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Hypothalamo-Pituitary Abnormalities in Adult Patients with Langerhans Cell Histiocytosis: Clinical, Endocrinological, and Radiological Features and Response to Treatment

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disorder in which granulomatous deposits occur at multiple sites within the body, but which often involves the hypothalamo-pituitary axis (HPA). Although diabetes insipidus (DI) is a well recognized complication, the frequency of anterior pituitary and other nonendocrine hypothalamic (NEH) involvement has not been well defined, particularly in adult patients with the disease. We have evaluated the frequency and progression of LCH-related anterior pituitary and other NEH dysfunction and their responses to treatment in 12 adult patients with histologically proven LCH and DI. They were followed up for a median of 11.5 yr (range, 3–28 yr) after the diagnosis of DI was made. Study evaluations comprised clinical (including formal psychometric assessment where appropriate), basal and dynamic pituitary function tests, and radiology with computed tomography and/or magnetic resonance imaging scanning. Eleven patients received systemic treatment, and 5 patients received external beam radiotherapy confined to the HPA.

The median age at diagnosis of DI was 34 yr (range, 2–47 yr); DI was the presenting symptom in four patients, whereas the remaining eight each developed DI 1–20 yr (median, 2 yr) after the diagnosis of LCH. Eight patients developed one or more anterior pituitary hormonal deficiencies at a median of 4.5 yr (range, 2–22 yr) after the diagnosis of DI: GH deficiency developed in eight patients (median, 2 yr; range, 2–22 yr), FSH-LH deficiency in 7 patients (median, 7 yr; range, 2–22 yr), and TSH and ACTH deficiency in five patients (median, 10 yr; range, 3–16 and 3–19 yr), respectively; five patients developed panhypopituitarism. In addition, seven patients with anterior pituitary dysfunction also developed symptoms of other NEH dysfunctions at a median of 10 yr (range, 1–23 yr): five morbid obesity (body mass index, >35), five short term memory deficits, four sleeping disorders, two disorders of thermoregulation, and one adipsia. All patients developed disease outside of the hypothalamus during the course of the study, and no fluctuation of disease activity in the HPA region was noted. Radiological examination of the HPA was abnormal in each of the eight patients with anterior pituitary involvement and in the seven patients with NEH dysfunction (one or more abnormalities): seven had thickening of the infundibulum, and one had hypothalamic and thalamic signal changes. All patients who had a magnetic resonance imaging scan had absence of the bright spot of the posterior pituitary on the T_1-weighted sequences, and in four patients with DI and normal anterior pituitary function this was the only abnormality. The five patients who received radiotherapy to the HPA achieved a partial or complete radiological response, and there was no evidence of tumor progression in this region. No form of therapy, including chemotherapy, improved any established hormonal deficiencies or symptoms of NEH.

In summary, in our adult patients with hypothalamic LCH and DI, anterior pituitary hormonal deficiencies developed in 8 of 12 patients; these occurred over the course of 20 yr. They were frequently accompanied by structural changes of the HPA, although these were often subtle in nature. In addition, symptoms of NEH dysfunction developed in up to 90% of such patients and complicated management. Radiotherapy may be useful in achieving local control of tumor, but established anterior, posterior pituitary, and other NEH dysfunctions do not improve in response to current treatment protocols. Patients with LCH and DI, particularly those with multisystem disease and a structural lesion on radiology, should undergo regular and prolonged endocrine assessment to establish anterior pituitary deficiency and provide appropriate hormonal replacement. (*J Clin Endocrinol Metab* **85:** 1370–1376, 2000)

LANGERHANS cell histiocytosis (LCH) is a rare disease characterized by aberrant proliferation of a specific dendritic (Langerhans) cell belonging to the monocyte-macrophage system (1). These atypical but mature cells of monoclonal origin can infiltrate many sites of the body and may occur as localized lesions or as widespread systemic disease (2). Infiltration of the hypothalamo-pituitary axis (HPA) has been reported in between 5–50% of autopsy patients with LCH (3–6). Diabetes insipidus (DI) is the most common endocrine abnormality, reported in 15–50% of patients with LCH (2, 5–7). Anterior pituitary dysfunction, although well recognized, has been reported in only 5–20% of patients (5, 8–12); however, anterior pituitary function has rarely been systematically studied, whereas most of these clinical details are derived from studies in children (7, 12, 13). LCH has been thought to occur even more rarely in adults and to have a different clinical phenotype from that seen in children; skin, lung, and bone involvement and DI are common, whereas involvement of the liver, spleen, lymph nodes, and bone marrow is much less frequent (7, 13).

