Central Diabetes Insipidus in Children and Young Adults: Etiological Diagnosis and Long-Term Outcome of Idiopathic Cases

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Context: Central diabetes insipidus (CDI) is considered idiopathic in 20% to 50% of affected subjects.

Objective: The purpose of this study was to determine whether a systematic diagnostic workup could achieve better etiologic diagnosis in children and adolescents presenting with polyuria and polydipsia.

Design and Setting: This is a prospective study conducted at a tertiary referral center. Patients underwent clinical and endocrine evaluations every 6 months and neuroimaging every 6 months for 2 years and yearly for 3 years. Endocrine function and neuroimaging were also reassessed after adult height achievement.

Participants: A total of 85 consecutive patients with CDI were enrolled at a median age of 7.5 years; those with idiopathic CDI were stratified based on pituitary stalk thickness.

Main Outcome Measures: To establish the etiology of CDI, we determined the time lag between its onset and the specific diagnosis, the long-term impact on pituitary function, and the overall long-term outcomes.

Results: Of the subjects, 24 (28.2%) received an etiologic diagnosis at presentation and 11 (13%) within 2.5 years (n = 7 germinomas and n = 4 Langerhans cell histiocytosis), 7 (8.2%) were lost to follow-up, and 43 (50.6%) were considered to have idiopathic disease and were followed until the median age of 17.3 years. Neuroimaging identified 40 of 43 patients with self-limited inflammatory/autoimmune pituitary stalk thickness within the first 6 months, the severity of which was significantly correlated to pituitary dysfunction. The probability of >10-year-survival without an anterior pituitary defect was related to the severity of pituitary stalk thickness, and 53% showed permanent anterior pituitary defects. Three patients developed Langerhans cell histiocytosis and 1 developed Hodgkin lymphoma after a median of 9 and 13 years, respectively.

Conclusions: A diagnostic etiology was achieved in 96% of patients with CDI. Risk stratification based on the degree of pituitary stalk thickness is of prognostic value for long-term outcomes including permanent pituitary dysfunction. New guidance is provided for the management of these patients. (***J Clin Endocrinol Metab*** **99: 1264–1272, 2014)**

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Abbreviations: CDI, central diabetes insipidus; CI, confidence interval; CT, computed tomography; LCH, Langerhans cell histiocytosis; MRI, magnetic resonance imaging.

To date, only limited and retrospective data on the outcome of patients with childhood-onset idiopathic central diabetes insipidus (CDI) are available, and the long-term consequences and morbidities of these patients have not been described (1–8). In a previous retrospective study, we reported idiopathic CDI in 52% of a large cohort of patients who had a first neuroimaging examination 1.5 years after the onset of polyuria and polydipsia (1). Because 44% of the latter patients displayed a pituitary stalk thickness, we wondered whether an early neuroimaging assessment and a longer follow-up might be helpful in the identification of additional patients with such a peculiar picture that underlies an etiological diagnosis. On the other hand, a recent retrospective study based on chart reviews of 105 patients and 30 others from 9 different medical centers identified a specific diagnosis of CDI in 89% of the first cohort and 24% of the second one, suggesting a recruitment bias (9). This latter hypothesis is also strengthened by the fact that none of the patients with idiopathic CDI showed pituitary stalk thickness because systematic neuroimaging follow-up was not undertaken.

Thus, the purposes of this prospective study were (1) to establish the diagnostic etiology of CDI, (2) to define the time lag between the onset of symptoms and the specific diagnosis, and 3) to describe the natural history of idiopathic CDI, providing at least a 4-year estimate of overall outcome for young adults with childhood-onset CDI.

Subjects and Methods

Study design

This was a prospective single-center study conducted in patients presenting with polyuria and polydipsia during childhood at the pediatric clinic of Istituto Giannina Gaslini between 1998 and 2006. The pediatric endocrine unit is a tertiary referral national care center for neuroendocrine diseases, and patients with CDI are usually tested based on a standard protocol as reported previously (10). Namely, the diagnosis of CDI is based on the clinical findings of polyuria and polydipsia, urine osmolality of <300 mOsmol/kg of water in a 24-hour urine specimen, and an increase in urinary osmolality in response to desmopressin acetate. In all patients, a 4- to 7-hour water deprivation test is performed. Assessments of serum sodium, plasma, and urinary osmolality are performed every 2 hours during water deprivation and at the beginning (time 0) and the end of the desmopressin test. All patients are then treated with desmopressin acetate (desamino-D-arginine-8-vasopressin), 2 or 3 times daily, either intranasal or orally.

Diagnosis and classification of CDI

After CDI was diagnosed, a detailed medical history was taken together with imaging studies of the brain and pituitary gland. Patients were then classified on the basis of the probable cause of CDI, such as Langerhans cell histiocytosis (LCH), intracranial tumor, midline defects, familial diabetes insipidus (at least 1 additional family member had to be affected), and skull fracture (ie, posttraumatic disease); CDI with no identifiable cause was considered idiopathic, and pituitary stalk biopsy was not performed in these patients, different from what we have reported previously (11–13). Based on our prior data showing that anti-vasopressin cell antibodies can be found in patients with LCH, lymphocytic-infundibulo-hypophysitis, or idiopathic pituitary stalk thickness (3), we decided not to evaluate such autoantibodies, and we classified isolated pituitary stalk thickness identified by magnetic resonance imaging (MRI) as an inflammatory/autoimmune condition. The term lymphocytic-infundibulo-hypophysitis was coined previously (1, 10) to distinguish children and adolescents with CDI, anterior pituitary hormone deficiency, reduced anterior pituitary size, and transient or persistent pituitary stalk thickening from adult patients showing increased posterior pituitary size without anterior pituitary involvement (2).

