
<td>5 (7.8%)</td>
<td>17 (19.8%)</td>
</tr>
<tr>
<td>Circulating AVPcAb</td>
<td>35 (23.3%)</td>
<td>21 (32.8%)</td>
<td>14 (16.3%)</td>
</tr>
</tbody>
</table>

m, Male; f, female.

* Autoimmune diseases detected in the patients included autoimmune hypopituitarism (1.3%) and hypogonadism (2.7%), Hashimoto thyroiditis (16.7%), Graves’ disease (2.0%), Addison’s disease (2.7%), diabetes mellitus type I (5.3%), myasthenia gravis (1.3%), vitiligo (2.0%), and atrophic gastritis (2.0%).

* Endocrine autoantibodies detected in the patients included anterior pituitary cell (15.3%), adrenal and gonadal steroid-secreting cell (2.7%), islet cell (5.3%), glutamic acid decarboxylase (5.3%), transmembrane protein tyrosine phosphatase-like molecule (5.3%), thyroperoxidase and thyroglobulin (22.7%), and TSH receptor autoantibodies (2.0%).
Circulating thyroid cell autoantibodies (thyroperoxidase and thyroglobulin antibodies) were measured by RIA using a Radim (Pomezia, Italy) kit. TSH receptor antibodies in patients with Graves’ disease were assayed by RIA using a Sorin (Saluggia, Italy) kit.

Immunological study

Circulating cytoplasmic AVPcAb were determined using an indirect immunofluorescence method (8, 9, 15). In particular, unfixed cryostat sections of young normal baboon hypothalamus were initially incubated with the sera. Fluorescein isothiocyanate (FITC)-conjugated goat antihuman immunoglobulins (Ig) and sera diluted 1:40 were used to detect the presence of antibodies to hypothalamic cells. The positive serum samples were subsequently tested with FITC-conjugated goat antihuman IgG, IgM, and IgA sera separately. Fresh normal human serum and FITC-conjugated goat antihuman complement factors diluted 1:40 were used to exclude nonspecificity or detect the presence of complement-fixing antibodies. Furthermore, the positive serum samples were tested with specific rabbit anti-AVP serum and rhodamine-conjugated goat antirabbit Ig and serum to prove that the antibodies specifically recognize the AVP-secreting cells. Finally, preabsorption of sera by rat liver acetone powder was performed to exclude other organ nonspecific reactivity in detecting all mentioned antibodies. Two known positive and two known negative sera were chosen for internal controls and included in each series. AVPcAb were measured in 150 healthy subjects, and results were negative in all cases. These subjects served as negative controls for the evaluation of AVPcAb. The levels of AVPcAb (exclusively IgG) were considered positive starting at a dilution of 1:2 and were expressed as the end-point dilution titer; levels below 1:8 were considered at low titer, whereas levels of 1:8 or more were considered at high titer. Anterior pituitary cell autoantibodies were measured by a standard indirect immunofluorescence method using unfixed cryostat sections of young baboon pituitary gland (16). Adrenal cell and gonadal steroid-secreting cell autoantibodies were measured by a conventional immunofluorescence method using unfixed cryostat sections of normal monkey adrenal gland and gonads, respectively (17). Islet cell autoantibodies were detected by an indirect immunofluorescence method (18) on unfixed cryostat sections of group 0 blood human pancreas according to the protocol of the Third International Workshop of Standardization of Islet Cell Antibodies (19). Preabsorption of sera with rat liver acetone powder was performed to exclude organ nonspecific reactivity in detecting all of the mentioned antibodies. Positive and negative control serum samples were also included for every antibody. All sera were tested blindly three times, and two investigators (A.D.B. and A.B.) evaluated the results in a double-blind manner. Assays to detect autoantibodies to glutamic acid decarboxylase and the transmembrane protein tyrosine phosphatase-like molecule IA-2 have been also performed in patients with type 1 diabetes mellitus by a solid phase RIA using human recombinant IA-2 and recombinant tyrosine phosphatase-like molecule 65 and [35S]CAS12, respectively (20). Circulating thyroid cell autoantibodies (thyroperoxidase and thyroglobulin antibodies) were measured by RIA using a Radim (Pomezia, Italy) kit. TSH receptor antibodies in patients with Graves’ disease were assayed by RIA using a Sorin (Saluggia, Italy) kit.

