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Original Article

Endocrine and metabolic assessment in adults with Langerhans cell histiocytosis

L. Montefusco[a,b], S. Harari[b,c,*], D. Elia[b,c], A. Rossi[a,b], C. Specchia[b,d], O. Torre[b,c], G. Adda[a,b], M. Arosio[e]

[a] U.O. di Malattie Endocrine e Diabetologia, Ospedale San Giuseppe Multimedica, Milan, Italy
[b] MultiMedica IRCCS, Milan, Italy
[c] U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria - Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe Multimedica, Milan, Italy
[d] Dipartimento di Medicina Molecolare e Traslazionale, Università di Brescia, Italy
[e] U.O. di Endocrinologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Dipartimento di Scienze Cliniche e di Comunità, Università di Milano, Milan, Italy

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ABSTRACT

Context: Diabetes insipidus (DI) is one of most common complications of Langerhans cell histiocytosis (LCH) but prevalence of anterior pituitary deficiencies and metabolic alterations have not been clearly defined yet.
Objectives: Evaluate prevalence of endocrine and metabolic manifestations in a cohort of patients affected by Pulmonary LCH.
Methods: Observational cross-sectional study on 18 adults (7 M/11 F, 42 ± 12 years) studied for complete basal and dynamic endocrine lab tests and glucose metabolism.
Results: Hypothalamic-pituitary endocrine alterations were found in 9 patients: 9 had DI, 5 Growth Hormone Deficiency (GHD), 5 central hypogonadism, 3 central hypothyroidism and 1 central hypoadrenalism. Hyperprolactinemia and hypothalamic syndrome were found in 2 patients each. All these central endocrine alterations were always associated to DI. Five of the 10 MRI performed showed abnormalities. Prevalence of obesity and glucose alterations (either DM or IFG/IGT) were respectively 39% and 33%, higher than expected basing on epidemiological data on general Italian population. Multi-system-LCH without *risk-organ* involvement (LCH MS-RO$^-$) seems to have slightly higher prevalence of insulin resistance, glucose alterations and metabolic syndrome than LCH with isolated lung involvement (LCH SS lung$^+$). A papillary BRAFV600E positive thyroid carcinoma was diagnosed in one patient.
Conclusions: The presence of anterior pituitary deficiencies should be systematically sought in all LCH patients with DI both at diagnosis and during the follow-up by basal and dynamic hormonal assessment. Patients with pulmonary LCH, particularly those with MS disease, have a worse metabolic profile than general population. Occurrence of papillary thyroid carcinoma has been reported.

1. Introduction

Langerhans cell histiocytosis (LCH) is an "orphan" disease characterized by clonal proliferation of specialized dendritic cell (Langerhans-like or Langerhans cell) and their infiltration potentially in every tissue of the body [1,2].

Recently has been proposed a revised classification of histiocytoses, consisting in 5 groups of diseases. Among those there is Langerhans-related group (LCH) including single system LCH (LCH SS), LCH involving lungs (LCH lung$^+$), multisystem LCH without *risk-organ* involvement (LCH MS-RO$^-$) and multisystem LCH with *risk-organ* involvement (LCH MS-RO$^+$) [3]. *Risk-organs* (bone marrow, liver and/or spleen) are frequently associated to worse prognosis [4]. Pulmonary Langerhans Cell Histiocytosis (LCH lung$^+$) is an interstitial lung disease with an estimated prevalence of about 0.27 and 0.07 per 100,000 population in males and females, respectively [5] but probably higher because of sometimes poor clinical symptoms and difficult diagnosis [6]. It affects more frequently young adult smokers [2,7].

The pathogenesis is unknown. There is still open debate about reactive [8] or neoplastic (also if not malignant) origin of the clonal

* Corresponding author at: U.O. di Pneumologia e Terapia Semi-Intensiva Respiratoria - Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe-MultiMedica IRCCS, via San Vittore 12, CAP 20123 Milan, Italy.
E-mail address: sharari@ilpolmone.it (S. Harari).

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Langerhans cell proliferation. In more than a half of cases oncogenic mutations could be found, more frequently BRAFV600E [6,9,10] or rarely KRAS and TP53 but probably LCH is not a classical neoplastic disease but a neoplastic process with inflammatory manifestations [11].

About pituitary gland, autoptic series showed infiltrative Langerhans cells in about 5–50% of the LCH population [12–15] but really few studies have examined the real prevalence of endocrine diseases among adult LCH patients prospectively [16,17].

Diabetes Insipidus (DI) is the most frequent endocrine alteration described, its prevalence being among 15% and 50% of LCH patients [18,19], in particular about 40% considering only LCH MS-RO$^-$ patients, and at present it is considered the most common LCH permanent complication [15,20]. In LCH patients with anterior pituitary involvement established the DI prevalence reaches 94% [16].

In patients with DI other endocrine deficiencies are described in 20–67% [16,17]. There is no long term follow-up study. No predictors of antero-pituitary deficiencies have been recognized. Most interesting adult cohort studied with this focus were retrospective studies collecting basal antero-pituitary hormonal data and dynamic data if appropriate on patients already known for LCH MS-RO$^-$ (respectively 12 and 17 subjects [16,17]), showing that more frequent anterior pituitary deficit are growth hormone deficiency (GHD, 53–67% [16,17]) and gonadotropines deficiency (GnD, 53–58% [16,17]). ACTH and TSH deficiency seem to be rare, only 1–2% of patients mostly in the setting of complete hypopituitarism [1,12,21]. PRL levels can be moderately high [16–17], mainly due to pituitary stalk infiltration [1]. Frequently MRI abnormalities were found (up to 82% [17]), mainly a loss of posterior pituitary gland hyperintensity but also pituitary stalk enlargement, pituitary infiltration, partial or complete empty sella or hypothalamic involvement.