Neuroradiological and anterior pituitary function study

Patients with CDI were enrolled in a prospective protocol including serial evaluations of (1) clinical characteristics, height, and height velocity, (2) MRI of the brain and pituitary gland, and (3) anterior pituitary function. Namely, clinical, height, and height velocity assessments were performed every 6 months by using a Harpenden stadiometer until the achievement of adult height, whereas brain and pituitary gland MRI were performed every 6 months in the first 2 years after diagnosis and yearly for the subsequent 3 years (total 8 MRIs in 5 years) as well as at the time of adult height achievement defined as the time of reassessment.

Brain sagittal and coronal T1-weighted MRI scans with 2- to 3-mm sections were obtained in all patients at the time of enrollment. A spin echo technique with a 1.5-T superconductive system and contrast enhancement with gadolinium was used(14). MRI data were blindly analyzed by the same neuroradiologist and independently validated by a second operator.

The pituitary stalk was measured at its proximal part. Pituitary stalk thickness was defined as normal when its size was between 1.0 and 3.0 mm (reference values up to 2.0 mm at midstalk and up to 3.0 mm at the level of median eminence) (15), as minimal enlargement when size was between 3.1 and 3.9 mm, as moderate enlargement when size was between 4.0 and 6.5 mm, and as severe enlargement for width larger than 6.5 mm.

The pituitary-thyroid-adrenal-gonadal axis was investigated both at the time of presentation and at reassessment. GH and IGF-I were measured within the first 24 months and in those with growth attenuation thereafter. Serum GH was measured before and 30, 60, 90, and 120 minutes after the administration of L-arginine monohydrochloride (0.5 g/kg of body weight, given iv over a period of 30 minutes) or insulin (0.1 U/kg, given iv) in patients with growth deceleration. Patients with serum peak GH concentrations of <10 μg/L were considered to have GH deficiency (16, 17).

Serum thyroid and cortisol concentrations were assessed every 6 months until the time of reassessment, whereas gonadotropin function was determined in adolescents with pubertal delay and at the time of adult height achievement.

The protocol was approved by the institutional review board of the hospital and was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and with

Good Clinical Practice as defined by the International Conference on Harmonization. No support was provided by pharmaceutical companies. All patients or their legal representatives gave written informed consent before enrollment and were asked to provide consent for continued acquisition of follow-up data.

Statistical analysis

Descriptive statistics values were reported in terms of absolute numbers and percentages for qualitative data, whereas median and minimum and maximum values were reported for quantitative data because of the small sample size and nonnormal (Gaussian) distribution. The Pearson χ^2 test or Fisher exact test, if appropriate, was applied to compare proportions among groups. Differences in quantitative data were assessed by the Mann-Whitney *U* test.

Patients with idiopathic CDI were stratified according to the pituitary stalk size at the time of the first MRI. The probability of survival without the development of other pituitary defects since the diagnosis of CDI was calculated by using the Kaplan-Meier method, and the 95% confidence interval (CI) of the estimates was calculated according to Greenwood's formula. Differences among the pituitary stalk groups were assessed by the log-rank test. All tests were two-tailed and a value of $P < .05$ was considered statistically significant. All analyses were performed by using Stata (release 11.0, StataCorp).

Results

Patients

During the study period, CDI was diagnosed in a total of 85 patients (44 female and 41 male, with a median age of 7.5 years and of range 1.0 to 12.9 years) (Figure 1). Twenty-four patients (28.2%) received an etiologic diagnosis at the time of presentation. Namely, 8 of them had LCH affecting bone and or skin, 6 had craniopharyngiomas, 3 had midline defects, 3 had familial forms of autosomal dominant CDI, 2 had germinomas with double localization (pineal gland and pituitary stalk simultaneously), and the remaining 2 had posttraumatic CDI.

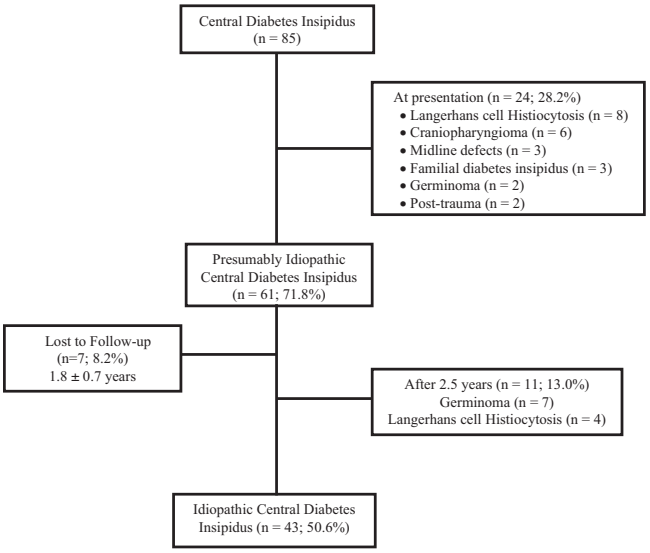

Figure 1. Flow chart showing the cohort of patients with CDI at presentation and during the study period.

Among the 61 patients (71.8%) with a presumable idiopathic form of CDI, 7 (8.2%) were lost to follow-up within 2 years and 11 (13.0%) received a specific diagnosis within 2.5 years since the diagnosis of CDI. Specifically, 7 of these 11 had germinomas (Supplemental Figure 1 published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.) and 4 had LCH. The remaining 43 patients (50.2%; 17 female and 26 male) were considered to have idiopathic CDI and underwent long-term clinical, endocrine, and imaging studies; their median age at diagnosis was 7.4 years (range, 2.5–12.5 years), and they were followed-up for a median of 10.1 years (range, 4.1–14.3 years).