Radiological study

MRI of the hypothalamus-pituitary region was performed with a 0.5 T Vectora scanner (General Electric, Milwaukee, WI) using T1-weighted gradient echo acquisitions (repetition time, 250 msec; echo time, 12 msec; flip angle, 90°; four signal averages) in the sagittal and coronal planes. In each measurement seven slices were obtained, centered on posterior pituitary and pituitary stalk region. The slices were 3 mm thick, with an in-plane spatial resolution of 0.94 mm (180 × 240 mm² field of view, 192 × 295 matrix in the sagittal acquisitions; 150 × 180 mm² field of view, 160 × 192 matrix in the coronal acquisitions). These acquisitions were repeated before and after the administration of 0.1 mm/kg body weight gadolinium diethylene-triamine pentacetate, analyzing the perfusion with a temporal resolution of 57 sec. The study of MRI of the hypothalamus-pituitary region was focused on three features: 1) the presence or absence of the neurohypophyseal bright spot; 2) the presence or absence of a pituitary stalk thickening, and 3) the presence or absence of an empty sella. Pituitary stalk thickening was defined when the maximum transverse dimension of the pituitary stalk was above 3.25 mm at the level of the optic chiasm or above 1.91 mm at the insertion of the neurohypophysis (21). Evaluation of MRI data was performed twice by one operator (F.D.S.), who was blind with respect to the CDI etiology of the patients in the current study.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 9.0 (SPSS, Inc., Chicago, IL). The comparison between continuous and categorical parameters was performed using ANOVA and χ² test, respectively. A logistic regression analysis was performed to identify the clinical, immunological, and/or radiological parameters independently associated with AVPcAb. The clinical parameters included gender (male/female), age of disease onset (<30 yr), disease duration (<5 months), and disease degree (complete/partial). The immunological parameters included the detection of autoimmunity diseases or circulating endocrine autoantibodies (presence/absence). The radiological parameters included the detection of neurohypophyseal bright spot, pituitary stalk thickening and empty sella (presence/absence). The two categories considered for age of disease onset and disease duration were chosen considering the median value of the two parameters in the series of patients in the current study.

On the basis of the results of the logistic regression analysis, the likelihood of an association between one or more parameters and the presence of AVPcAb was calculated using the following formula: 1/(1 + e⁻x), where "x" is the sum of the products of the coefficients (β) and the individual predictor values. Nonparametric tests were used to compare the continuous variables. The χ² test was used to analyze the categorical variables.
where \( z \) is the linear combination \( B_0 + B_1X_1 + B_2X_2 + \ldots + B_nX_n \), \( B_0, B_1, B_2 \ldots \) and \( B_n \) are coefficients estimated from the data for each independent variable \( X \). The likelihood of an association between one or more parameters, progressively added to the previous one, and the presence of AVPcAb was calculated on the basis of the Bayes theorem using the following formula: prevalence \times \text{sensitivity} / (\text{prevalence} \times \text{sensitivity}) + [(1 - \text{prevalence}) \times (1 - \text{specificity})]. Data were expressed as a percentage or as the mean \( \pm \text{SEM} \). Significance was set at 5%.

