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ORIGINAL PAPER

Clinical, hormonal and imaging findings in 27 children with central diabetes insipidus

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Abstract Clinical, auxological, biological and neuroradiological characteristics of 27 children with central diabetes insipidus (CDI) were retrospectively analysed. Median age at diagnosis was 8.6 years (range: 0.3–16.1 years). Final aetiologies were postsurgical infundibulo-hypophyseal impairment (*n*=7), cerebral tumour (*n*=8), Langerhans cell histiocytosis (*n*=3), septo-optic dysplasia (n=1), ectrodactyly ectodermal dysplasia clefting syndrome (*n*=1), and idiopathic (*n*=7). In the non-postsurgical CDI patients, major cumulative and often subtle presenting manifestations were: polyuria (*n*=20), polydipsia (*n*=19), fatigue (*n*=11), nycturia (*n*=10), growth retardation (*n*=9), and headache (*n*=9). An associated antehypophyseal insufficiency, mainly somatotropic, was documented in 11 children. All patients except one who initially had a cerebral tomography, underwent magnetic resonance imaging revealing the lack of the physiological posterior pituitary hyperintense signal. One third of the idiopathic patients initially had a thickened pituitary stalk. All patients with idiopathic CDI were intensively followed up with 3-monthly physical examination, antehypophyseal evaluation, search for tumour markers, and cerebral MRI every 6 months. In one of them the pituitary stalk had normalized after 4.3 years. In one patient Langerhans cell histiocytosis was diagnosed after 7 months of follow-up, and in another patient a malignant teratoma was found after 2.4 years of follow-up. *Conclusion*: CDI may be the early sign of an evolving cerebral process. The association of polyuria-polydipsia should incite a complete endocrine evaluation and a meticulous MRI evaluation of the hypothalamo-hypophyseal region. A rigorous clinical and neuroradiologic follow-up is mandatory to rule out an evolving cerebral process and to detect associated antehypophyseal insufficiencies.

Keywords Central diabetes insipidus · Cerebral tumour · Hypophyseal insufficiency · Langerhans cell histiocytosis · Pituitary stalk

Abbreviations

CDI	central diabetes insipidus
MRI	magnetic resonance imaging
HP	hypothalamo-pituitary
EEC	ectrodactyly ectodermal dysplasia and cleft lip/palate syndrome
SOD	septooptic dysplasia
TRH	thyreotropin releasing hormone
GnRH	gonadotropin releasing hormone
AFP	alpha foetoprotein
β HCG	beta human chorionic gonadotrophin
CAT scan	computed tomography scan
CSF	cerebral spinal fluid
GHD	growth hormone deficiency
LH	luteinizing hormone
FSH	follicle stimulating hormone

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Introduction

Central diabetes insipidus (CDI), characterised by the passage of large volumes of diluted urine (>2 l/m^2/day or

approximately 150 ml/kg/day at birth, 100–110 ml/kg/day at 2 years and 40–50 ml/kg/day after 2 years; osmolality <300 mOsmol/kg water), results from a deficient secretion of osmoregulated vasopressin [2, 14]. It is a rare disorder in children [10]. Without treatment it may result in severe dehydration sometimes causing death, especially in infants with disorders of thirst regulation. The presenting sign(s) and symptoms are variable, and can initially by very subtle. Hence, the diagnosis of CDI is often late compared to the apparition of the initial sign(s) and symptom.

The aetiology of CDI in childhood is heterogeneous [3, 24]. It can be familial and/or congenital or acquired. In 30 to 50% of the acquired CDI no aetiology can be demonstrated and these forms are actually considered as 'idiopathic' [9]. The long-term course of this disorder is largely undefined. Regular clinical and biological follow-up with repeated cerebral MRI is advocated to reveal developing abnormalities of hypothalamo-pituitary (HP) structures, such as an intracranial tumour or Langerhans cell histiocytosis [4].

In this study, we retrospectively analysed the clinical, biochemical, hormonal and neuroradiological data of 27 children diagnosed with CDI between 1986 and 2002 at the department of Paediatric Endocrinology of the Hôpital Universitaire des Enfants Reine Fabiola of Brussels, Belgium. We illustrate the importance of a careful clinical, biological and neuroradiological follow-up to rule out the development of associated hormonal deficiencies or an evolving cerebral pathology.