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Because the disease is rare in adults, leading to a paucity of long term follow-up studies, the prevalence and biological predictors of the specific deficits of anterior pituitary function have not been well defined (4, 7, 13, 14). In addition, although symptoms of generalized hypothalamic dysfunction have been described in patients with LCH and central nervous system (CNS) involvement, the prevalence, severity, and clinical implications of such involvement are unknown (13). Disease activity in some sites, such as skin and bone, is known to fluctuate spontaneously, but whether this is so in other sites in adults is less certain. Further, responses to treatment have not been clearly delineated in adults (2, 7, 13).

This study was undertaken to determine the frequency of defects in anterior pituitary function in adult patients with DI and LCH followed for a prolonged period. We have attempted to identify whether there is any particular pattern of evolution of pituitary dysfunction, to detemine the presence of biological predictors with relation to structural changes observed on computed tomography (CT) or magnetic resonance imaging (MRI) scanning, and to monitor the progress of the disease and its response to treatment. Furthermore, we have investigated the development of generalized nonendocrine hypothalamic (NEH) dysfunction and its implications for the management of these complex cases.

Subjects and Methods

We reviewed retrospectively the case notes of all patients above the age of 16 yr with a histologically confirmed diagnosis of LCH, initially referred to our department with DI, for complete endocrine and radiological evaluation of the HPA. The case notes of 12 patients referred over a 20-yr period (1975–1998) were complete for analysis (7 females); 3 patients had childhood-onset LCH. The diagnosis of LCH was established according to proposals of the Writing Group (15); particular attention was paid to clinical symptoms/signs, endocrine and radiological features of the HPA, as well as the presence of other nonendocrine hypothalamic involvement and their responses to treatment. According to the Gramatovic and D'Angio classification (16), LCH was divided into localized and multifocal forms. Localized disease was defined as LCH involving one soft tissue site with or without one site of bone involvement. Multifocal disease was defined as the involvement of two or more soft tissue sites with or without bone involvement. Disease activity was defined as chronic progression, local disease recurrence after successful initial therapy, or new symptomatic, histologically verified, organ extension based on clinical, biochemical, and radiological features (17).

Symptoms/signs suggestive of 1) mass effects specific to the HPA either at presentation and/or at regular follow-up, 2) anterior and posterior pituitary hormone deficiencies, and 3) other NEH involvement (appetite, thirst, sleep disturbances, memory deficit, temperature, and food intake dysregulation) were particularly recorded. Complete endocrine evaluation consisted of baseline serum hormonal measurements (serum cortisol, T_4, T_3, TSH, PRL, LH, FSH, estradiol, progesterone, testosterone, and GH/insulin-like growth factor I levels), early morning plasma and urinary osmolality measurement, and, when appropriate, dynamic endocrine tests: the insulin tolerance test for assessment of GH and/or ACTH/cortisol reserve, TRH and GnRH stimulation tests, and a water deprivation test for assessment of partial states of vasopressin deficiency (18). Neuroendocrine assessment was performed at the time of diagnosis of DI in nine patients, 1 yr after the diagnosis in two patients, and 11 yr after the diagnosis in one patient. Five patients received treatment before the first neuroendocrine assessment; two patients had been given chemotherapy 1 and 15 yr previously, two had been given systemic corticosteroids, and two had been given localized radiotherapy (one of whom was also given corticosteroids). Whenever there was clinical suspicion of NEH involvement, formal neuropsychological-psychometric evaluation was performed. The assessment included tests of general intellectual functioning, memory, attention, and concentration and in some cases the Halstead-Reitan battery. Assessments were carried out at intervals over a period of more than 20 yr, and the tests used have varied as test revisions and innovations have appeared; the tests used were therefore not necessarily the same for each patient. Five patients in total had formal psychometric assessment; two were assessed before any form of radiotherapy was applied to the HPA, whereas two were assessed 2 yr or more after radiotherapy was given.

