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ORIGINAL ARTICLE

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Clinical presentation and outcome of children with central diabetes insipidus associated with a self-limited or transient pituitary stalk thickening, diagnosed as infundibuloneurohypophysitis

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Summary

Objective: Despite lymphocytic or autoimmune infundibuloneurohypophysitis (INH) is an increasingly recognized aetiology in children with central diabetes insipidus (CDI); clinical data on epidemiology (clinical evolution, predisposing factors, complications), diagnosis and management of this entity are limited and mostly based on published case reports. The aim of this study was to gain a broader insight in the natural history of this disease by analysing the clinical presentation, radiological pituitary stalk changes, associated autoimmunity and hormonal deficiencies in children with CDI and a self-limiting or transient stalk thickening (ST), diagnosed as autoimmune infundibuloneurohypophysitis, during the last 15 years in four Belgian university hospitals.

Design and Patients: The medical files of nine CDI patients with a ST at initial presentation and no signs of Langerhans cell histiocytosis or germinoma at presentation and/or during follow-up of more than 1.5 years were reviewed.

Results: Age at presentation ranged from 3 to 14 years. Two patients had a positive family history of autoimmunity. Three children presented with associated growth failure, two with nausea and one with long-standing headache. Median maximal diameter of the stalk was 4.6 mm (2.7-10 mm). Four patients had extra-pituitary brain anomalies, such as cysts. One patient had central hypothyroidism, and another had a partial growth hormone deficiency at diagnosis. Within a mean follow-up of 5.4 (1.5-15) years, stalk thickening remained unchanged in two patients, regressed in one and normalized in six children. CDI remained in all, while additional pituitary hormone deficiencies developed in only one patient.

Conclusions: In this series of children INH with CDI as initial presentation, CDI was permanent and infrequently associated with anterior pituitary hormone deficiencies, despite a frequent association with nonstalk cerebral lesions.

KEYWORDS

autoimmune hypophysitis, diabetes insipidus, neurogenic, paediatrics

1 | INTRODUCTION

Central diabetes insipidus (CDI), a rather uncommon disorder in children, which is caused by a deficiency of antidiuretic hormone (ADH), is due to different aetiologies, including genetic, traumatic, inflammatory and neoplastic diseases.[1] About one-third of children with recent onset CDI display pituitary stalk thickening (ST) at first MRI evaluation.[2,3] At neuroimaging follow-up, a range of pituitary stalk size variations can be observed, from spontaneous resolution to further enlargement.[4,5] In those cases with a self-limited and/or transient stalk thickening and a normal (or sometimes decreasing) anterior pituitary size at serial imaging, the diagnosis of (lymphocytic or autoimmune) infundibulo-neurohypophysitis (INH) has been made more frequently during the last years,[6-9] even in the absence of circulating auto-antibodies or a histological confirmation of lymphocytic infiltration. The diagnosis of INH is frequently made by exclusion and remains in the first years of presentation uncertain, even with histological confirmation.[10,11] Furthermore, pituitary stalk biopsies, especially in children, are in general reserved for those patients with progressive or severe stalk thickening, visual complaints and/or evolving pituitary hormonal deficits.[4,12-15] Beside the diagnostic uncertainty, there is also discussion on the need of corticoid treatment or other immuno-modulating treatments in children.[8,16-18]

To date, there have been only two paediatric cohort studies published that have mainly detailed the hormonal and the neuroimaging changes of CDI patients with either an inflammatory/autoimmune or idiopathic isolated ST, but provided only limited clinical data.[4,5] To have a better understanding of the natural history of the disease, we initiated a retrospective study on the clinical presentation, the evolution of stalk thickness at serial MRI and eventual associated endocrine deficits in children with CDI and a self-limited or transient stalk thickening, in whom the diagnosis of INH was made after a negative work-up for germinoma and Langerhans cell histiocytosis.

2 | METHODS

2.1 | Patients

Cases were identified from the *paediatric endocrine* databases of four participating Belgian pediatric university hospitals (UZ Brussel, Brussels; UZ Gent, Ghent, Cliniques Universitaires Saint Luc, Brussels and UZ Leuven, Leuven). All paediatric (age<16 years) patients with CDI, presenting with a pituitary stalk thickening at diagnosis and a regular clinical and MRI follow-up for at least 18 months, with negative work-up and surveillance for germinoma or Langerhans cell histiocytosis, were eligible for the study. Patients with a previously known congenital (midline) brain defect, with a history of a central nervous system insult (including surgery, radiation and/or infection), with a positive family history of CDI or with a known systemic inflammatory disease, such as sarcoidosis (secondary hypophysitis), were excluded. Unfortunately, in most participating hospitals, paediatric patients with stalk thickening related to Langerhans cell histiocytosis or germinoma were under the supervision of paediatric oncologists and were not available for a comparative analysis.

