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# LETTERS TO THE EDITOR

## Timing of Pituitary Stalk Assessment in Langerhans Cell Histiocytosis: "When" Is Sometimes More Important than "What"

*To the editor:*

We read with great interest the paper by Donadieu *et al.* (1) reporting the incidence of endocrine dysfunction, mainly central diabetes insipidus (CDI) and GH deficiency (GHD), in a large cohort of pediatric-onset Langerhans cell histiocytosis (LCH) patients from the LCH French study group. Growth velocity decreased soon after LCH diagnosis in patients who developed GHD, and a significantly reduced anterior pituitary height estimated by magnetic resonance imaging (MRI) was found in the GHD patients compared with the remaining unaffected LCH subjects. The predictive value of anterior pituitary size was emphasized, whereas that of the pituitary stalk was not relevant. These conclusions have important clinical implications in the follow-up of a disease with long-lasting evolving endocrinopathy (2). We wish, however, to make some comments.

In the study, only 46 of the 145 patients had undergone MRI study; indeed, only one single MRI scan was available in approximately half of them. Among the 26 patients without GHD, the size of the anterior pituitary differed according to subsequent GH secretory status. Hence, future GH-deficient patients were more likely to have a smaller anterior pituitary, whereas pituitary stalk size was not significantly different. No information was given about the time lag between the onset of LCH-related endocrine sequelae and the timing of the MRI study (1).

In our series of 71 patients with CDI of different etiology, thickening of the pituitary stalk was the second most common MRI abnormality after the loss of posterior pituitary hyperintensity (3), in agreement with another study (4). Relevantly, 27 (93%) of our 29 patients had thickened pituitary stalk in association with anterior pituitary deficits as compared with six of the 36 patients (17%) with a normal pituitary stalk size (odds ratio, 18; 95% confidence interval, 4–115; $P < 0.001$). Moreover, anterior pituitary hormone deficits were strongly associated with a smaller-than-normal anterior pituitary in 91% of the GH-deficient patients (odds ratio, 54; 95% confidence interval, 6–606; $P < 0.001$) (3).

It is our opinion that the role of the pituitary stalk is crucial because the identification of a bulky stalk is helpful in the differential diagnosis of CDI as the first central nervous system involvement by LCH. In our study, the risk of an anterior pituitary abnormality was dependent on pituitary stalk size except in patients with LCH-related CDI. However, this finding was explained by certain distinctive LCH disease features such as unpredictable chronic reactivation or the effects of steroid treatment, or perhaps both of them together (3). More specifically, the timing of pituitary stalk assessment is fundamental because spontaneous changes and recovery of pituitary stalk size may occur (3, 4). The protracted interval of 1.5 yr between CDI onset and the first assessed MRI scan, in our study, may have concealed a rapid change, as suggested by the discovery that the size of the pituitary stalk recovered within a median of 1.2 yr in other patients (3). On the other hand, a reduction of anterior pituitary size appears to be a late consequence of upstream vascular or functional hypothalamic-pituitary stalk damage (*i.e.* lack of GHRH as a trophic factor) (2) because it is widely established that the anterior pituitary is spared from LCH infiltration (5). It is worth pointing out that anterior pituitary size reduction and dysfunction may also occur in the absence of structural changes visible at imaging and could be attributed to previous pituitary stalk microinjury leading to vascular impairment and scarring (6).

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## Authors' Response: Timing of Pituitary Stalk Assessment in Langerhans Cell Histiocytosis: "When" Is Sometimes More Important than "What"

*To the editor:*

We agree that magnetic resonance imaging (MRI) studies of the anterior and posterior pituitary must be interpreted according to the timing of pituitary symptom onset in a range of diseases, including Langerhans cell histiocytosis (LCH). In our study (1), MRI was performed shortly (median, 7 wk) after diabetes insipidus (DI) onset in patients who were free of GH deficiency (GHD).

The main limitation of our study is the relatively small number of patients whose MRI studies could be reviewed (91 studies, 46 patients). This explains why we were very cautious when discussing the results, stating that "the value of MRI for early detection of patients at high risk of GHD must be confirmed."

Our study nonetheless has the merit of being the largest series of LCH-associated endocrinopathies reported to date and the largest series of MRI studies in this setting (2–7). For example, Maghnie's study (2) involved only 17 patients with LCH, of whom nine had pituitary involvement. This latter report did not state the interval between DI onset and MRI and did not analyze features potentially predictive of GHD (3). All clinical studies of LCH come up against both the rarity of the disease and the possibility of late permanent sequelae.

In their letter, Maghnie and Malattia (8) refer to a recent publication addressing the issue of central DI (CDI) in 71 children (9); CDI was related to LCH in only 12 patients, whereas it was idiopathic in 42 cases and tumor-related in 18 cases. Clearly, the progression patterns of these different entities are very different and should therefore be analyzed separately. No firm conclusions can be drawn on the basis of only 12 (or

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even 46) cases. In isolated CDI, the main reason why repeat MRI is recommended is to rule out a brain tumor. Until now, repeat MRI has not been recommended for patients with LCH, including those with pituitary dysfunction (10, 11), unless a new endocrinopathy or neurological symptoms occur.

However, our findings, and previous results from another group (12), show that repeat cranial MRI can provide very useful information in LCH and, incidentally, on pituitary status. We very recently reported that LCH patients with pituitary involvement have an increased risk of neurodegenerative changes (13). This rare but dramatic complication may be preceded by MRI changes, especially in the cerebellum. Because retinoids may slow this neurological degeneration, early diagnosis by means of repeated MRI may be beneficial (14).

If MRI becomes an accepted part of the standard management of patients with LCH endocrinopathy, the predictive value of anterior pituitary size for GHD could be addressed with more confidence.

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