Radiological assessment included conventional radiology of the localized and/or generalized disease and enhanced CT and/or, since 1993, MRI of the HPA at the time of initial assessment and before and after each therapeutic session in 11 patients; in the other patient HPA involvement was noted at autopsy.

Treatment modalities were categorized as local (radiotherapy) or systemic (glucocorticoid and/or cytotoxic drugs) therapy (see Table 4). Radiotherapy was applied to localized lesions and in five patients with disease confined to the HPA (median dose, 2000 cGy; range, 1000–2500 cGy). All patients received radiotherapy to the HPA region after all their endocrine deficiencies had developed. Response criteria were considered according to disease activity: no response, indicating progressive disease or no improvement or system dysfunction, and local recurrence, *vs.* complete or partial remission, were differentiated (17). During the assessment of evolving hypothalamo-pituitary dysfunction, particular attention was paid to the effect of possible confounding factors on the development of the dysfunction after treatment with local radiotherapy (19).

Results

Our series included 12 patients (7 female) with a median follow-up period of 11.5 yr (range, 3–28 yr) after the diagnosis of DI had been made. The median age at diagnosis of LCH was 28.5 yr (range, 1–47 yr). The median age at diagnosis of DI was 34 yr (range, 2–47 yr), and the median age at first endocrine assessment was 34 yr (range, 5–53 yr). Patients were reassessed at least annually after the original endocrine assessment.

Extent of disease (Table 1)

All patients developed multisystemic disease; 7 patients presented with bone involvement, whereas 11 of 12 subsequently developed bone lesions. Five patients presented with soft tissue involvement, besides DI, but eventually all patients developed some form of other soft tissue infiltration. Eleven patients developed both soft tissue and bone disease, 7 multifocal soft tissue, whereas 6 had evidence of multifocal bone disease. There was persistent disease activity despite different treatment modalities, and no patient obtained complete remission. In addition, none of the patients showed spontaneous improvement in disease activity before any form of treatment was applied, and no remission of established endocrine deficiencies was noted. Two of the patients died during the period of the follow-up. One patient died from Creutzfeldt-Jacob disease as a consequence of treatment with cadaveric GH for growth retardation. The other patient died after a severe gastrointestinal bleed secondary to esophageal varices (the patient also suffered from micronodular cirrhosis of the liver, probably alcohol related).

Posterior pituitary dysfunction (DI; Table 2)

Four patients initially presented with DI (defined as raised plasma osmolality, >295 mosmol/kg, in the presence of inappropriate low urine osmolality), but subsequently all patients developed DI during the course of the disease (median, 2 yr; range, 0–20 yr). DI was the earliest hormonal deficiency

TABLE 1. Extent of involvement at presentation and during the course of the disease in patients with LCH and DI

Patient no.	Bone involvement		Soft tissue involvement	
	At presentation	Follow-up	At presentation	Follow-up
1		Facial bones[a]		Vulva/cerebellum
2	Jaw (mandible)[a]			Skin + ear
3		Spine	Neck[a]	
4	Facial bones[a]	Skull		Ear
5			Skin[a]	
6		Facial bones		Skull + vulva[a] + thyroid
7	Pelvis		Liver + lung + skin[a]	
8		Jaw (mandible)[a]		Skin + anus + ear + axilla[a]
9	Skull	Spine + long bones[a]	Vulva	Eye
10	Skull	Pelvis + long bones		Ear[a]
11	Spine	Jaw (mandible)[a]	Lung	Lung + breast
12	Skull + long bones			Groin[a] + skin

[a] Site of biopsy.

noted and predated the development of any other endocrine deficiency in all patients with anterior pituitary involvement by a median of 2 yr (range, 1–16 yr). Eight patients with DI developed at least one other anterior pituitary hormone deficiency; DI remained the only endocrine abnormality in the other four patients. All patients with DI eventually developed multisystem disease; no spontaneous improvement in posterior pituitary function was noted.