Subjects and methods

Subjects

Clinical, auxological, biological and neuroradiological variables of 27 children diagnosed in our department between 1986 and 2002 with CDI were retrospectively analysed. Nine patients (six post-surgery) presented initially with polyuria and hypo-osmolar urine, or hypernatremia. In 18 patients diagnosis of CDI was confirmed by a positive water deprivation test, followed by desmopressin administration [2, 14, 19]. An urinary osmolality lower than 300 mOsmol/kg in the presence of polyuria and hypernatremia was considered as complete CDI. A maximum level of urinary osmolality between 300 and 750 mOsmol/kg was considered as partial CDI. In all patients urinary osmolality increased above 500 mOsmol/kg after the administration of 10 to 20 microgram desmopressin intranasally. After confirmation of the diagnosis treatment with intranasal desmopressin was given.

The patients were classified according to the diagnosis at the initial evaluation. Group 1: CDI following surgery for a tumour in the hypothalamo-pituitary area; group 2: CDI due to an intracranial tumour (diagnosed on MRI and tumour markers); group 3: CDI due to Langerhans cell histiocytosis (osteolytic bone or cutaneous lesions biopsy-proven); group 4: CDI associated with malformative syndromes (ectrodactyly ectodermal dysplasia with cleft lip/palate syndrome (EEC) or septooptic dysplasia (SOD)); group 5: idiopathic CDI without any identifiable aetiology.

Methods

All patients underwent a complete evaluation of antehypophyseal function. Somatotropic and corticotropic axes were evaluated with insulin tolerance or glucagon stimulation tests. Thyroid axis was evaluated with a TRH test and the gonadotropic axis with a GnRH test. Standard radioimmunoassays were performed for all hormonal dosages. In the patients of groups 2, 3 and 5 a search for tumour markers (AFP and β HCG) in serum and spinal fluid was done in order to detect a secreting germ-cell tumour.

Except one patient who initially was evaluated by a cranial CAT scan (focussed on HP axis and with contrast), cranial MRI with gadolinium was performed in all. A search for a pituitary or parapituitary mass, analysis of the posterior pituitary hyperintense signal, of the thickness of the pituitary stalk and of the height of the anterior hypophysis were performed on the mediosagittal section (T1 ponderation, thickness of 3 mm) by the same experienced investigator [C.C.]. The pituitary stalk was considered as thickened if the diameter was larger than 2 mm in at least one of its 3 portions (proximal, median, distal) [8]. The antehypophyseal height was compared to age and pubertal norms established by Argyropoulou et al. [1].

Radiological evaluation of the complete skeleton was performed in 11 children to document or positively identify a Langerhans cell histiocytosis. Biopsy of enlarged hypothalamo-hypophyseal structures was done in seven patients, by transsphenoidal or extracranial methods, based on MRI findings.

All patients with idiopathic CDI were intensively followed up with 3-monthly physical examination, antehypophyseal evaluation (according to auxological and clinical data), and search for tumour markers (in serum and CSF) and cerebral MRI every 6 months, over at least 2 years following CDI diagnosis. Further follow-up depended on the evolution of the patients. Identical follow-up, except tumour marker research, was performed in the patients with proven histiocytosis. In the other patients appropriate follow-up has been carried out, according to CDI aetiology.

Results

Baseline aetiological data

Baseline data of the patients (10 girls; 17 boys) are shown in Table 1. Twenty-two patients had complete CDI, and five partial CDI. Patients were classified on the basis of the initially most probable aetiology of their CDI. Seven patients developed CDI post-surgery (group 1): primary indications for surgery were astrocytoma (n=2), embryonal tumour (n=1), craniopharyngioma (n=1), colloid cyst (n=1), Rathke pouch cyst (n=1), and macroprolactinoma (n=1). In seven patients (group 2) a tumoural process was detected during initial work-up: three had a germ cell tumour (two germinoma and one teratoma) and four had a craniopharyngioma. In two patients (group 3) Langerhans cell histiocytosis was diagnosed. Two patients (group 4) had a malformative syndrome: one an EEC syndrome and one a SOD. In nine patients (group 5) CDI was initially considered as idiopathic.

