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EDITORIAL

Langerhans cell histiocytosis and pituitary function

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Langerhans cell histiocytosis (LCH), although initially described in children, it is now-a-days increasingly recognized in adults albeit with an incidence of 1–2 cases per million yearly and is thus considered to be an orphan disease [1]. Until recently, LCH was thought to exhibit a strong inflammatory component and was regarded as a reactive disorder. However, over the last years, a distinctive clonal component along with a tumor-associated mutation (BRAFV600E) have been identified indicating that LCH is more a neoplastic than a reactive disorder; however, its exact pathogenesis is still not defined [2, 3]. The disease may affect any organ or system but the involvement of the so-called risk organs such as the hematopoietic system (mainly in children), spleen, liver, or central nervous system (CNS) heralds a more aggressive course and a worse patient outcome [1]. In adults, LCH is most often a multisystem disorder, and there seems to be a particular predilection for pituitary gland involvement [4]. Indeed, in the largest series of adult patients with LCH published up-to-date which included 274 patients with biopsy-proven LCH, 81 (29.6 %) patients had diabetes insipidus (DI) [5]. Considering that DI is mostly found in patients with multisystem disease, its prevalence was regarded as being even higher approaching 40 % of cases in this setting [5]. Unfortunately, that study did not provide information regarding the involvement of the anterior pituitary gland and its function, although a previous retrospective study in a pediatric population had indicated that anterior pituitary deficiency is common in patients with DI [6]. It was only after a retrospective study which evaluated 12 adult patients with LCH, who presented either with DI or developed DI during the course of the disease, assessed regularly using a consistent investigational protocol of pituitary function that the evolution of anterior pituitary hormonal deficiency and associated implications became apparent [7]. Since then, a number of studies, mainly including relatively small number of patients, have provided more information on the evolution of pituitary dysfunction in patients with LCH along with the morphological changes that involve the hypothalamic-pituitary region [6, 8]. Although it has been argued that systemic treatment, in the form of chemotherapy and/or or focal radiotherapy, could be related to anterior pituitary dysfunction, it is now accepted that anterior pituitary involvement develops as a result of the disease process [1, 4]. The recently published recommendations from the Euro-Histio-Net recognize the high prevalence of anterior pituitary dysfunction (approximately 20 %) in patients with LCH and propose a specific investigational and follow-up protocol [1]. Anterior pituitary dysfunction although not invariably associated with abnormal hypothalamic-pituitary region imaging, it is almost always encountered in patients with multisystem disease who have DI and hypothalamic-pituitary pathology on magnetic resonance (MR) imaging [4, 7, 8]. Growth hormone deficiency is the most frequent disease-related anterior pituitary deficiency found in up to 50 % of patients, followed by gonadotrophin deficiency, whereas adrenocorticotrophin (ACTH) and thyreotrophin (TSH) are relatively less common; moderately elevated prolactin (PRL) levels are less commonly found and are attributed to pituitary stalk involvement [1, 4]. Established deficiencies almost never recover over time,

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although abnormal imaging may improve either in response to treatment or as a result of the disease process [1, 4].

In the current issue, a further retrospective study of nine patients with LCH (six adults), seven of whom presented with DI and the remaining two developed DI during the course of the disease (eight had multisystem disease), were followed up for a period of 92 months [9]. On initial assessment, two patients were found to have anterior pituitary hormonal dysfunction (one hypogonadism and the other panhypopituitarism), and four had elevated PRL levels. Hypothalamic-pituitary MRI imaging was abnormal in all; seven patients (78 %) had infundibular enlargement, one a thalamic mass, and the remaining absence of the bright spot of the posterior pituitary [9]. Seven patients were assessed during the follow-up period four of whom developed anterior pituitary deficiency (57 %); three developed GH and one gonadotrophin deficiency. In two patients, MRI showed some improvement in the infundibular thickening but persisted in the remaining. Anterior pituitary hormonal deficiencies and DI persisted during the follow-up period irrespective of the treatment administered, except in one patient in whom hypogonadism resolved [9]. The results of the present study confirm previous findings and highlight the importance of assessing and following up pituitary function in patients with multisystem LCH and DI or abnormal hypothalamic-pituitary region imaging [7, 8, 10]. Anterior pituitary hormonal deficiencies should be diagnosed early and treated appropriately as they can affect quality of life and can also be life threatening. This is particularly important as the majority of patients have a prolonged life expectancy even in the presence of multisystem and extensive disease. This study also identifies the important limitation of providing retrospective data from small number of patients to reveal the natural history of pituitary dysfunction in LCH and identify predisposing or initiating factors for anterior pituitary dysfunction. In addition, questions as to the effect that different therapeutic modalities may have in the development of particular hormonal deficiencies, the timing and duration of treatment in particular clinical settings (i.e., GH replacement in patients with pituitary pathology), and long-term outcome need to be defined from a prospective multicenter study that may take time to be concluded due to the rarity of the disease. Until such good quality data are available, physicians looking after patients with LCH at high risk for pituitary involvement need to implement follow-up protocols as recently suggested by Euro-Histio-Net to identify such deficiencies, apply proper treatment, and identify potential associations with other disease components [1].

Conflict of interest Authors report no conflict of interest.

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