Anterior pituitary dysfunction (Table 2)

Three patients had pituitary assessment at initial presentation (1 patient with DI). Eight patients in total developed 1 or more anterior pituitary hormonal deficiencies; 6 of 12 patients showed more than 1 hormonal deficiency, whereas 5 patients developed panhypopituitarism.

GH deficiency (GHD). GHD (defined as a peak serum GH <9 mU/L during insulin-induced hypoglycemia or a glucagon test) developed in eight patients (median, 8 yr after diagnosis of DI; range, 2–20 yr). GHD preceded the development of all other endocrine deficiencies in four patients, whereas two patients (cases 5 and 11) developed LH-FSH deficiency at an earlier stage, and one patient (case 8) developed concomitant ACTH deficiency. One patient with GHD and short stature was treated with cadaveric GH, but eventually developed terminal Creutzfeldt-Jacob disease. Two adult patients have received synthetic GH replacement therapy.

FSH-LH deficiency. Gonadotropin deficiency (defined as low basal gonadal steroids with concomitant inappropriately low gonadotropins) developed in six patients at a median of 7 yr after the diagnosis of DI (range, 2–22 yr). Gonadotropin deficiency was the second most common evolving anterior pituitary hormone deficiency, but in two patients (cases 5 and 11) it preceded GHD. One male patient with infertility was successfully treated with gonadotropin treatment.

TSH deficiency. Thyroid hormone deficiency (defined as a lack of elevation of TSH in the presence of low levels of thyroid hormones) developed in five patients (median, 10 yr; range, 3–16 yr) and preceded the development of ACTH deficiency in all except one patient (Table 2). TSH deficiency developed only in the context of panhypopituitarism. One patient developed primary hypothyroidism, which resulted from histologically proven LCH of the thyroid, whereas another with primary hypothyroidism had positive thyroid antibodies; although no biopsy was performed to exclude thyroidal infiltration with LCH, a presumptive diagnosis of autoimmune hypothyroidism was made.

ACTH deficiency. ACTH deficiency [defined as either a 0900 h cortisol level of <100 nmol/L or an impaired cortisol rise (<550 nmol/L) during insulin-induced hypoglycemia or a glucagon test] developed in five patients (median, 10 yr; range, 3–19 yr). ACTH deficiency, similar to TSH deficiency, only developed in the context of panhypopituitarism (cases 6–9 and 11) and was the latest evolving deficiency; no patient presented in adrenal crisis.

PRL levels. PRL levels in excess of the upper extent of the normal range (360 mU/L) were found in two patients (1600 and 1800 mU/L) during the course of the disease (cases 1 and 8). One of these two patients (case 1) had normal anterior pituitary function and no abnormality on imaging, whereas the other was panhypopituitary.

NEH dysfunction (Table 3)

Symptoms of NEH dysfunction, although not noted at initial presentation, developed in seven patients at a median of 10 yr (range, 1–23 yr) after the diagnosis of DI was made. Each of the seven patients developed an abnormal eating pattern (hyperphagia) at a median of 10 yr (range, 1–28 yr); five had morbid obesity, defined as a body mass index (BMI) greater than 35 (median BMI, 40; range, 35–44), and required pharmacological intervention with dexamphetamine; although this treatment may have halted the progression of further weight gain and helped overcome somnolence, it did not improve obesity overall. However, minor abnormalities not requiring treatment were observed in the majority of patients (median BMI, 31; range, 20–44). Four patients developed worsening short term memory formally assessed with neuropsychological tests at a median of 10 yr (range, 2–24 yr). Two patients developed problems with thermoregulation, one of them requiring recurrent admissions for life-threatening hypothermia. Another patient developed adipsia, making the management of DI extremely difficult; this patient was treated with a fixed volume of fluid intake, and the dose of desmopressin was then adjusted to requirements according to body weight, fluid balance, and osmolality mea-