Neuroimaging findings in idiopathic CDI

Images displayed in Figure 2 report the results of the serial MRI evaluations performed over 5 years and at the time of reassessment after the patients were stratified based on the pituitary stalk size at the time of diagnosis. At the time of the first MRI, 9 patients (20.9%) had a normal pituitary stalk, 27 (62.8%) had minimal enlargement of pituitary stalk thickness, and 7 (16.3%) had moderate enlargement of pituitary stalk thickness.

Of the 9 patients with a normal pituitary stalk (Figure 2A), 6 showed minimal enlargement of pituitary stalk size during follow-up. In all patients (100%), this finding normalized within the second year and then remained unchanged until reassessment.

Of the 27 patients with minimal enlargement of pituitary stalk thickness (Figure 2B), 15 showed further enlargement at the second MRI. Five of them had minimal enlargement of pituitary stalk thickening at the 5-year evaluation (18.5%), but all 27 (100%) were had normal pituitary stalks at reassessment (Figure 3).

Among the 7 patients with moderate enlargement of pituitary stalk thickness (Figure 2C), 4 showed enlargement of the pituitary stalk within 2 years after the diagnosis of CDI. Although a reduction in pituitary stalk size was subsequently observed, it was not normalized in any (0%) of these patients.

In summary, 40 patients of 43 (93%) showed some pituitary stalk involvement within 6 months after the diagnosis of idiopathic CDI. Posterior pituitary hyperintensity was absent in all patients. Anterior pituitary size was reduced in patients with mild/moderate enlargement of pituitary stalk thickness during MRI follow-up, and 1 patient showed increased anterior pituitary size at the first MRI with progressive reduction to a small pituitary gland.

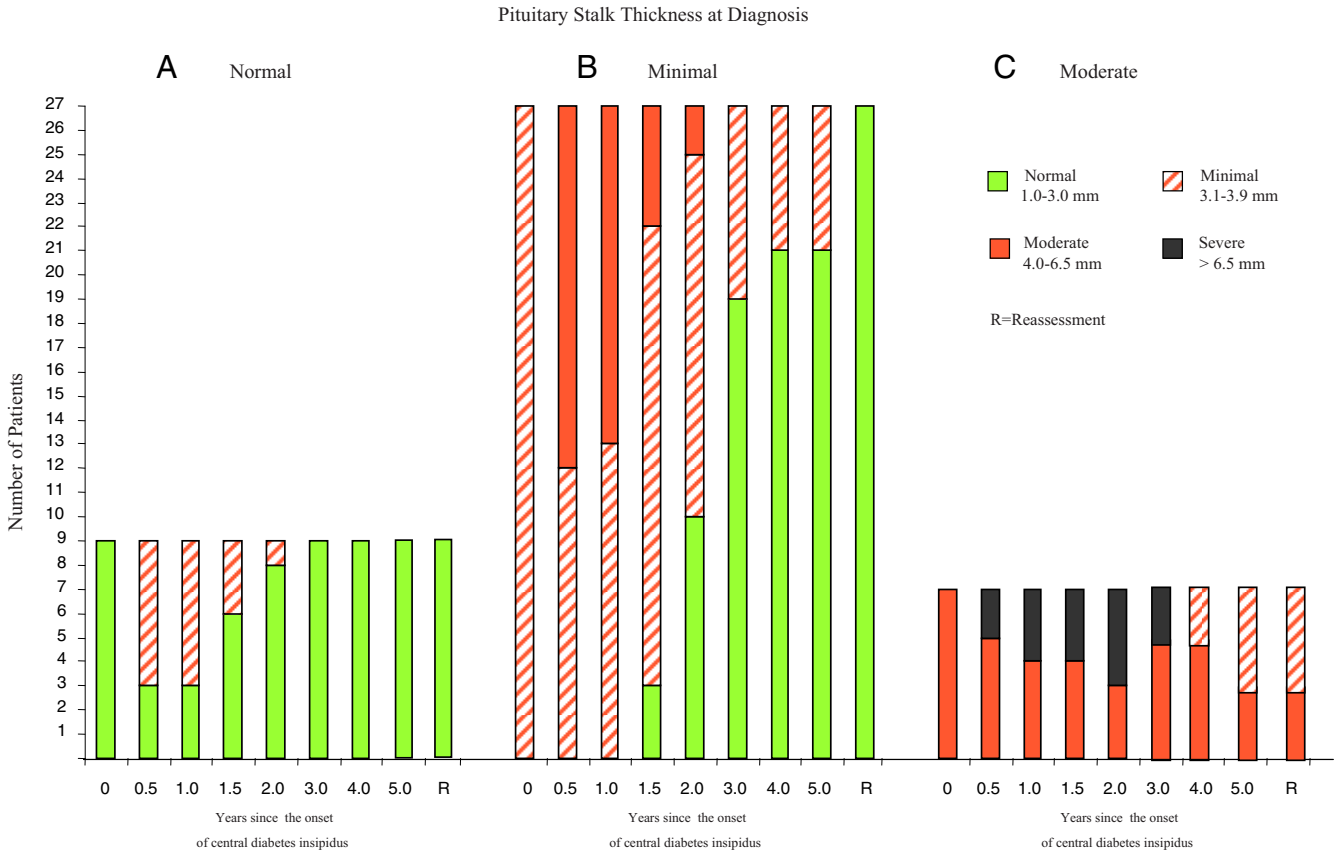

Figure 2. Pituitary stalk size based on MRI scans at times 0, 5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 10.0 years. The size of pituitary stalk was defined as normal (1.0–3.0 mm), minimal enlargement (3.1–3.9 mm), and moderate enlargement (4.0–6.5 mm). Progression of pituitary enlargement to >6.5 mm during follow-up was defined as severe.