Table 1 Baseline data of all patients with central diabetes insipidus

Patient no.	M/F	Age (y) at:		CDI	Post. signal	Thickness pituitary stalk (mm)			Antehypophysis (mm)	
		Initial symptom	Diagnosis	Co/Pa	Pr/Ab	Prox.	Med.	Dist.	Height	Deficit
Group 1: Postsurgery										
1 astrocytoma	M	4.3	4.3	Co						
2 craniopharyngioma	F	4.8	4.8	Co						
3 colloid cyst	M	6.6	6.6	Co						
4 Rathke pouch cyst	F	13.4	13.4	Pa						
5 embryonal tumour	M	14.1	14.1	Pa						
6 macroprolactinoma	M	14.7	14.7	Co						
7 astrocytoma	F	15.7	15.7	Co						
Group 2: Cerebral tumour										
8 craniopharyngioma	M	1.0	1.2	Co	Ab	I	I	I	I	GH,TSH,ACTH
9 craniopharyngioma	M	5.0	7.5	Co	Ab	I	I	I	I	GH,TSH,ACTH
10 craniopharyngioma	F	6.0	8.6	Co	Ab	I	I	I	I	GH
11 germinoma	M	8.0	12.8	Co	Ab	I	I	I	I	–
12 malignant teratoma	F	8.8	9.8	Co	Ab	I	I	I	>N	GH, LH/FSH
13 germinoma	F	9.5	13.4	Co	Ab	6.0	5.0	2.0	<N	GH,TSH,ACTH, LH/FSH
14 craniopharyngioma	F	13.0	14.8	Co	Ab	1.2	1.2	1.2	I	GH,TSH, LH/FSH
Group 3: Langerhans cell histiocytosis										
15	F	0.0	3.8	Co	Ab	2.0	3.5	2.0	N	–
16	F	1.7	4.2	Co	Ab	1.5	1.5	1.5	<N	–
Group 4: Malformative syndrome										
17 EEC	M	0.3	0.3	Co	Ab	2.0	0.8	0.8	N	–
18 SOD	M	0.3	0.5	Co	Ab	I	I	I	I	LH/FSH
Group 5: Idiopathic										
19	F	6.1	6.3	Co	Ab	*	*	*	*	–
20	M	9.1	9.2	Co	Ab	1.5	1.0	1.0	>N	GH
21	M	2.0	2.3	Pa	Ab	0.3	1.5	1.0	N	–
22	M	4.0	7.0	Co	Ab	10.0	10.0	8.0	<N	GH
23	M	7.0	8.3	Co	Ab	1.8	1.2	1.0	>N	–
24	M	9.75	11.1	Co	Ab	5.6	4.7	1.3	<N	GH
25	M	9.8	9.9	Co	Ab	I	*NA*	*NA*	*NA*	GH,TSH, ACTH, LH/FSH
26	M	10.7	11.8	Pa	Ab	1.5	1.0	1.0	N	–
27	M	15.1	16.1	Pa	Ab	5.1	5.7	1.9	<N	–

M: male; F: female; Co: complete; Pa: partial; Pr: present; Ab: absent
N: normal; NA: not available; I: indistinct
GH: growth hormone; TSH: thyroid-stimulating hormone; ACTH: adrenocorticotropic hormone; LH: luteinizing hormone; FSH: follicle stimulating hormone
*CAT scan was initially done