TABLE 2. Evolution of anterior pituitary deficiencies and NEH in patients with LCH and DI in respect to imaging findings of the HPA (the time that radiotherapy was applied to the HPA in five patients is also noted)

Patient no.	Sex	Age at diagnosis of DI (yr)	Endocrine and NEH involvement at diagnosis	RT to HPA (years from diagnosis of DI)	Endocrine and NEH involvement during follow-up (yr to development)	Radiology[a]
1	F	39	DI		↑ PRL	[b]
2	M	47		(3)	DI (1), GH (2), NEH (3)	Infundibular thickening/mass
3	F	18			DI (3)	
4	F	3			DI (20), GH (22), NEH (10)	Infundibular thickening
5	M	46	DI	(10)	LH-FSH (5), GH (9), NEH (1)	Infundibular thickening-thalamic involvement
6	F	34	DI	(20)	GH (16), TSH (17), LH-FSH (19), ACTH (19), NEH (23)	Infundibular mass
7	F	4		(12)	DI (3), GH (5), LH-FSH (10), TSH (10), ACTH (10) NEH (16)	Infundibular thickening
8	M	30	DI	(5)	GH (2), LH-FSH (3), TSH (3), ACTH (3), ↑ PRL	Infundibular thickening
9	F	2			DI (2), GH (3), LH-FSH (7), TSH (11), ACTH (27) NEH (27)	Infundibular thickening/mass
10	M	41			DI (2)	
11	F	45			DI (7), GH (9), LH-FSH (8), TSH (9), ACTH (8) NEH (10)	MB[c]
12	M	34			DI (5)	

[a] Abnormalities other than loss of the bright spot of the posterior pituitary are shown only.
[b] Cerebellar involvement.
[c] No imaging (postmortem findings).
MB, Mamillary bodies; NEH, nonendocrine hypothalamic; RT, radiotherapy.

surement. Symptoms of NEH dysfunction developed only in patients with anterior pituitary dysfunction (seven patients) accompanied by structural lesions on pituitary imaging (see below). There was one patient with panhypopituitarism in whom the only evidence of NEH was severe obesity (BMI, 41; case 8; Table 3). Of the five patients who underwent formal psychometric assessment, four (two preirradiation, two postirradiation) had evidence of varying degrees of memory impairment involving recall and/or recognition of verbal material (designs, faces, pictures of common objects, and spatial position of pictures and objects). The fifth patient, and the only one of the five to show no HPA abnormality on imaging, had no evidence of memory impairment or neuropsychological impairment generally (Halstead-Reitan impairment index, 0.14; normal, 0.00–0.30).

Radiological findings (Table 2)

In total, 11 patients had imaging of the HPA (the other patient had anterior pituitary and NEH involvement demonstrated at autopsy). The most commonly encountered abnormalities were infundibular thickening (7 patients) and hypothalamic and thalamic signal changes (1 patient). Four patients had apparently normal imaging of the HPA; all of these had intact anterior pituitary function, and 1 of these patients had extensive cerebellar involvement without any obvious hypothalamic involvement. However, all patients who had imaging with MRI scanning showed a lack of the bright spot of the posterior pituitary on T_1-weighted sequences. Radiological abnormalities always predated the development of anterior pituitary dysfunction.

Patients with panhypopituitarism

Five patients progressed to panhypopituitarism (cases 6–9 and 11); two of these initially presented with DI. The median age at the development of DI was 30 yr (range, 2–45 yr); PRL levels were elevated in only one (case 8). Radiology revealed infundibular thickening in all four patients who were imaged, whereas one patient who did not have pituitary imaging was found to have mamillary body involvement on autopsy; all patients had NEH involvement. However, no particular pattern of clinical presentation, disease extension, evolving endocrine deficiency, or radiological appearance was found that could predict more severe impairment of pituitary function.