2.2 | Data collection

In total, nine (five female and four male) children with CDI had been diagnosed with an inflammatory/autoimmune stalk thickening or INH in the preceding 15 years in these collaborating university hospitals. The following parameters were retrieved from the medical files: gender, body weight and height, symptoms at initial presentation, known chronic (autoimmune) diseases, MRI findings (only stalk or stalk and infundibulum involvement, stalk thickness at widest diameter, stalk contrast enhancement at diagnosis and during follow-up, pituitary hormone deficiencies at diagnosis and at follow-up, autoimmune markers at diagnosis and follow-up, cerebrospinal fluid analyses at diagnosis, family history of autoimmune diseases, histopathology data when available and eventual treatments). Diagnosis of CDI was made by the local paediatric endocrinologist on the presence of polydipsia and polyuria with inappropriate dilute urine in the presence of high plasma osmolality, either spontaneously or after water deprivation. MRI was performed according to local protocols, and in all cases, an entire brain survey, including gadolinium enhancement contrast enhanced T1-weighted sequences in sagittal and coronal planes, was obtained. A change in stalk thickness was defined as a variation of at least 20% in the larger axis on two consecutive examinations.

3 | RESULTS

3.1 | Clinical presentation

As shown in Table 1, median age of the children at diagnosis was 6.7 (range 3-14) years. All patients presented with recent onset polydipsia and polyuria, and in two patients, the initial presentation was secondary enuresis nocturna. Urinary symptoms were less than 1-month present. Two patients had recent onset of nausea, and one patient had a long-lasting (around 1 year) headache. None of the patients had visual

TABLE 1 Clinical characteristics at diagnosis (n=9)

Age at diagnosis yr (median [range]):	6.7 (3-14)
Girls (n=5)	7.6 (3-14)
Boys (n=4)	6.3 (4-9)
Mean (SD) Height (SDS)	+0.5 (±1.0)
History of autoimmunity (Y/N)	0/9
Family history of autoimmunity (Y/N)	2/9
Symptoms at presentation:	
Enuresis nocturna	2/9
Failure to thrive	2/9
Headache	1/9
Nausea	2/9
Polydipsia	9/9
Polyuria	9/9

complaints. Weight loss in the preceding weeks or months (on average 1.5 kg) was present in three cases, while none of the children had an excessive weight gain. Mean height of the children at initial evaluation was 114.2±6.7 cm (+0.5 SDS), and mean BMI was 14.0±0.4 kg/m². All anthropometric data were within normal limits for age (according to Belgian reference charts[19]). None of the patients had recurrent otitis, skin rash, bone pain or chronic cough at diagnosis or during follow-up.

3.2 | Laboratory findings

All patients had a biochemical and haematological work-up, including sedimentation rate, blood cell count, kidney and liver function tests, which were normal in all patients. All patients tested negatively for the classical tumour markers β-HCG and α-fetoprotein in blood and six tested negatively in the cerebrospinal fluid.

3.3 | Pituitary function

All patients had an evaluation of the anterior pituitary function by basal hormonal analysis at diagnosis. One patient had an asymptomatic central hypothyroidism at presentation. A low GH response after insulin tolerance test was noticed in one of the three patients, who had an insulin tolerance test in their complementary hormonal work-up, but this patient had had normal growth in preceding years and normal IGF-1 values at follow-up. Pubertal onset and development were normal in the three children observed during adolescence.

3.4 | Autoimmunity parameters

None of the patients had a personal history of autoimmunity, but two patients had a positive family history of autoimmunity (auto-immune thyroiditis, type 1 diabetes mellitus). In only two patients, a diagnostic work-up for associated autoimmunity was done. The first patient screened positive for antipituitary antibodies, antinuclear antibodies (ANF, titre: 1:40, 2+), antineutrophil cytoplasmic antibodies (ANCA, titre: 3+) and antismooth muscle antibody (ASMA, titre: 1:20, 3+), but was negative for antimitochondrial antibodies (AMA) and liver kidney microsome type 1 antibodies and had normal levels of IgG4. The second patient had a negative work-up for antipituitary antibodies, ANF, antithyroid microsomal antibodies (TPO) and antigrowth hormone antibodies.

3.5 | MRI findings

At presentation, all patients had a thickening of the pituitary stalk (>2.5 mm), which was limited to the proximal part in two patients. The average diameter of the stalk was 4.6 mm (range 2.7-10 mm). Beside the ST, all patients had at first clinical presentation an absent posterior pituitary bright spot, a diffuse contrast enhancement of the stalk and a normal anterior pituitary size. A small infundibular mass lesion was present in two children and a pineal gland cyst in one patient. One patient had bulging of the diaphragma sellae and a small cyst within the stalk, suspected to be a Rathke cleft cyst.