Anterior pituitary function in idiopathic CDI

The results of anterior pituitary function tests performed during the study period and stratified by pituitary stalk thickness at diagnosis are summarized in Table 1. Thirty-five patients (81.4%) showed at least 1 anterior pituitary defect within the first 2 years.

Among the 9 patients with normal pituitary stalk size at diagnosis, 5 of 6 with minimal enlargement of the pituitary stalk 6 months after diagnosis developed a GH defect between 0.3 and 1.9 years (Figure 2A). In this group, the probability of more than 10-year-survival without development of a GH defect was 44.4% (95% CI, 13.6–71.9) (Figure 4A).

Among the 27 patients with minimal increases in pituitary stalk thickness at diagnosis, only 4 did not develop anterior pituitary defects. The remaining 23 patients (85.2%) developed 1 or more anterior pituitary defects. Namely, the probabilities were 14.8% (95% CI, 4.7–30.4) for more than 10-year survival without development of a GH defect, 17.0% (95% CI, 1.4–48.2) for 12 years without development of a TSH defect (Figure 4B), and 88.9% (95% CI, 69.4–96.3) for 12 years without development of an adrenal insufficiency (Figure 4C). Hypogonadotropic hypogonadism was diagnosed in 5 patients (18.0%). A survival analysis was not performed for this hormonal defect because its diagnosis is possible only at the time of puberty.

Among the 7 patients with moderate enlargement of pituitary stalk thickness at the first MRI, panhypopituitarism was observed in 6 patients (86%), whereas the remaining patient had multiple pituitary hormone deficiencies (n = 3). the GH defect occurred between 0.8 and 1.9 years, the TSH defect between 0.2 and 2.1 years, and adrenal insufficiency between 0.8 and 12.3 years; all patients had hypogonadism. The probability of survival without a hormone defect was 0% for each defect.

As reported in Table 1, a clear association was found between pituitary stalk thickness at diagnosis and the probability of developing TSH, adrenal, and gonadotropin defects ($P < .001$), whereas the pituitary stalk thickness at diagnosis was only borderline associated to the risk of development of a GH defect ($P = .05$). Similarly, a clear association between pituitary stalk thickness at diagnosis and the probability of development of additional hormonal deficiencies ($P < .001$) was also unveiled.

Reassessment of anterior pituitary function in idiopathic CDI

Summary results of anterior pituitary function at the time of reassessment are reported in Table 2. GH function

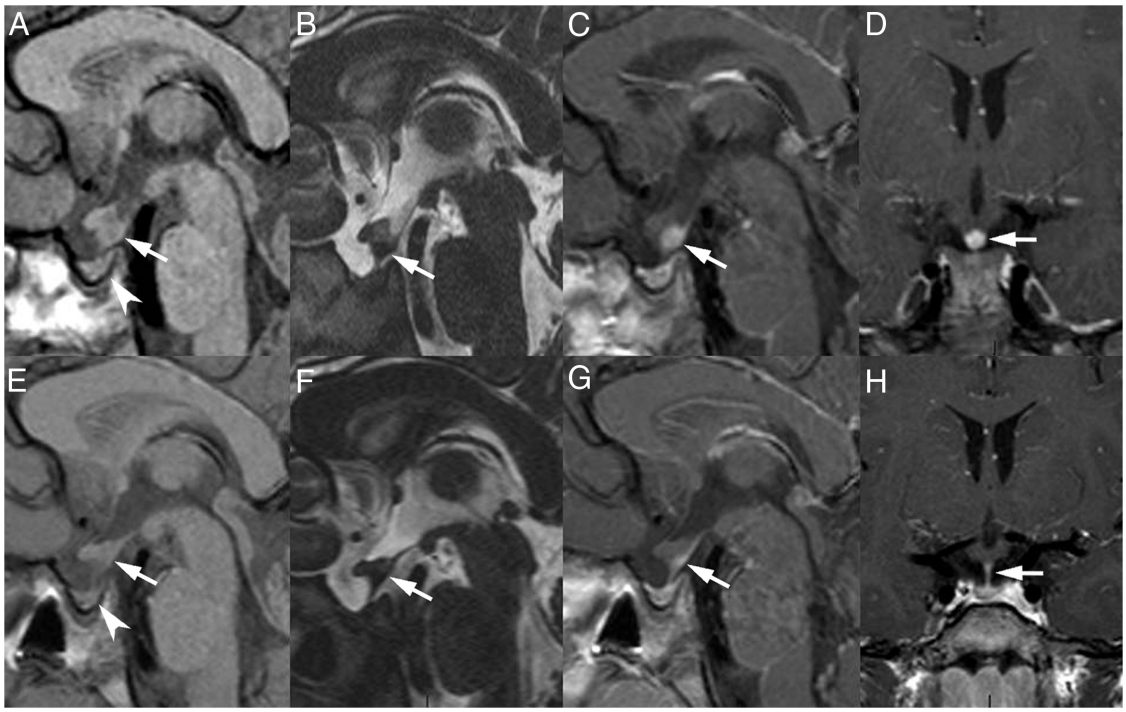

Figure 3. MRI follow-up of a patient with inflammatory pituitary stalk thickness. A–D, sagittal T1-weighted image (A); sagittal T2 DRIVE image (B); and sagittal (C) and coronal (D) postcontrast T1-weighted images at presentation. There is an absence of the posterior pituitary bright spot (arrowhead, A) and thickening of the infundibulum (arrows, A and B), which enhances after contrast material administration (arrows, C and D). E–H, sagittal T1-weighted image (E), sagittal T2 DRIVE image (F), and sagittal (G) and coronal (H) postcontrast T1-weighted images after 2 years. The posterior pituitary bright spot is still undiscernible (arrowhead, E); however, the infundibulum has normalized (arrows, E–H).

normalized in 21 of the 35 patients, accounting for 100% of those with normal pituitary stalk size, in 70% of those with minimal enlargement of pituitary stalk thickness, and in none of those with moderate enlargement of pituitary stalk thickness ($P < .001$).