Response to treatment (Table 4)

Treatment regimens included a wide range of therapeutic modalities. Radiotherapy was given to six patients with bone and bone/soft tissue lesions; partial responses were initially obtained in all six in terms of tumor mass regression, and during the period of follow-up no irradiated lesion showed progression. However, five of six patients eventually developed additional lesions elsewhere. Five patients with HPA involvement on imaging received treatment with local radiotherapy either alone (median dose, 2000 cGy; range, 1000–2500 cGy) or in combination with other chemotherapeutic agents at a median of 11 yr (range, 2–30 yr) after the diagnosis of DI. All five patients showed evidence of partial

or temporary radiological improvement, although the hormonal deficiencies remained. Eleven patients received some form of systemic treatment, which included chemotherapy (etoposide, vinblastine, and/or cyclosporin) and high dose corticosteroids. Although partial responses were obtained, all patients finally relapsed or had progression of the disease. No established endocrine or NEH deficiency responded to treatment.

Two patients developed other malignancies during the course of the disease. One patient (case 5) developed chronic granulocytic leukemia 6 yr after the diagnosis of LCH, and he is currently under regular follow-up with stable disease. Another patient developed a squamous carcinoma of the tongue that is currently in remission.

Discussion

LCH is a rare disorder, mainly affecting children, with clinical manifestations that can vary widely (4, 7, 13). It is only recently that well defined pathological criteria have evolved to allow clear definition of the natural history of the disease (7, 13, 17). Adults comprise less than 30% of all reported cases, with an incidence of approximately $1.8/10^6$ (7, 13), but the extent and long term outcome of the disease in adults have not been clearly defined (20). Anterior pituitary dysfunction has been described in up to 20% of patients with LCH, usually associated with DI (4, 8–10, 13); it has also been observed after radiation therapy (2, 21, 22). However, anterior pituitary function has not been systematically studied in adults, and most information has been obtained from studies in children (6, 7, 13).

In our subgroup of adult patients with LCH involving the HPA and DI, anterior pituitary dysfunction developed in two thirds of patients followed for a median of 11.5 yr after the diagnosis of DI, unrelated to radiotherapy, but with a wide dispersion of the time to onset. This prevalence is much higher than that previously noted (4, 5, 9, 10, 23), but might be explained by the fact that we studied a particular group, patients with LCH and DI, who are at higher risk for developing anterior pituitary deficiency for a prolonged period (13). However, careful analysis of other studies with prolonged follow-up and more detailed investigation of pituitary involvement in patients with DI demonstrates a similar high incidence (1, 4, 5, 8, 17, 23, 24). As particular attention was paid to eliminate the confounding effects of treatment, particularly radiotherapy, that have previously been implicated in the development of pituitary dysfunction in patients with LCH (4, 13), it seems very likely that anterior pituitary dysfunction develops as a consequence of the disease.

Anterior pituitary deficiency in LCH has almost always been associated with DI (4, 5, 17, 23); only a few cases have

TABLE 3. Symptoms and signs of NEH involvement with respect to anterior pituitary dysfunction in patients with LCH and DI

Patient no.	Anterior pituitary function	Max BMI (kg/m^2)	Eating disorder[a]	Sleeping disorder[a]	Memory deficit[a]	Thermoregulation[a]	Thirst disorder[a]	PRL (mU/L)
1	Not impaired	26			3			1600
2	GH deficiency	28			3			120
3	Not impaired	20						188
4	GH deficiency	39	10					185
5	GH, LH-FSH deficiency	44	1	3	3	5	4	450
6	Panhypopituitary	35	23	23	24	23		370
7	Panhypopituitary	34	16		16			218
8	Panhypopituitary	41						1800
9	Panhypopituitary	25	28	27				205
10	Not impaired	25						160
11	Panhypopituitary	36	10	10	10			
12	Not impaired	25	14					

[a] Years to the development of the NEH dysfunction.