3.6 | Other complementary examinations

Six patients had cerebrospinal fluid examination and a chest X-ray, five patients had a whole skeletal X-ray survey, and one patient had a bone scintigraphy. All these examinations were normal. No patient underwent a stalk biopsy.

3.7 | Treatment

All patients received desmopressin from the diagnosis of CDI. The patient with central hypothyroidism was treated with thyroxin supplementation and received during 8 weeks oral glucocorticoids, starting 4 weeks after diagnosis, as an evolving anterior pituitary insufficiency was expected, given an initial increase in ST. None of the patients received surgical or any other medical treatment at diagnosis or at later stage.

3.8 | Outcome

Follow-up data for at least 18 months were available for all patients. All patients were kept under close clinical (3 monthly in the first year) and MRI (6 monthly in the first 2 years) observation over a mean period of 5.4 years (range 1.5-15 year). In two patients, the ST remained unchanged over time (Table 2). One patient had a small progression of the thickening of the stalk before a spontaneous regression occurred. Six patients had a complete normalization of the ST. ST regression was documented after a mean follow-up of 17 months (range 3-48 months). The patient who received 8 weeks of oral glucocorticoids had a documented ST regression after 3 months. The two patients with a persisting stalk thickening had a follow-up of 3 and 6 years. Progression to panhypopituitarism was seen in the patient with several positive auto-antibodies, about 15 months after diagnosis, although there was a partial ST regression (to 4 mm). The patient

TABLE 2 Hormonal and MRI findings at presentation and during follow-up (mean duration 5.4 (±4.2 yr))

Pituitary hormone deficiencies:	
At presentation:	
CDI	9/9
Central hypothyroidism	1/9
Low GH response at insulin tolerance test	1/3
At follow-up:	
CDI	9/9
Panhypopituitarism	1/9
Isolated hormonal deficiency	0/9
MRI stalk findings	
Stalk thickness at presentation (median [range])(mm)	4.6 (2.7-10)
Stalk evolution at follow-up:	
No change	2/9
Initial thickening and subsequent regression	1/9
Regression	6/9

with a low GH response at diagnosis had normal IGF-1 values at follow-up and was not treated with GH. In all other patients, the hormonal results remained normal or unchanged during follow-up (Table 2).

In none of the patients, extracranial signs of Langerhans cell histiocytosis or other diseases or new findings on brain imaging were observed.

4 | DISCUSSION

We report the clinical and hormonal data and the MRI changes from a retrospective file study in nine (four male) children with INH, who presented with CDI and isolated stalk or a stalk and infundibulum thickening. These cases were collected during the last 15 years in four Belgian university hospitals, confirming the rarity of this disease. The experience gained by paediatric endocrinologist on this entity is thus limited, explaining the variation in biochemical and especially immunological and radiological examinations performed. Furthermore, clinical guidelines for the diagnosis and follow-up of children with ST have not been published until very recently in literature.[15]

This so-called stalkitis or inflammatory ST is suspected to be of autoimmune origin, based on histological and anti-vasopressin-cell auto-antibody findings in those subjects with a far reaching diagnostic work-up.[3] However, none of the patients in our survey had an associated autoimmune disease, and in contrast to some adult series,[20] no female preponderance was observed in our study. In only two patients of our cohort, a screening for circulating auto-antibodies was performed, being positive in one patient. Vasopressin-cell auto-antibodies and other auto-antibodies are frequently, but not always present in children with INH, but might be useful in confirming the diagnosis.[3] Stalk biopsy was not performed in our patients, although severe thickening of the pituitary stalk (>6.5 mm) was present in one patient and a suprasellar mass was seen in two patients. By most paediatric endocrinologists, a stalk biopsy was considered to be a potentially hazardous procedure, even though the more recent surgical methods have minimized risk. Furthermore, the detection and biopsy of extracranial lesions will allow the diagnosis of patients with Langerhans cell histiocytosis and CDI as initial presenting sign.[21]

Clinically, our cohort of young patients, who presented all with CDI, had no clinical symptoms of anterior lobe dysfunction or hypothalamic dysfunction, besides some limited growth retardation in three patients. Failure to thrive in children with CDI has been reported previously and is not associated with a specific underlying condition.[22] Subnormal GH responses to insulin induced hypoglycaemia have been reported previously in series of adult and paediatric patients with inflammatory/autoimmune ST, but was observed in only one of the three patient tested in our cohort. Only a minority of the patients in our study had additional complaints of nausea and headache and none had visual complaints, in contrast to what has been observed in case of (anterior gland) hypophysitis.[9,17]