Thyroid function did not normalize in any patient, regardless of pituitary stalk thickness, whereas corticotropin and gonadotropin functions were recovered in all of those with minimal and in none of those with moderate enlargement of stalk thickness ($P = .012$ and $P = .001$, respectively) (Table 2).

As shown in Supplemental Table 1 reporting growth data, patients with persistent GH defects had a significantly lower height velocity ($P = .001$), greater height loss ($P < .001$), and lower IGF-I values ($P < .001$) at the time of diagnosis than those whose GH function normalized.

Table 1. Frequency of Anterior Pituitary Hormone Defects During Follow-Up Based on Pituitary Stalk Size at Diagnosis of Idiopathic CDI

	Pituitary Stalk Thickness[a]				
Hormone Defect	**Normal (n = 90**	**Minimal (n = 27)**	**Moderate (n = 7)**	**Total (n = 43)**	***P***
Type					
GH, n (%)[c]	5 (56)	23 (85)	7 (100)	35 (81)	.05
TSH, n (%)	0	16 (59)	7 (100)	23 (53)	<.001
ACTH, n (%)	0	3 (11)	6 (86)	9 (21)	<.001
LH and FSH, n (%)	0	5 (18)	7 (100)	12 (28)	<.001
Total number					
0, n (%)	4 (44)	4 (15)	0	8 (18.6)	<.001
1, n (%)	5 (56)	7 (26)	0	12 (27.9)	
2, n (%)	0	8 (29.5)	0	8 (18.6)	
3, n (%)	0	8 (29.5)	1 (14)	9 (20.9)	
4, n (%)	0	0	6 (86)	6 (14)	

[a] Normal, between 1.0 and 3.0 mm; minimal enlargement, between 3.1 and 3.9 mm; and moderate enlargement, between 4.0 and 6.5 mm.

[b] The probability of development of anterior pituitary hormone defects is associated with pituitary stalk size at the time of diagnosis.

[c] All subjects (n = 35) with at least 1 hormone defect during follow-up have a GH defect.

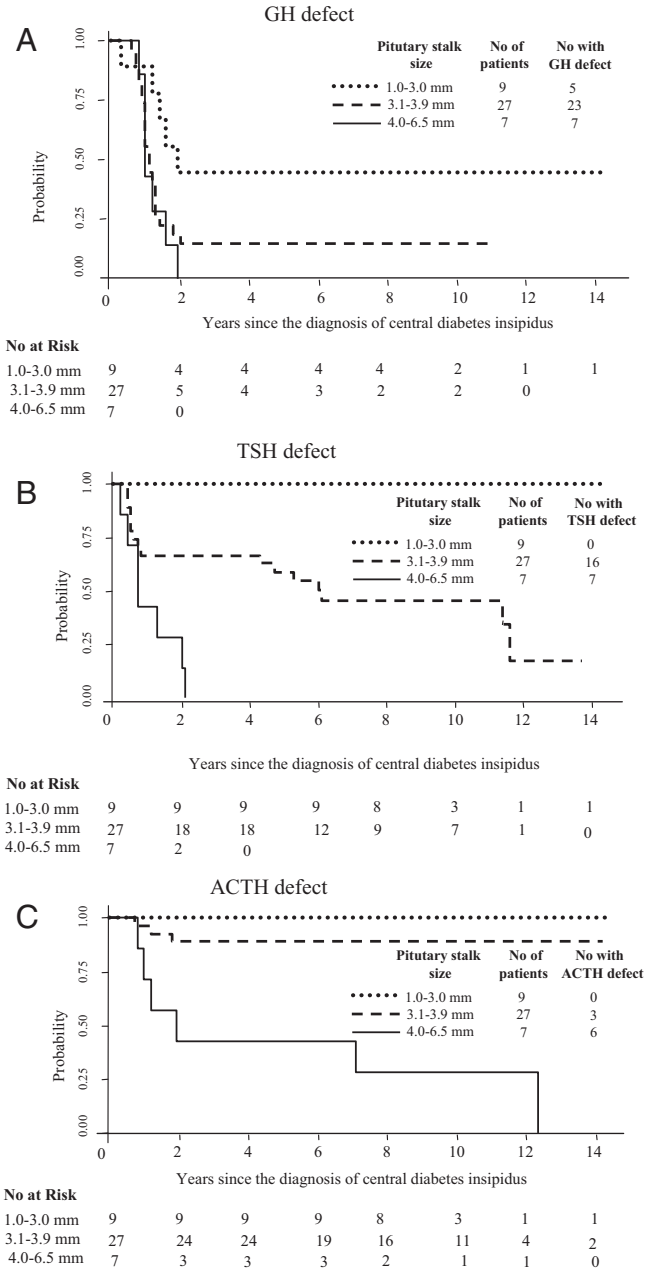

Figure 4. Probability of survival without an anterior pituitary hormonal deficit in children with idiopathic CDI based on pituitary stalk size at the time of diagnosis of CDI. This figure shows the Kaplan-Meier estimates of the probability of disease-free survival for the 43 patients based on the size of pituitary stalk both at the time of diagnosis of CDI and during the follow-up.