**Results**

The most important clinical, immunological, and radiological features of the general population of CDI patients are summarized in Table 1a. Circulating AVPcAb were found in 35 of 150 (23.3%) patients (Table 1a). Particularly, AVPcAb were detected in 32.8% of patients with idiopathic and in 16.3% of patients with nonidiopathic CDI (\( \chi^2 = 13.1; P < 0.001 \)) and were present in 50% of CDI associated with granulomatous diseases (66.7% of patients with histiocytosis X) and 11.8% of CDI secondary to cranial trauma, tumor, or surgery (15.4% of patients with CDI secondary to surgery), but in none of the patients with familial CDI (Table 1a). The AVPcAb titer ranged from 1:32 to 1:2, without a significant difference among patients with idiopathic and nonidiopathic CDI (Fig. 1). However, AVPcAb titers were significantly different in patients with idiopathic CDI or CDI associated with histiocytosis X and those with CDI secondary to surgery (\( P < 0.05 \); Fig. 1).

**Idiopathic CDI**

The most important clinical, immunological, and radiological features of idiopathic CDI patients are summarized in Table 1a. Circulating AVPcAb were found in 21 of 64 patients (32.8%; Table 1). The AVPcAb titer was high in 16 patients (76.2%) and low in the remaining 5 (23.8%) patients (Fig. 1). In 19 patients (29.7%), it was associated with other autoimmune manifestations (presence of different autoimmune diseases and/or autoantibodies). On the other hand, AVPcAb were negative in 11 patients (17.2%) with presence of autoimmune manifestations (presence of autoimmune thyroid diseases or type I diabetes mellitus and/or thyroid and islet cell autoantibodies). AVPcAb were significantly associated with female gender (\( P = 0.008 \)), age of disease onset less than 30 yr (\( P < 0.001 \)), disease duration more than 5 months (\( P < 0.001 \)), complete CDI (\( P = 0.005 \)), history of autoimmune diseases (\( P < 0.001 \)), presence of endocrine autoantibodies (\( P < 0.001 \)), absence of neurohypophyseal bright spot (\( P = 0.02 \)), and presence of pituitary stalk thickening (\( P < 0.001 \)). No association was found between AVPcAb and empty sella. At the logistic regression analysis, the parameters significantly and independently associated with AVPcAb were history of autoimmune diseases, age of disease onset less than 30 yr, and pituitary stalk thickening (Table 2). On the basis of the logistic regression analysis, the isolated presence of age of disease onset less than 30 yr, history of autoimmune disease, or pituitary stalk thickening was associated with 25.6%, 27.8%, and 25.3% likelihoods of positive AVPcAb, respectively. Two of the three parameters mentioned above were associated with a 80–82% likelihood, whereas all three parameters were associated with a 99% likelihood of AVPcAb positivity (Table 2). On the basis of the Bayes theorem, an age of disease onset less than 30 yr, independently from any other parameter, was associated with AVPcAb with a probability of 53%; this probability increased 91% when history of autoimmune diseases was associated and to 99% when pituitary stalk thickening was also associated (Fig. 2).