Absence of the posterior pituitary bright spot in association with ST, which was seen at different levels of the stalk, and contrast enhancement were constant MRI findings in our patients. Thickening of the central part has been described as the first sign of Langerhans cell histiocytosis,[23] while a more proximal thickening might precede the diagnosis of a germinoma.[10] Most children with a germinoma are diagnosed within the first 18 months after CDI onset,[14] and those children with Langerhans cell histiocytosis will present with extracranial lesions during the first year, in case of initial isolated stalk involvement and have frequently skull involvement.[11] All of our patients had at least 3-monthly clinical evaluations and 6-monthly MRI evaluations during the first 2 years. No growth of tumorous lesions, especially in the hypothalamo-pituitary region or pineal gland region, was seen at brain imaging. Therefore, it is unlikely that low aggressive dysgerminoma or isolated Langerhans cell histiocytosis has been responsible for the ST in our patients. However, two of our patients had an associated suprasellar mass visible on the first MRI, but without any progression at follow-up. This mass effect has been described previously in children with so-called idiopathic stalk thickening, although it is not yet understood what the clinical implications are.[4] One patient had a pineal gland cyst and another a Rathke cleft cyst. It is unclear of the presence of these brain anomalies are eventual risk factors for INH. It has been speculated that the partial rupture of a Rathke cleft cyst may lead to a local inflammatory reaction.[6] We did not find any extension of the inflammatory process beyond the stalk in our children. In some adult cases presenting with INH, extension of the inflammatory process to the cavernous sinus, chiasma opticum and adenohypophysis has been observed.[24,25]

The natural course of this inflammatory stalk disorder is unique by its spontaneous regression, which however shows a variable pattern. In six patients, a normalization of the ST was seen within 17 months. In all patients in our study, CDI was permanent and in general, easily treatable without episodes of hypernatremic dehydration or water retention. There was no association between the MRI stalk changes and additional hormonal deficits on follow-up. In a recent series of 27 paediatric CDI patients with ST, a clear association between stalk thickness at diagnosis and the probability of developing additional hormone deficiencies was observed, but these patients had also a decrease in the size of the anterior pituitary at MRI imaging, which was not the case in our series.[15] Only one child developed additional pituitary hormone deficiencies, while the ST regressed. We cannot exclude that with a prolonged follow-up, more patients develop pituitary hormone deficits, although in most children with an initial pituitary ST, these deficiencies were observed within the first 24 months.[4,5] Of interest, no prolactin elevation was seen in our patients. Also in adults with INH, hyperprolactinaemia has rarely been documented, whereas in the two largest studies of children with idiopathic stalk thickening, prolactin levels have not been assessed.[4,5]

Only one patient was treated with glucocorticoids. No randomized controlled trials with synthetic glucocorticoids have been performed in INH patients. Given that the inflammatory process is self-limiting in most cases, the paediatric endocrinologist in the collaborating hospital agreed that there is no case for routine glucocorticoid treatment and that glucocorticoid therapy or surgical decompression should be reserved for those patients with evolving anterior pituitary hormone deficiencies or compromised vision.

A limitation of our study is the retrospective study design. All children underwent different hormonal and biological testing at different moments in the follow-up, and in particular, the autoimmune parameters were only tested in a limited group of children. The degree of pituitary dysfunction might thus be underestimated. Antipituitary antibodies were only determined in two patients, and no data on vasopressin-cell auto-antibodies were available, because no laboratory in Belgium provides this analysis. Several methods exist for the detection of antipituitary antibodies, with indirect immunofluorescence the most commonly available technique. But even with the same immunofluorescence methodology, several substrates, such as rat, which was used in our patients, as well as baboon, *Macaca mulatta*, bovine and guinea pig pituitaries, and fixation methods are used, complicating its interpretation.[26] Also, the utility of vasopressin-cell autoantibodies is still debated, because of the variability between methods and low specificity and sensitivity, although recently the measurement of anti-rabphilin-3A antibodies was found to have a specificity of 96%.[3,27] In addition, no central reading of MRI findings was performed in this retrospective study and the more innovative MRI analysis, such as texture analysis, was not performed.[28]

In conclusion, the present study confirms that CDI related to INH is an uncommon condition in paediatrics. INH was found to occur in young children, even from the age of 3, without a female gender prevalence, as commonly seen in adults, and only rarely associated with other symptoms, as visual complaints. CDI was permanent and infrequently associated with anterior pituitary hormone deficiencies, despite a frequent association with nonstalk lesions. It is unclear of the presence of other brain anomalies are eventual risk factors for INH. Prospective collection of cases through a national registry is advocated to enable a better assessment of this condition and to develop evidenced based guidelines for management of this rather rare condition.

CONFLICT OF INTERESTS

Nothing to declare.

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