Pituitary stalk size was not associated with differences in the former parameters, neither in patients whose functions normalized nor in those who showed persistent pituitary dysfunction.

Long-term complications in patients with idiopathic CDI

Several years (range, 8.5–10 years) after the onset of CDI, 3 patients developed LCH and 1 had Hodgkin lymphoma. All 3 patients with LCH showed a permanent GH deficiency, accounting for 21% of the 14 patients with a confirmed GH deficiency at reassessment.

Case 1

A 12.5-year-old girl with minimal enlargement of pituitary stalk thickness developed moderate enlargement of pituitary stalk thickness during follow-up. At the age of 21, she presented with a chronic long-lasting cough and progressive dyspnea that were underestimated. Chest computed tomography (CT) scans showed multiple cysts, and results of a CT-guided biopsy were compatible with LCH. The patient has been scheduled for lung transplantation.

Case 2

A 8-year-old girl with moderate enlargement of pituitary stalk thickness developed GH and TSH defects within 2 years. Ten years after the onset of CDI, she developed back pain whose etiology remained unidentified for 2 years. Standard radiographs revealed lesions in the proximal right femur and L5 vertebral body, and a femur biopsy led to the diagnosis of LCH. Five years after LCH diagnosis she is well without active disease.

Case 3

A 10-year-old girl with persistent moderate enlargement pituitary stalk thickness developed GH, TSH, and adrenal deficiencies. Nine years after the diagnosis of CDI, she presented with chronic cough. A chest x-ray and CT scans were suggestive for pulmonary LCH that was confirmed by CT-guided biopsy. The disease was rapidly progressive, and she died 1.5 years later.

Case 4

A 10-year-old boy with minimal enlargement of pituitary stalk thickness developed GH deficiency that was treated until adult height achievement. Thirteen years after the onset of CDI, he developed cervical, supraclavicular, and mediastinal lymphadenopathy, and Hodgkin lymphoma was diagnosed. Treatment was successful, and he is alive and in complete remission 3 years after the diagnosis.

Discussion

The approach designed in our study allowed us to precisely determine the underlying etiology of this condition in 75 of 78 patients (96%), to avoid diagnostic delay for intracranial germ cell tumors (18), and to identify the inflammatory/autoimmune condition as the most frequent cause of idiopathic CDI (51.3%, 40 cases). The prevalence of idiopathic CDI commonly reported in the range of 20%

Table 2. Normalization of Anterior Pituitary Hormone Defects at Reassessment Based on Pituitary Stalk Size at Diagnosis of Idiopathic CDI

	Pituitary Stalk Thickness[a]				
Hormone Defect Type	**Normal**	**Minimal**	**Moderate**	**Total**	***P***
GH, n (%)[b]	5/5 (100)	16/23 (70)	0/7 (0)	21/35 (60)	<.001
TSH, n (%)		0/16 (0)	0/7 (0)	0/23 (0)	NV
ACTH, n (%)†		3/3 (100)	0/6 (0)	3/9 (33)	.012
LH and FSH, n (%)†		5/5 (100)	0/7 (0)	5/12 (42)	.001

Abbreviation: NV, not valuable.

[a] Normal, between 1.0 and 3.0 mm; minimal enlargement, between 3.1 and 3.9 mm; and moderate enlargement, between 4.0 and 6.5 mm.

[b] The probability of normalization of GH secretion, ACTH secretion, and LH and FSH secretion is associated with pituitary stalk size at diagnosis of CDI.

to 55% (1, 3, 4, 7, 8, 19–25) was, thus, reduced to 4% in our study, due to a systematic diagnostic work-up and long-term follow-up with use of appropriately tailored tests. Forty patients displayed variable pituitary stalk thickness within the first 6 months based on neuroimaging examination; 37 of these had a self-limited inflammatory process, whereas 3 developed additional organ involvement by LCH over time. Furthermore, we herein demonstrate that the severity of the inflammatory course at the level of the pituitary stalk correlates with that of pituitary hormone deficiencies, leading to a robust prognostic value of the neuroimaging findings.

Because earlier reports were retrospective and lacked systematic neuroimaging data and/or long-term follow-up (7–10, 20–25), a direct comparison with ours is very difficult. In the most recent published study, data showed 11 and 76% frequencies of idiopathic CDI among 105 patients with a diagnosis between 1980 to 1989 and 30 patients with a diagnosis after 1990, respectively; a thickened pituitary stalk did not occur in these 2 cohorts, indicating that MRI assessment was seldom and not regularly performed (10). Indeed, the incidence of pituitary stalk thickness reported in the current study is twice than previously described either by others (7, 8, 10) or by our group in a large cohort of patients who had a first neuroimaging examination 1.5 years after the onset of polyuria and polydipsia (1). In addition, the second MRI scan performed 6 months after the onset of CDI was the most informative, showing pituitary stalk involvement in the great majority of our patients, thus strengthening the hypothesis that early systematic MRI assessment is essential for the etiological diagnosis of CDI.