**Nonidiopathic CDI**

The most important clinical, immunological, and radiological features of nonidiopathic CDI patients are summarized in Table 1a and b. AVPcAb were found in 14 of 86 patients (16.3%). However, they were present in 50% of patients with CDI associated with granulomatous diseases; 11.8% of patients with CDI secondary to cranial trauma, tumor, or surgery; and none of the patients with familial CDI (Table 1a). When patients with CDI associated with granulomatous diseases or CDI secondary to trauma, tumor, or surgery were divided into the different subgroups, AVPcAb...
were found in 66.7% of patients with histiocytosis X, in 15.4% of patients with CDI secondary to surgery, and in none of the patients in the other subgroups (Table 1b). The AVPcAb titer was high in all patients with histiocytosis X and low in all patients with CDI secondary to surgery except for 2, who had a borderline titer of 1:8. In 10 patients (11.6%) with nonidiopathic CDI (4 with CDI associated with histiocytosis X and 6 with CDI secondary to surgery) AVPcAb were associated with other autoimmune manifestations. On the other hand, AVPcAb were negative in 5 (5.8%) patients (1 with CDI associated with histiocytosis X, 3 with CDI secondary to tumor, and 1 with CDI secondary to surgery) with other autoimmune manifestations. The autoimmune manifestations found in the group of patients with nonidiopathic CDI were mostly represented by autoimmune thyroid diseases and type I diabetes mellitus and/or thyroid and islet cells autoantibodies; pituitary autoimmunity was only detected in 3 (33.3%) patients with CDI associated with histiocytosis X and in 6 (11.5%) patients with CDI secondary to surgery. AVPcAb were significantly associated with female gender ($P = 0.013$), history of autoimmune diseases ($P = 0.009$), presence of endocrine autoantibodies ($P = 0.005$), and pituitary stalk thickening ($P = 0.001$). At the logistic regression analysis, history of autoimmune diseases and pituitary stalk thickening were the only parameters independently associated with AVPcAb (Table 2). However, when patients with CDI associated with granulomatous disease and CDI secondary to trauma, tumor, or surgery were analyzed separately, these associations were confirmed for the first, but not for the second, group of patients.

**Discussion**

Firstly, the results of the current study demonstrated that neurohypophyseal autoimmunity represents a common aspect of CDI; it is associated with 33% of CDI di-

**TABLE 2.** Results of the stepwise multivariate logistic regression analysis in patients with idiopathic and nonidiopathic CDI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B</th>
<th>SE (B)</th>
<th>R</th>
<th>Exp (B)</th>
<th>CI (Exp B)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic CDI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of disease onset $&lt;$ 30 yr</td>
<td>2.4700</td>
<td>0.9531</td>
<td>0.2413</td>
<td>11.8219</td>
<td>3.689–22.752</td>
<td>0.0096</td>
</tr>
<tr>
<td>Clinical history of autoimmune diseases</td>
<td>2.5829</td>
<td>0.9486</td>
<td>0.2585</td>
<td>13.2354</td>
<td>2.920–20.724</td>
<td>0.0065</td>
</tr>
<tr>
<td>Radiological evidence of pituitary stalk thickening</td>
<td>2.4580</td>
<td>1.0531</td>
<td>0.2063</td>
<td>11.6909</td>
<td>1.901–21.347</td>
<td>0.0196</td>
</tr>
<tr>
<td><strong>Nonidiopathic CDI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical history of autoimmune diseases</td>
<td>1.6355</td>
<td>0.7339</td>
<td>0.2015</td>
<td>5.1321</td>
<td>0.620–9.644</td>
<td>0.0258</td>
</tr>
<tr>
<td>Radiological evidence of pituitary stalk thickening</td>
<td>2.3133</td>
<td>0.7683</td>
<td>0.3110</td>
<td>10.1077</td>
<td>3.527–16.688</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

B, Logistic regression coefficient; SE (B): SE of the logistic regression coefficient; R, correlation coefficient; Exp (B), odds ratio of the logistic regression coefficient; CI (Exp B), 95% confidence interval of the odds ratio of the logistic regression coefficient.

**FIG. 2.** Flow chart illustrating the relationship between clinical, immunological, and radiological characteristics and the probability of neurohypophyseal autoimmunity in patients with idiopathic CDI according to the Bayes theorem. Starting from a baseline probability of 32.8% (the prevalence of circulating AVPcAb in our study population), the addition of the characteristics significantly and independently associated with autoimmunity increases this probability up to 99%.
agnosed as idiopathic and 66.7% of CDI secondary to histiocytosis X, although it is only sporadically associated with CDI secondary to surgery and is never associated with familial CDI.