Baseline clinical data

The clinical manifestations were often subtle, cumulative and very variable. Excluding the post-surgery patients, the age at appearance of the first manifestation ranged from the neonatal period in a patient with Langerhans cell histiocytosis, to up to 15.1 years for a patient with idiopathic CDI. The most frequently presenting sign and symptoms were polyuria (n=20) and polydipsia (n=19). One patient (EEC syndrome) presented with polyuria without polydipsia, but with severe hypernatremia because of a defective thirst regulation mechanism [23]. Other initial cumulative manifestations were: fatigue (n=11), nycturia (n=10), growth retardation (n=9), headache (n=9), visual disturbances (n=5), behaviour troubles (irritability, aggressiveness) (n=5), secondary nocturnal enuresis (n=4), nausea (n=4), vomiting (n=4), anorexia (n=3), primary nocturnal enuresis (n=3), hypernatremia (n=3), rash (n=2), secondary amenorrhoea (n=1), convulsions (n=1), and memory disturbances (n=1). The growth retardation observed in nine patients (four cerebral tumours, two Langerhans cell histiocytosis, three idiopathic) was estimated at a median height loss of 1.3 (range: 0.5 to 1.9) standard deviation scores. Median age at diagnosis of CDI was 8.6 (range: 0.3–16.1) years. The interval between the initial manifestation and the diagnosis of CDI was very variable, and extended up to 4.8 years in a patient with a germ cell tumour (patient 11). In this child, the presenting signs were growth retardation, polyuria-polydipsia and nycturia appearing 4 years before diagnosis. In the patients with idiopathic CDI the median delay between appearance of polyuria-polydipsia and diagnosis was 1.1 (range: 0.1–3.0) years. Two children had an exacerbation of their clinical manifestations following an infection. This allowed the diagnosis of a germ cell tumour in one patient (patient 13), and of idiopathic CDI in another (patient 22).

Baseline radiological data (Figure 1)

Imaging studies revealed the absence of the normal posterior pituitary hyperintense signal in all patients. Cerebral MRI identified a suprasellar mass in seven patients: craniopharyngioma (n=4), germinoma (n=2) and teratoma (n=1), based on histological examination after surgery. In five of them the pituitary stalk and antehypophysis were unexplorable due to the infiltrating process. One child with a germinoma (patient 13) had a thickened pituitary stalk in the proximal and medial portion. In one child (patient 14), the suprasellar craniopharyngioma compressed the antehypophysis. The pituitary stalk was normal. In group 3 (Langerhans cell histiocytosis), patient 15 had a moderate thickening in the medial portion of the pituitary stalk with a normal antehypophysis. Patient 16 presented a normal pituitary stalk with an hypoplastic antehypophysis. In group 4, the patient with EEC had a normal antehypophysis but a thin pituitary stalk. The patient with SOD had a very thin pituitary stalk and his antehypophysis was almost absent. In group 5 (idiopathic), four patients had a thickened pituitary stalk ranging from 4.7 to 10.0 mm, either limited (proximal portion n=1, proximal and median portion n=2) or generalized (n=1). Three among them had a small antehypophysis. In three patients with idiopathic CDI the initial exploration of the hypothalamo-hypophyseal structures revealed a normal pituitary stalk. One of them (patient 20) had an enlarged antehypophysis. Except the absence of the posterior pituitary hyperintense signal, HP structures were completely normal in the two other children of group 5. In one patient (patient 25), the images were lost, and no description of the pituitary stalk or antehypophysis was available.

Baseline hormonal, biochemical and histological data

Six out of the seven children with a cerebral tumour (group 2) had antehypophyseal deficits, most frequently growth hormone deficiency (GHD). The patients with Langerhans cell histiocytosis (group 3) had initially no associated antehypophyseal deficits. The patient with EEC did not have any associated deficits, whereas the patient with SOD had associated gonadotrophine deficiency (group 4). Five patients with idiopathic CDI did not have any anterior hypophyseal deficits, whereas three had GHD and one had complete anterior pituitary deficiency.

Measurement of tumour markers contributed to the diagnosis of cerebral tumour in two children. A malignant teratoma was diagnosed in one girl (patient 12) with β hCG and AFP present in serum and the spinal fluid. In another child (patient 13), a secreting germinal tumour was diagnosed with AFP present within the malignant cells, but absent in spinal fluid and serum.

In addition to the seven patients who developed CDI postsurgery, a biopsy of the mass around the HP area was performed in seven patients. Four of them had a suprasellar tumour (group 2, patients 8,10,11,13). In one other patient Langerhans cell histiocytosis was diagnosed (group 3). Two patients (patients 25,27) were considered as idiopathic.