The great majority of our patients exhibited anterior pituitary defects within the first 24 months after the onset of CDI, with an incidence of 81%, the highest ever reported in patients with idiopathic CDI (7, 8, 10). Although GH defects occurred early and were the most common, thyroid and adrenal deficiencies developed up to 12 years after the diagnosis of CDI. Indeed, recovery of endocrine function was documented in 46.5% of the patients, with the lowest risk for both persistent anterior pituitary dysfunction and pituitary stalk involvement being found in those with a normal pituitary stalk size at diagnosis. In contrast, patients with moderate enlargement of pituitary stalk thickness at presentation displayed the worst prognosis because their pituitary stalk or anterior pituitary function was not normalized during follow-up. It is worth noting that, although evolving pituitary stalk enlargement of >6.5 mm caused a diagnostic challenge in the latter patients, careful neuroimaging assessment led to a conservative approach that allowed avoidance of a pituitary stalk biopsy, which was recommended in our previous work (12, 13).

Different from those with normal or moderate enlargement of pituitary stalk thickness at the onset, the patients with minimal enlargement of pituitary stalk thickness were characterized by the most unpredictable endocrine and neuroimaging features as 63% of them showed persistent pituitary stalk involvement during the first 5 years, all of them had permanent central hypothyroidism, and approximately one third had GH deficiency. Despite the reduction in anterior pituitary gland size observed in our patients with minimal to moderate enlargement of pituitary stalk thickness, we believe that partial rescue of anterior pituitary function is related to the severity of local vasculopathy or fibrosis caused by inflammation of the pituitary stalk, suggesting that potential vascular plasticity at the level of the portal system might occur in some of them (4, 26).

Our patients showed a favorable long-term outcome, but LCH was diagnosed in 3 patients >8 years after the onset of CDI, a late event that has seldom been reported in LCH series (27). The LCH affected the bone in 1 patient and the lungs in 2 young adults with a particularly aggressive course that lead to death in 1 patient and to lung transplantation in the other. In these latter patients, the subsequent involvement of other organs is highly suggestive of primary pituitary stalk–related LCH leading to CDI

and raises an argument about a possible relationship between idiopathic CDI and a single central nervous system target of LCH. Several cases of isolated CDI as the first manifestation of LCH developing shortly after the onset of polyuria and polydipsia have been reported (27), and recently the fact that LCH may develop even years after the onset of CDI was clearly confirmed by a report of the French LCH Registry (18). Thus, our data emphasize that early recognition of the signs and symptoms of organ involvement by LCH, including cough and pain, in subjects with the "triad" of long-lasting CDI, anterior pituitary dysfunction, and pituitary stalk thickness should be carefully monitored to avoid diagnostic delay and LCH-related morbidities and mortality.

The fourth patient who developed Hodgkin lymphoma 13 years after CDI raised the question of a possible chance occurrence or a potential association between these 2 conditions. Although no LCH localizations were depicted in this patient, it is worth mentioning that the association between LCH and malignancy has been reported to occur at a rate higher than expected (28, 29). At the last update of the LCH-Malignancy Registry of the Histiocyte Society, which collects information on subjects with LCH in whom a malignancy occurred either before, concurrent with, or after LCH diagnosis, 5 of 96 subjects with childhood-onset LCH developed Hodgkin lymphoma either 1 year before or after LCH diagnosis and 1 subject developed Hodgkin lymphoma 7 years before the diagnosis of LCH was made (unpublished data). Despite Hodgkin lymphoma occurring 13 years after CDI in our patient, we believe that an unrecognized single system/pituitary stalk involvement by LCH leading to CDI could also be possible in this peculiar case.

Because 7 of our patients were lost to follow-up, we cannot exclude a progression of pituitary stalk thickness over time toward a large mass by local inflammatory or LCH reactivation with evolving pituitary dysfunction in some patients. This picture has already been reported in one of our patients at puberty (30), highlighting the need for long-term careful monitoring of patients with an apparently idiopathic condition.

In conclusion, the natural history of idiopathic CDI in terms of both etiology and morbidities is dissected for the first time, supplying new guidance for long-term surveillance of children and adolescents presenting with polyuria and polydipsia. The systematic neuroimaging and endocrine follow-up we propose has proven to be highly sensitive in the identification of an inflammatory/autoimmune process as the major cause of CDI and to be a powerful prognostic tool for risk stratification based on pituitary stalk size.

We suggest that neuroimaging assessment should be performed in subjects presenting with CDI every 6 months for the first 2 years, at the third year, and then withdrawn afterward because MRI scans beyond year 3 did not provide an additional contribution to diagnosis and outcomes in any of our subjects. We also underscore the paramount importance of long-term clinical follow-up and reassessment of endocrine function. Careful monitoring of signs or symptoms of organ involvement by LCH is recommended after the diagnosis of idiopathic CDI.