The high incidence of AVPcAb in apparently idiopathic CDI, which does not have a known etiology, strongly suggests that an autoimmune process may be the actual cause of a great proportion of these patients, at least the one third of cases associated with circulating AVPcAb. Indeed, in line with classical endocrine autoimmune diseases, the autoimmune process against hypothalamic AVP-secreting cells should be characterized by AVP deficiency and circulating autoantibodies to AVP-secreting cells (8, 9), as found in these cases of CDI, suggesting that in a large series of patients with CDI, a subgroup with autoimmune CDI should be identified. The natural history of autoimmune CDI has been recently studied in a group of patients initially without overt CDI but presenting with an autoimmune disorder associated with AVPcAb (22). According to this study, autoimmune CDI evolve through three functional stages. The only common feature of all three stages is the presence of AVPcAb. Posterior pituitary function is normal in stage 1, partially insufficient in stage 2, and totally insufficient in stage 3 (22). This evidence suggests that an autoimmune process for AVP-secreting cells progressively induces global damage of the hypothalamic regions involved in AVP secretion, leading to complete CDI. Pituitary changes at the radiological examination strictly follow the clinical and immunological changes; the neurohypophyseal bright spot is present in the early stages of subclinical or partial CDI and progressively disappears with the development of complete CDI (22). The present study has been designed as a transversal study and therefore gives a static picture of the clinical, immunological, and radiological features of patients with CDI at the diagnosis of the disease. Indeed, this may explain the relatively high prevalence of partial CDI and the presence of a neurohypophyseal bright spot, because these findings are common at the early stage of CDI (22). Most of these patients would have complete CDI and complete disappearance of the bright spot at later stages of the disease. However, evaluation of the longitudinal behavior of clinical, immunological, and radiological features of these patients has been described in previous studies (22, 23).

The second important message of the current study is that autoimmune CDI is associated with specific clinical, immunological, and radiological features in patients with idiopathic CDI. Indeed, AVPcAb were significantly and independently associated with age of disease onset less than 30 yr, clinical history of autoimmune diseases, and radiological evidence of pituitary stalk thickening.

The association between age of disease onset less than 30 yr and AVPcAb suggests that autoimmunity may cause CDI especially in young subjects and particularly in young women, given the relative association between female gender and AVPcAb. These findings are in agreement with the epidemiological profile of autoimmune disorders, which frequently occur in young women (24, 25). The likelihood that a subject with idiopathic CDI and age of disease onset less than 30 yr with no history of autoimmune diseases or pituitary stalk thickening has autoimmune CDI is 25.6%. It is noteworthy, however, that in idiopathic CDI an age of disease onset less than 30 yr, independently from any other parameter, is associated with a 53% probability of having autoimmune CDI. This evidence strongly demonstrated the importance of age of disease onset as an epidemiological factor for autoimmune CDI.

The association between history of autoimmune diseases and AVPcAb suggests that a general predisposition to autoimmunity is present in subjects developing autoimmune CDI. This is confirmed by the existence of pluri-systemic autoimmune disorders (7), and it is in line with the described association between polyendocrine autoimmune disorders and idiopathic CDI (9). The likelihood that history of autoimmune disease, in the absence of age of disease onset less than 30 yr and pituitary stalk thickening, is associated with an autoimmune CDI is 27.8%. However, a history of autoimmune disease in a patient with age of disease onset less than 30 yr, with or without pituitary stalk thickening, is associated with autoimmunity with a likelihood of 82–91%. This evidence suggests that a history of autoimmune disorders in patients with idiopathic CDI might be considered a marker suggestive of autoimmune CDI. Similarly, a history of autoimmune disease in patients without CDI may be a risk factor, especially in young women, for developing autoimmune CDI (26).