Follow-up of the patients with idiopathic CDI

Follow-up data of the patients with idiopathic CDI are presented in Table 2. In one patient with initial idiopathic CDI (patient 19), a teratoma was diagnosed after 2.4 years of follow-up. Clinically the patient developed growth retardation and visual disturbances. Diagnosis was based

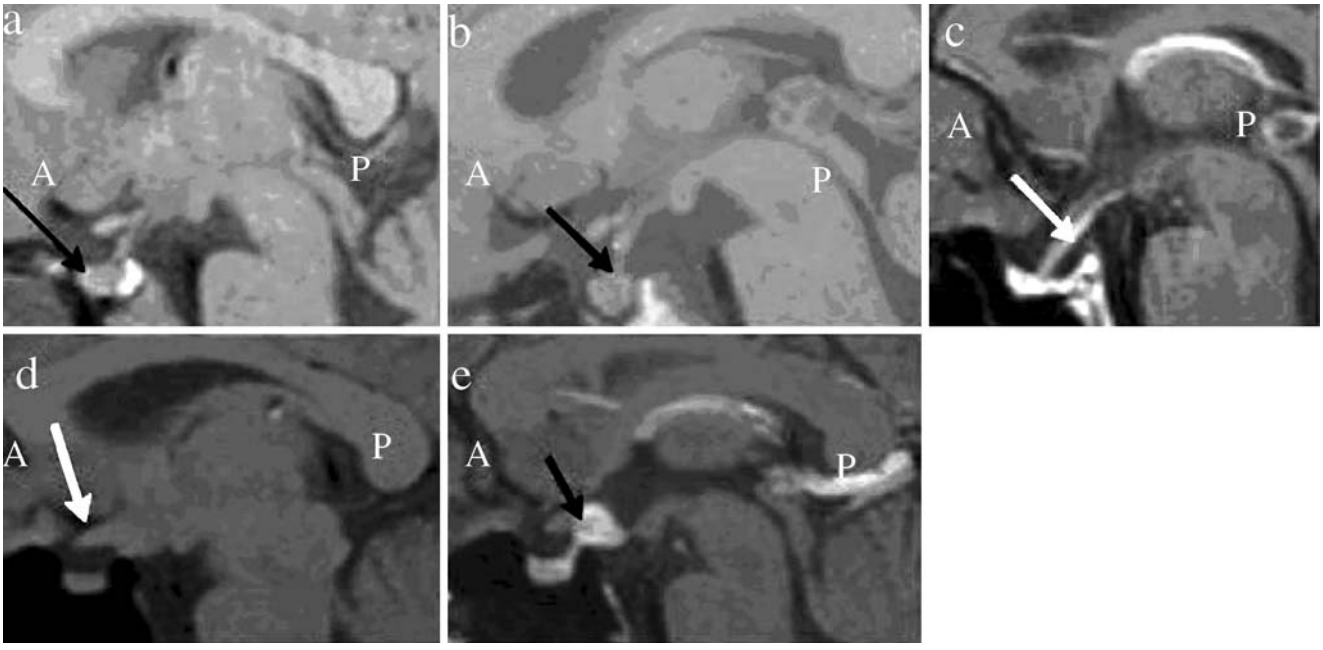

Fig. 1 Sagittal T1-weighted images of hypothalamo-hypophyseal structures (A: anterior side; P: posterior side). **a** Normal image of pituitary stalk in a 10 year old girl: presence of the normal hyperintense signal of the posthypophysis (*black arrow*), and normal height of the anterior pituitary gland. **b** Absence of normal hyperintense signal of the posthypophysis (*black arrow*) in a patient with CDI. **c** Mild enlarged pituitary stalk (*white arrow*) well delineated after iv Gd-DTPA. **d** Proximal enlarged portion of the pituitary stalk (*white arrow*) and absence of the normal hyperintense signal of the posthypophysis in a 15 year old boy. **e** The same proximal enlarged portion of the pituitary stalk (*black arrow*) after iv Gd-DTPA

on the development of a mass on MRI and positive tumour markers: AFP and β hCG were detected in serum and spinal fluid. In another patient (patient 20), initially considered as idiopathic, a diagnosis of Langerhans cell histiocytosis was established after 7.2 months of follow-up on the basis of lytic lesions on osseous radiography and thickening of pituitary stalk. The thickening of the stalk during follow-up led to the performance of a biopsy.