Acknowledgments

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References

1. **Maghnie M, Cosi G, Genovese E, et al.** Central diabetes insipidus in children and young adults. *N Engl J Med*. 2000;343:998–1007.
2. **Imura H, Nakao K, Shimatsu A, Ogawa Y, Sando T, Fujisawa I, Yamabe H.** Lymphocytic infundibuloneurohypophysitis as a cause of central diabetes insipidus. *N Engl J Med*. 1993;329:683–689.
3. **Maghnie M, Ghirardello S, De Bellis A, et al.** Idiopathic central diabetes insipidus in children and young adults is commonly associated with vasopressin-cell antibodies and markers of autoimmunity. *Clin Endocrinol (Oxf)*. 2006;65:470–478.
4. **Maghnie M, Altobelli M, Di Iorgi N, et al.** Idiopathic central diabetes insipidus is associated with abnormal blood supply to the posterior pituitary gland caused by vascular impairment of the inferior hypophyseal artery system. *J Clin Endocrinol Metab*. 2004;89:1891–1896.
5. **Babey M, Kopp P, Robertson GL.** Familial forms of diabetes insipidus: clinical and molecular characteristics. *Nat Rev Endocrinol*. 2011;7:701–714.
6. **Abu Libdeh A, Levy-Khademi F, Abdulhadi-Atwan M, et al.** Autosomal recessive familial neurohypophyseal diabetes insipidus: onset in early infancy. *Eur J Endocrinol*. 2010;162:221–226.
7. **Mootha SL, Barkovich AJ, Grumbach MM, et al.** Idiopathic hypothalamic diabetes insipidus, pituitary stalk thickening, and the occult intracranial germinoma in children and adolescents. *J Clin Endocrinol Metab*. 1997;82:1362–1367.
8. **Leger J, Velasquez A, Garel C, Hassan M, Czernichow P.** Thickened pituitary stalk on magnetic resonance imaging in children with central diabetes insipidus. *J Clin Endocrinol Metab*. 1999;84:1954–1960.
9. **Richards GE, Thomsett MJ, Boston BA, DiMeglio LA, Shulman DI, Draznin M.** Natural history of idiopathic diabetes insipidus. *J Pediatr*. 2011;159:566–570.
10. **Ghirardello S, Garrè ML, Rossi A, Maghnie M.** The diagnosis of children with central diabetes insipidus. *J Pediatr Endocrinol Metab*. 2007;20:359–375.
11. **Haupt R, Minkov M, Astigarraga I, et al.** Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treat-

ment for patients till the age of 18 years. *Pediatr Blood Cancer*. 2013;60:175–184.
12. **Maghnie M.** Diabetes insipidus. *Horm Res*. 2003;59(suppl 1):42–54.
13. **Di Iorgi N, Napoli F, Allegri AE, et al.** Diabetes insipidus— diagnosis and management. *Horm Res Paediatr*. 2012;77:69–84.
14. **Morana G, Maghnie M, Rossi A.** Pituitary tumors: advances in neuroimaging. *Endocr Dev*. 2010;17:160–174.
15. **Di Iorgi N, Allegri AE, Napoli F, et l.** 2012 The use of neuroimaging for assessing disorders of pituitary development. *Clin Endocrinol (Oxf)*. 2012;76:161–176.
16. **Maghnie M, Aimaretti G, Bellone S, et al.** Diagnosis of GH deficiency in the transition period: accuracy of insulin tolerance test and insulin-like growth factor-I measurement. *Eur J Endocrinol*. 2005; 152:589–596.
17. **Secco A, di Iorgi N, Napoli F, et al.** Reassessment of the growth hormone status in young adults with childhood-onset growth hormone deficiency: reappraisal of insulin tolerance testing. *J Clin Endocrinol Metab*. 2009;94:4195–4204.
18. **Sethi RV, Marino R, Niemierko A, Tarbell NJ, Yock TI, Macdonald SM.** Delayed diagnosis in children with intracranial germ cell tumors. *J Pediatr*. 2013;163:1448–1453.
19. **Marchand I, Barkaoui MA, Garel C, Polak M, Donadieu J.** Central diabetes insipidus as the inaugural manifestation of Langerhans cell histiocytosis: natural history and medical evaluation of 26 children and adolescents. *J Clin Endocrinol Metab*. 2011;96:E1352–E1360.
20. **Pomarède R, Czernichow P, Rappaport R, Royer P.** ADH-deficient diabetes insipidus in children. A study of 93 cases. *Arch Fr Pediatr*. 1980;37:37–44.
21. **Greger NG, Kirkland RT, Clayton GW, Kirkland JL.** Central diabetes insipidus. 22 years' experience. *Am J Dis Child*. 1986;140: 551–554.
22. **Wang LC, Cohen ME, Duffner PK.** Etiologies of central diabetes insipidus in children. *Pediatr Neurol*. 1994;11:273–277.
23. **Charmandari E, Brook CG.** 20 years of experience in idiopathic central diabetes insipidus. *Lancet*. 1999;353:2212–2213.
24. **Al-Agha AE, Thomsett MJ, Ratcliffe JF, Cotterill AM, Batch JA.** Acquired central diabetes insipidus in children: a 12-year Brisbane experience. *J Paediatr Child Health*. 2001;37:172–175.
25. **Santiprabhob J, Likitmaskul S, Boonyasiri A, Boonsathorn S, Buddawong T.** Etiologies of central diabetes insipidus in Thai children. *J Pediatr Endocrinol Metab*. 2005;18:653–661.
26. **Maghnie M, Genovese E, Aricò M, et al.** Evolving pituitary hormone deficiency is associated with pituitary vasculopathy: dynamic MR study in children with hypopituitarism, diabetes insipidus, and Langerhans cell histiocytosis. *Radiology*. 1994;193:493–499.
27. **Haupt R, Nanduri V, Calevo MG, et al.** Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society-Late Effects Study Group. *Pediatr Blood Cancer*. 2004;42:438–444.
28. **Egeler RM, Neglia JP, Aricò M, et al.** The relation of Langerhans cell histiocytosis to acute leukemia, lymphomas, and other solid tumors. The LCH-Malignancy Study Group of the Histiocyte Society. *Hematol Oncol Clin North Am*. 1998;12:369–378.
29. **Haupt R, Nanduri V, Egeler RM.** Late effects of Langerhans cell histiocytosis and its association with malignancy. In: Weitzman S, Egeler RM, eds. *Histiocytic Disorders of Children and Adults*. Cambridge, UK: Cambridge University Press; 2005:272–292.
30. **Maghnie M, Genovese E, Sommaruga MG, et al.** Evolution of childhood central diabetes insipidus into panhypopituitarism with a large hypothalamic mass: is 'lymphocytic infundibuloneurohypophysitis' in children a different entity? *Eur J Endocrinol*. 1998;139:635–640.