Presently, the diagnosis of autoimmune CDI is based on the presence of AVPcAb or the coexistence of autoimmune polyendocrine syndromes, although it can be also suggested by the presence of lymphocytic neurohypophysitis, usually expressing with radiological evidence of pituitary stalk thickening (23). In the current study AVPcAb were found in 33% of patients with apparently idiopathic CDI, among whom 29% also had other autoimmune manifestations. The absence of autoimmune manifestation in the 4% of cases with CDI and AVPcAb suggests that in those cases, CDI may represent the first autoimmune disorders and that those patients are at higher risk to develop other autoimmune diseases. It has to be outlined that 17% of patients without AVPcAb also had other autoimmune manifestations. This finding is only apparently surprising considering that the autoimmune manifestations of these patients are mostly represented by autoimmune thyroid diseases and/or thyroid autoantibodies, which are relatively common in the normal population. Therefore, although the presence of autoimmune CDI in these patients is not likely, the possibility that a cell-mediated, rather than an antibody-mediated, autoimmune process to the hypothalamus is the origin of CDI cannot be completely ruled out. Until this autoimmune mechanism, independent of the presence of AVPcAb, has been clearly demonstrated, these cases should be considered idiopathic CDI.

The association between radiological evidence of pituitary stalk thickening and AVPcAb suggests that lymphocytic neurohypophysitis may be the pathological counterpart of autoimmune CDI. In fact, the pathological basis of autoimmune CDI has never been completely clarified. However, lymphocytic neurohypophysitis was suggested in several cases of idiopathic CDI on the basis of histological features of the neurohypophysis, similar to those found in adenohypophysitis affected by lymphocytic adenohypophysitis and in
other endocrine glands affected by an autoimmune disorder (27). This evidence strongly supports the hypothesis that most patients with idiopathic CDI have lymphocytic neurohypophysitis, possibly due to an autoimmune process. Therefore, as lymphocytic neurohypophysitis is radiologically characterized by pituitary stalk thickening (28), it can be hypothesized that this feature is the expression of autoimmune lymphocytic neurohypophysitis in idiopathic CDI. The likelihood that pituitary stalk thickening, in the absence of disease onset less than 30 yr and history of autoimmune diseases, is associated with autoimmune CDI is 25.3%, but this likelihood increases to 80–82% in the presence of age of disease onset less than 30 yr or history of autoimmune diseases. These findings demonstrated that pituitary stalk thickening in patients with idiopathic CDI may be considered a diagnostic marker suggestive of autoimmune CDI.

It is important to emphasize that the presence of all three parameters independently associated with AVPcAb, namely, age of disease onset less than 30 yr, history of autoimmune diseases, and radiological evidence of pituitary stalk thickening, is associated with a 99% probability of autoimmune CDI. This evidence suggests that the diagnosis of autoimmune CDI may be strongly suspected by accurately examining the patients’ clinical characteristics and history and by a standard MRI of the hypothalamus-pituitary region. The diagnosis of autoimmune CDI is highly likely in patients with idiopathic CDI younger than 30 yr and with a history of autoimmune diseases and pituitary stalk thickening. The measurement of circulating AVPcAb might thus be considered a helpful test only in cases with one or two of these clinical, immunological, and/or radiological parameters to disclose or confirm the presence of neurohypophysial autoimmunity.

The diagnosis of autoimmune CDI may be accurately performed at any stage of the disease. Indeed, a recent longitudinal study performed in patients with autoimmune and idiopathic CDI demonstrated that although the hypothalamus-pituitary stalk thickening usually improves or disappears after long-term disease, AVPcAb, which are frequently present at high titer in recent phases, persist subsequently, although at lower titer, for several years after disease onset (23). On the other hand, the absence of AVPcAb at the onset of apparently idiopathic CDI is able to exclude the subsequent appearance of these antibodies and, consequently, autoimmune CDI.