Follow-up radiological data

During follow-up of the other patients with idiopathic CDI, the pituitary stalk (initially thickened) widened out in three of them (patients 22, 24, 27), to reach a thickness of 2.2 to 10.0 mm, which spread over the totality of the stalk. These morphologic changes appeared after, respectively, 4.8, 4.3 and 1.9 years of follow-up. Hypoplasia of the antehypophysis did not normalize with time. During follow-up, three other idiopathic patients had moderately thickened their stalk: in patient 21, in the proximal portion (delay=10.7 years), in patient 26 in the medial portion (delay=4.2 years), and in patient 23 in the proximal and medial portions (delay=4.0 years). In patient 25, who initially presented a thickening, the pituitary stalk normalized after 4.3 years.

Follow-up hormonal data

An additional associated deficit of LH and FSH was diagnosed in one child (patient 24) 2.4 years after diagnosis of CDI. In the others, no additional antehypophyseal insufficiencies were documented so far during follow-up.

Discussion

In the present study we analysed retrospectively the clinical, biochemical, hormonal and neuroradiological aspects of 27 children with CDI. In these series, seven of the 27 patients had CDI from a postoperative origin while in only two CDI was due to a polymalformative syndrome. No familial cases were observed. Seven children in our series had a cerebral tumour, four of them a craniopharyngioma and three a germ cell tumour. This finding is in agreement with the data from Maghnie et al. [10] who observed a tumour in 18 out of 79 patients. In contrast, Greger et al. found only in 7 out of 73 children a tumoural origin [6]. Two of our patients presented Langerhans cell histiocytosis [17], which is comparable to the 6 out of 73 children reported by Greger et al. [6]. In contrast, none of the patients reported by Wang et al. [24] had CDI due to Langerhans cell histiocytosis.

Table 2 Follow-up data of patients with idiopathic CDI

Patient no.	Tumour marker	Follow up (y)	Age (y)	Post. signal	Thickness pituitary stalk (mm)			Antehypophysis	
					Prox.	Med.	Dist.	Height (mm)	Additional deficit
19 (malignant teratoma)	AFP, βHCG	2.4	8.8	Ab	10.0	13.5	12.0	I	–
20 (Langerhans cell histiocytosis)	ND	0.6	9.8	Ab	3.1 (+1.6)	2.2 (+1.2)	1.9 (+0.9)	<N	–
21	–	10.7	13.6	Ab	2.5 (+2.2)	1.0 (+0.5)	1.0	N	–
22	–	4.8	11.8	Ab	10.0	10.0	10.0 (+2.0)	<N	–
23	–	4.0	12.4	Ab	3.0 (+1.2)	1.5 (+0.3)	1.0	>N	–
24	–	4.3	15.4	Ab	8.0 (+2.4)	6.0 (+1.3)	6.0 (+4.3)	<N	LH/FSH
25	–	4.3	14.0	Ab	N	N	N	N	–
26	–	4.2	15.9	Ab	0.3 (−1.2)	1.5 (+0.5)	1.0	>N	–
27	–	1.9	17.2	Ab	7.7 (+2.6)	6.4 (+0.7)	2.2 (+0.3)	<N	

AFP: α foeto protein; βHCG: β human chorionic gonadotrophin; LH: luteinizing hormone; FSH: follicle stimulating hormone
Ab: absent; I: indistinct; ND: not done; N: normal

We could not identify any specific aetiology in 7 out of 27 patients with CDI, despite a follow-up period of 7 months to 13.6 years. In line with the data from other studies [10, 16], the number of idiopathic cases decreased during follow-up, proportionally to an increase of Langerhans cell histiocytosis and tumoural origin. The prevalence of idiopathic CDI was estimated to be 26% in the series of Pomarede et al. [16] and 52% in the series of Maghnie et al. [10]. This discrepancy can partly be explained by the early diagnosis and management of CDI, and by the systematic use of MRI. As during the studied time period measurement of circulating autoantibodies to AVP-secreting cells was not available, we could not rule out an autoimmune aetiology of CDI in patients with a thickened pituitary stalk [18].