Once established, anterior pituitary deficiencies are permanent [1,20,22] although abnormal imaging may improve in response to treatment or spontaneously. Only one patient having spontaneous remission of GnD despite a permanent GHD and DI has been described [23], and a recent retrospective study [24] on 9 LCH patients with known DI confirmed that while DI was permanent during the follow up, hormonal assessment could change (in particular one GnD recovered at follow up).

In the guidelines published in 2013 [1] it is suggested to perform TSH, FT4 and urine osmolarity assessment in all patients affected by LCH. Further analysis such as cortisol plasma levels, IGF-I, sex steroids, and plasma osmolarity should be obtained only if a clinical suspect is raised, even if no study at the moment has systematically excluded that patients affected by LCH could have antero-pituitary unrecognized partial deficiencies.

Another interesting aspect of the disease is the possible association with metabolic derangement.

Only a few old papers and case reports make comments on this topic [25,26]. In 2008 has been published the only study [27] evaluating metabolic alterations in LCH patients, involving 14 adult LCH patients, 10 with DI and 7 with other pituitary deficiencies. Comparing LCH (both the whole group and 2 subgroups basing on presence of pituitary deficit) to 42 control subjects authors found that LCH patients without anterior pituitary deficiency had significantly decreased GIR (glucose to insulin ratio), also if not obese and independently from the presence of pituitary involvement. No systematic evidence till now is available on the association with possible metabolic alterations and cardiovascular risk of those patients.

Several case reports of direct thyroid LCH involvement, most of them in multi-systemic disease but some as isolated disease localizations [28–33], are reported, but the prevalence of thyroid involvement is unknown. Generally it is manifested as diffuse multinodular goiter (59%) or uninodular goiter (25.8%) rarely with compressive symptoms or painful on palpation or with dysphonia [32]. Differential diagnosis of thyroid LCH localizations with more common pathologies, such as undifferentiated carcinomas, lymphomas, lymphocytic thyroiditis, chronic granulomatosys and cystic degenerations of multinodular goiter, can be a challenge. Immunohistochemistry for CD1a and S-100 or presence of Birbeck granules at electronic microscopy can lead to diagnosis [34–35]. One published case report show coexistence of pulmonary LCH, anteropituitary deficiencies and papillary thyroid carcinoma in the same patient [36].

The following study was conducted in order to evaluate the presence of anterior and posterior pituitary involvement and metabolic abnormalities in a small population of patients affected by LCH referred to the Pulmonary Division of Ospedale San Giuseppe (Milan Italy) a reference centre for rare pulmonary diseases.

2. Population and methods

2.1. Population

The population of this observational cross-sectional study comprised 18 patients, 6 M/12 F, aged 42 ± 12 years, ranging from 18 to 68 years, affected by known Pulmonary Langerhans cell histiocytosis that were consecutively referred to the Pneumology Division of San Giuseppe Multimedica Hospital in Milan between 2013 and 2015. All patients had adult onset of disease and diagnosis was made in 5 patients with biopsy, 3 patients with bronchoalveolar lavage (CDa1 Pos cells > 5%) in the presence of a clinical radiological compatible features and in the latters on the basis of satisfactory clinical and radiological criteria. The mean age at diagnosis was 34 ± 14 years, (ranging from 18 to 63 years), and mean disease duration from diagnosis to the moment of enrolment in this study was 8 ± 6 years. Clinical data at the diagnosis of the disease were collected by patient's medical report. Seven patients were active and 11 were past smokers. First presentation symptom was diabetes insipidus (DI) in 5 patients, pneumothorax in 3 patients, persistent cough in 3 patients and hemoptysis, mandibular bone lesion, back pain, lipotimia, comitial crisis and radiological occasional findings respectively in 1 patient each. At the moment of the study 8 patients besides smoking cessation had already been treated with some systemic therapies for pulmonary or skin or bone involvement (in detail, 2 patients received low doses prednisolone, 1 patient steroid treatment followed by vinblastine and then because of side effects sequentially by 6 mercaptopurine, etoposide and methotrexate, 1 patient vinblastine and then 6 mercaptopurine, 1 patient prednisone then vinblastine and finally 6 mercaptopurine, 2 patients by steroid then by vinblastine and finally vincristine; one patient received just smoking cessation and topical therapy for pulmonary involvement with indacaterol and glycopyrronium). Only 3 patients received steroids for > 6 months. None received radiotherapy. No patient was in treatment at the moment of the study. All patients had pulmonary involvement, 3 had also skin involvement (one with vulvar involvement), 3 had bone involvement (1 femoral and mandibular, 1 femoral and supra-orbital and 1 skull lesions) (Table 1).

The study was approved by the hospital ethic committee (Prot. n. 8/2014) and all patients gave their written informed consent. After the enrollment 3 patients with known DI were excluded from subsequent statistical analysis on anterior pituitary functions, because incomplete hormonal evaluation. Among them 2 patients (Pts 7 e 8, Table 1) due to the impossibility to submit them to endocrine dynamic evaluations and 1 patient due to concomitant pharmacological treatments interfering with endocrine functions (Pt 9, Table 1).

Data collected included familiar history and physical status, smoking habits, other concomitant diseases or treatments. Moreover symptoms or signs suggestive of anterior and posterior pituitary hormone deficiencies with or without mass effects specific to the HPA and other neuro-endocrine involvement (appetite, thirst, sleep disturbances, memory deficit, temperature, and food intake dysregulation) either at presentation and/or at the moment of the study, were investigated.