However, the importance of an early diagnosis of autoimmune CDI is demonstrated by two findings: 1) although spontaneous remission was demonstrated (29), patients with CDI associated with neurohypophysial autoimmunity, if untreated, acquire persistent and frequently progressively worsening CDI (22); and 2) early desmopressin treatment was reported to stop or even regress the neurohypophysial autoimmune process and neurohypophysial damage in patients with preclinical or clinically partial CDI (22). These findings are in line with the concept of isohormonal therapy, a strategy of immunomodulatory therapy using hormonal products of the target organ to influence autoimmunity in the preclinical stage of the disease when the target gland is not yet completely and irreversibly destroyed (30). This treatment may act by feedback inhibition of glandular function, by determining the suppression of autoimmunity, or by a combination of both mechanisms (30). However, although the isohormonal therapy was demonstrated to be successful in Addison’s disease (31, 32), it was failed in type I diabetes mellitus (33, 34). On the basis of this evidence, the effectiveness of isohormonal therapy in endocrine autoimmune diseases, particularly in CDI, is a fascinating hypothesis that needs to be definitively demonstrated.

The third important finding of the current study is that autoimmune to hypothalamic AVP-secreting cells may be present in a large percentage of patients with CDI associated with histiocytosis X as well as in a small percentage of patients with CDI secondary to neurosurgery for sellar lesions. Similarly to idiopathic CDI, patients with nonidiopathic CDI have been tested for the presence of AVPcAb at diagnosis, thus during the early rather than the late phase of the disease. This may explain the relatively high percentage of partial CDI with radiological persistence of the neurohypophysial bright spot. Conversely, the relatively high percentage of autoimmune disorders or autoantibodies in these patients is only apparent because they are mostly represented, as in the group of AVPcAb-negative idiopathic CDI, by, respectively, autoimmune thyroid diseases and thyroid autoantibodies, which are common in the normal population. The presence of AVPcAb has been previously demonstrated in about 50% of patients with histiocytosis X (9), and it was hypothesized to be due to two important factors: 1) histiocytosis X cells bear class II major histocompatibility antigens on their surface so that specific infiltration of the hypothalamus may trigger T helper cells to induce an autoimmune reaction to hypothalamic antigens; and 2) histiocytosis X is associated with T suppressor cell defects that may increase this autoimmune response against the hypothalamic cells (9). Therefore, a secondary autoimmune process against the hypothalamic AVP-secreting cells occurs in these patients, probably contributing to the complete destruction of these cells and the development of a complete CDI.

The results of the current study demonstrated that in this category of patients, similarly to patients with idiopathic CDI, the presence of AVPcAb was significantly and independently associated with a history of autoimmune diseases and the presence of pituitary stalk thickening. The presence of AVPcAb has also been previously demonstrated in a few patients with idiopathic CDI to surgery (9). In our study a relatively higher percentage of AVPcAb has been found in this category of CDI patients. However, the antibody titer was low in all cases, and the main titer was significantly lower in this category of CDI patients compared to those with idiopathic CDI and to those with CDI associated with histiocytosis X. Therefore, in these patients the presence of AVPcAb could be considered an epiphenomenon, probably due to a transient and reversible inflammatory process mediated by lymphocyte migration from the barrier to the hypothalamus favored by increasing endothelial adhesion to the cerebral circulation (35, 36). This adhesion could be due to a stimulation of endothelial cells by interferon, TNF, and IL-1 (37, 38). Therefore, although a longitudinal evaluation of these cases is needed to correctly interpret these data, it can be hypothesized that a group of patients with CDI secondary
to surgery may have transient autoantibodies to hypothalamic AVP-secreting cells without developing true autoimmune CDI. The lack of a significant association of these autoantibodies with a history of autoimmune diseases or the presence of other endocrine autoantibodies supports this hypothesis.

In conclusion, autoimmunity to hypothalamic AVP-secreting cells probably represents the etiology of one third of patients with apparently idiopathic CDI and an epiphennemon in more than half of the patients with CDI associated with hypothalamic localization of histiocytosis X and in a minority of patients with CDI secondary to neurosurgery for sellar lesions. On the basis of this evidence, autoimmune CDI may be considered one of the most important etiologies of CDI, and it may be strongly suspected in young females with autoimmune disorders and radiological evidence of pituitary stalk thickening.

Acknowledgments

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