The age at the initial clinical manifestation was very variable. After exclusion of post-surgical cases, we observed a semiological association of polyuria-polydipsia in all patients, except in the child with the EEC syndrome. This observation confirms the high frequency of these two symptoms in CDI [2, 9, 14]. All children presented additional manifestations. Growth retardation was observed in nine patients, of whom three were classified as idiopathic. Hence, disturbed growth is not exclusively associated with cerebral tumours, as suggested in other publications [3, 24]. Headache and visual disturbances are two other frequent symptoms, also not specific for a cerebral tumour.

We observed a widely variable latency, up to 4 years, between the initial manifestation and the diagnosis of CDI. As the association polyuria-polydipsia is the most constant early sign, this clinical presentation should incite the paediatrician to perform a check-up including a careful anamnesis and physical examination, blood sampling (for investigation of the renal function and exclusion of diabetes mellitus, natremia and osmolality). A water deprivation test followed by a desmopressine test should be performed. Measuring plasma vasopressin levels can also be used as a tool in the differential diagnosis: a normal to increased concentration reflects a primary potomania or a nephrogenic origin [20]. The disadvantage of this technique is that it cannot be applied in emergency situations.

The presence of the posterior pituitary hyperintense signal on MRI, reflects the functional integrity of the neurohypophysis. The absence of this signal is an important but not pathognomonic element in the diagnosis of CDI [5, 11, 13]. We confirmed the constant character of this feature in all patients in our study. A thickening of the pituitary stalk was also frequently observed, isolated or associated with a mass, in patients with idiopathic CDI, cerebral tumours and Langerhans cell histiocytosis. The pituitary stalk of six out of nine children with idiopathic CDI was thickened during follow-up. Among them three presented initially a thickened stalk and an antehypophyseal deficit. An increase of the thickness of the stalk should lead to the suspicion of a Langerhans cell histiocytosis or a tumoural process, especially if antehypophyseal deficits are associated. Czernichow et al. reported the apparition of a germinal tumour after more than 7 years of follow-up [4]. In view of the fast evolution of this kind of tumour, it is imperative to perform a MRI and to search for tumour markers every 3 to 6 months after the diagnosis of CDI. A biopsy has to be considered if the thickening is larger than 7 mm [4]. In our study, the lesion of the proximal portion was always present. An extension of the thickening suggests a progression of this anomaly. One patient has normalized his pituitary stalk after more than 4 years of follow-up, illustrating that the thickening can be reversible and transient. We emphasize, however, that we have to be

cautious in the interpretation of the HP structure measurements and to integrate the limits of the operator-dependence and the non-reproductibility of exactly identical sections on MRI. Another important component in the MRI analysis is the antehypophyseal size. Data of Maghnie et al. suggest that the association of an increased size of the antehypophysis and a thickened stalk is highly suspicious for a germinal tumour [10]. Other authors suggest that this may be due to the same inflammatory process as involved in the thickness of the stalk [7, 8, 15].

All the children in this study, with associated single or multiple hormonal deficits, had a deterioration of the antehypophyseal size. Our data confirm that GHD is the most precocious and the most frequent feature [10, 12]. Growth retardation does, however, not refer to any specific aetiology.

Our data also confirm that the absence of tumour markers does not exclude the presence of a tumoural process [21, 22]. Nevertheless, their presence in serum, spinal fluid or intracellular compartment, confirmed the diagnosis of cerebral tumour in three of the children included in this study. One among them presented a malignant teratoma diagnosed after a follow-up of 2.4 years.

In conclusion, CDI may be the early sign of an evolving cerebral process. The association of polyuria-polydipsia should incite a complete endocrine evaluation and a meticulous MRI evaluation of the hypothalamo-hypophyseal region.

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