TABLE 4. Responses of bone and soft tissue involvement to treatment in 12 patients with LCH and DI according to the different therapeutic modalities employed

Patient no.	Bone	Treatment	Response	Soft tissue	Treatment	Response
1	+			+	Cyclosporin, Etoposide	NR
2	+	RT/Etoposide	PR→R	+	Etoposide	NR
3	+			+	RT	PR (radiological only)
4	+	RT/Vinblastine	PR→R	+	Vinblastine	NR
5				+	RT/Etoposide	PR→R
6	+	Vinblastine	NR	+	RT/Etoposide	PR→R
7	+	RT	PR→R	+	Vinblastine	NR
8	+	RT/steroids	PR	+	Steroids	NR
9	+	RT/steroids	PR→R	+	Vinblastine	PR→R
10	+			+	Cyclosporin, Etoposide	PR→R
					Vinblastine	PR→R
11	+	RT	PR	+	Vinblastine	
12	+	Steroids	NR	+	Steroids	PR→R
				+		
				+		

NR, No response; PR, partial response; R, relapse; RD, radiotherapy; +, presence of disease.

been noted in the literature of pituitary hormone insufficiency without DI (25). Although DI may predate the diagnosis of LCH, it develops most commonly at about 12 months, with a range that can extend to many years from diagnosis (2, 4, 26). Associated features are multisystem disease with skull vault defects, but particularly temporal bone or orbital lesions with intracranial tumor extension (5). Similarly, Baumgartner *et al.* in another recent study found a 21% prevalence of DI in their adult patients with LCH; half of these had concomitant panhypopituitarism, which appeared sporadically and always in combination with DI (17). These researchers concluded that although the frequency of isolated involvement of the pituitary gland is unknown, this should be considered in all patients with DI (6, 17, 27). Kilpatrik *et al.* (23) found a 15.5% prevalence of DI in adults with LCH; 15% of patients with DI had anterior pituitary involvement. However, as partial forms of DI may also occur and remit spontaneously, this figure may well be an underestimate (4, 17).

GHD occurs in approximately 40% of affected children, and it has been related to histiocytic infiltration of the hypothalamus (14, 22). GHD has frequently been observed as the first endocrine defect in addition to DI, with a median latency of about 1 yr from diagnosis (4, 10, 14, 26, 27). Others have found it only in relation to treatment with radiotherapy (22); however, none of our patients who developed GHD had received any previous radiotherapy to the HPA. Growth retardation, although previously described (21, 22), is thought to be an infrequent presentation of LCH (6, 22). However, it was a common finding in a recent study (14), and GHD should therefore always be considered in children with LCH and DI. As adults with GHD may show an increase in well-being and a favorable metabolic profile in response to GH therapy, assessment of GHD may be an important part of the evaluation of adult patients with LCH (28).

There are only a few reports on gonadal function in patients with LCH, as most studies have been of prepubertal children (14). Although the early studies in adults with LCH and DI failed to demonstrate abnormalities of gonadotropin secretion (8), a few cases of amenorrhea in adults have been described (6, 13). We found a high incidence of gonadotropin deficiency (50% of our patients with DI), which is also apparent in other detailed studies in adults (1, 4, 5, 8, 17, 23, 24). Similarly, thyroid hormone deficiency can be a major component of anterior pituitary dysfunction in patients with LCH (1, 4–8, 17, 23, 24). One of our patients also developed primary hypothyroidism due to LCH infiltration of the thyroid gland, an involvement that has only rarely been previously described (29). ACTH deficiency mostly presented in the context of generalized pituitary involvement; however, a case of isolated ACTH deficiency has also been described (4). PRL levels were elevated in 2 patients, with only 1 showing HPA involvement, and is therefore unlikely to be a significant factor in the pathogenesis of gonadotropin deficiency. Similarly, Maghnie *et al.* (26) reported that basal and TRH-stimulated PRL levels were normal in 17 children with LCH.

Imaging studies of patients with LCH and CNS involvement have shown that more than one type of lesion was present in 87% of individual patients, including patients with DI (5, 30). In addition, abnormalities of the HPA were observed in 68% of patients with CNS lesions and in 81.5% of patients with DI (infundibular thickening, partial or complete empty sella with a lack of posterior pituitary bright spot on T_1-weighted MRI sequences, or a pituitary mass lesion) (5, 24, 26, 30). Morphological changes in the HPA are currently optimally demonstrated by MR imaging with administration of gadolinium-dimeglumine gadopentetate (26, 31). A small pituitary or empty sella has also been described in cases of combined anterior and posterior pituitary insufficiency (4). However, anterior pituitary dysfunction may also occur in the absence of structural changes on imaging and has been attributed to microinjury leading to vascular impairment and scarring (24). Other possible mechanisms include cytokine modulation from adjacent osseous lesions or an autoimmune effect (32). We noted that all of our patients who developed anterior pituitary deficiency had a form of abnormal HPA imaging other than loss of the bright spot of the posterior pituitary on MRI imaging. Similarly, Broadbent *et al.* (4), studying children with DI, demonstrated that a mass lesion with an empty sella or pituitary stalk thickening was present when multiple hormonal deficiencies were identified; in addition, when DI occurred either alone or with GHD, the findings were more variable, although the majority of patients had similar abnormalities.

Maghnie *et al.* attempted to identify predictors of late endocrine sequelae in children with LCH and concluded that dynamic endocrine pituitary testing was not a useful predictor (14). Neither the site of involvement nor the extent of the disease was associated with further endocrine deterioration. Therefore, it seems that only DI in association with markedly abnormal HPA imaging indicates patients with LCH at higher risk for anterior pituitary dysfunction. As DI is associated with multisystem disease in the majority of studies (4, 5, 8, 14), and progression may be greatly delayed (23), such patients should be receiving regular and prolonged follow-up to identify such dysfunction and provide adequate replacement.

DI with structural changes in the HPA often heralds the involvement of other parts of the brain with more global neurological or neuropsychological sequelae, depending on the location of the involvement (5, 30). The signs and symptoms of NEH involvement range from disturbances in social behavior, appetite, and temperature regulation to abnormal sleeping patterns (5). Surprisingly, research is limited on neuropsychological manifestations of the disease, but early findings suggest that these may be relevant in a significant proportion of patients. We found a high prevalence of NEH abnormalities in patients with DI and LCH; all were associated with anterior pituitary deficiency and structural lesions on imaging. The most prominent abnormality was an abnormal eating pattern and obesity; five patients developed morbid obesity, which was difficult to control. Further abnormalities, such as disturbances in thermoregulation and adipsia, can make DI difficult to treat and complicate the overall management of these problematic cases (33, 34). This is particularly significant when there is also memory impairment and problems with compliance (34). Our neuropsychological and radiological findings flag up a link between memory impairment in LCH and structural changes

in the HPA, which is consistent with some of the recent work on diencephalic amnesia (35).

It has been suggested that none of the treatments currently available is able to alter the course of LCH or to prevent its progression (23), whereas established endocrine abnormalities do not respond to treatment (8, 23). Although Rosenzweig *et al*. renewed suggestions that radiotherapy to the HPA when applied early for incipient DI may be effective with partial or even complete remission (27), this has not been found to be the case in other studies (10, 23, 30). In our patients there was clear evidence that localized HPA radiotherapy was associated with tumor regression and stabilization, and none of these patients showed subsequent tumor progression at this site. However, some patients showed little in the way of abnormal imaging of the HPA. Recent advances in MRI imaging have shown absence of the bright spot of the posterior pituitary at the onset or soon after of the development of LCH (5, 26, 30) as well as other HPA abnormalities that may revert to normal at follow-up (5). LCH in adults may run a relatively indolent course (20, 23), and a more conservative approach, especially in elderly or debilitated patients, has been proposed (30). Thus, long term follow-up with proper replacement of hormonal deficiencies may be as important in improving quality of life as other more aggressive interventions.

In summary, adult patients with LCH presenting with DI are at high risk for the development of anterior pituitary deficiency, especially when associated with abnormal HPA imaging. Generalized hypothalamic involvement is also a prominent feature of this disease, and the progressive hypopituitarism appears to be poorly responsive to current modalities of treatment, although localized disease at the HPA responded well to radiotherapy in that region. On the basis of our experience and a review of the literature, systemic chemotherapy appears to be of little benefit in controlling the progression of the disease over the long term, although focal radiotherapy may halt local disease progression in terms of mass effects. We suggest that such endocrine abnormalities should be actively sought in patients with LCH, as their recognition and management play important parts in the treatment of this difficult condition.

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