Pituitary stalk thickening: neoplastic or not? - author's response to the letter by Wang *et al.*

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We thank Dr Shirui Wang and colleagues for their interest in our recent publication on the distinction of neoplastic from non-neoplastic lesions in adult patients presenting with central diabetes insipidus (CDI) and pituitary stalk thickening (PST) (1). We acknowledge the fact that they could not confirm in their population our previous observation that a higher prolactin (PRL) concentration at diagnosis increases the likelihood of a neoplastic origin (2). As they mentioned, such an association of CDI and PST represents a rare and heterogeneous disorder, raising challenging issues in both diagnosis and management. It is interesting to mention that only 46 out of their original cohort of 321 patients with PST (3) were eligible for this comparative analysis. As there are limited data about the prevalence and significance of hyperprolactinemia in such patients, any additional insight is most welcome and worth to debate.

We want to provide several potential explanations for the discordance observed between their findings and our results. First, the definition of PST was not exactly the same in the two studies. While they used a constant cut-off of PS thickness ≥ 3 mm along the stalk (3), we rather used differential cut-offs based on the previously reported normal dimensions of the hypothalamic-pituitary axis on MRI (1, 4, 5, 6, 7, 8). More specifically, the pituitary stalk was considered enlarged when its largest diameter was greater than 4.0 mm in its proximal portion at the level of the optic chiasm, 2.8 mm in its medial portion and/or 2.5 mm in its distal portion at the level of pituitary insertion. This may have led to a slightly different selection of patients, in particular, more severely affected patients at the level of the infundibulum.

We do not believe that gender may have influenced our different results as prolactin concentrations were normalized against sex-specific normal range. However, the upper normal limits (ULN) of prolactin concentrations were not based on the Guidelines of the Pituitary Society (9) but rather on the respective reference ranges given by the different laboratories of the three participating centers. Thus, PRL ULN was 23–25 µg/L in women and 12–15 µg/L in men. Again, this may lead to substantial differences in the relative prolactin levels (xULN), raising them in particular in men who were predominant in the malignant group.

Ethnic differences in PRL concentrations and in PRL response to physiological or pathological conditions may have also affected the results obtained in the different Caucasian and Asian populations, respectively. Such differences have been reported for prolactin. It has been for example reported that Caucasians have a less prominent prolactin response to haloperidol than Asians (10) and that prolactin concentrations may be different between Caucasian and Japanese women at risk for breast cancer (11).

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In patients with PST and CDI, one of the main goals of the medical workup should be to exclude a neoplastic underlying pathology. Others and we showed that PS thickness was slightly larger in patients with malignant disease (12, 13) but a large overlap exists with benign lesions, making this criterion of limited use in the differential diagnosis (1). When analyzing the weak correlation between the thickness of pituitary stalk and serum PRL concentration in our series (r = 0.363, $P = 0.063$), one can easily observe that prolactin was much higher in most malignant cases than in patients with benign disease, independent of the size of the stalk (Fig. 1). This suggests that the mechanisms of hyperprolactinemia in this setting are not simply related to stalk compression or infiltration but probably also depends on other factors such as cancer-induced structural damage of the tuberoinfundibular neurons. Heterogeneity in the case severity or in the course of the disease could obviously affect such results.

We agree with Wang and colleagues that ongoing controversy subsists regarding the classification of 'L'-type histiocytosis as being a malignant or inflammatory process. Our work did not try to solve this issue and we decided to simply follow the classification proposed by the well-recognized Histiocyte Society (14). We however compared in our paper the specific features of the three most frequently observed etiologies of PST (i.e. neuroinfundibulitis, histiocytosis and germinoma) and we could observe many similarities in the baseline characteristics of the two first subgroups as opposed to the third one.

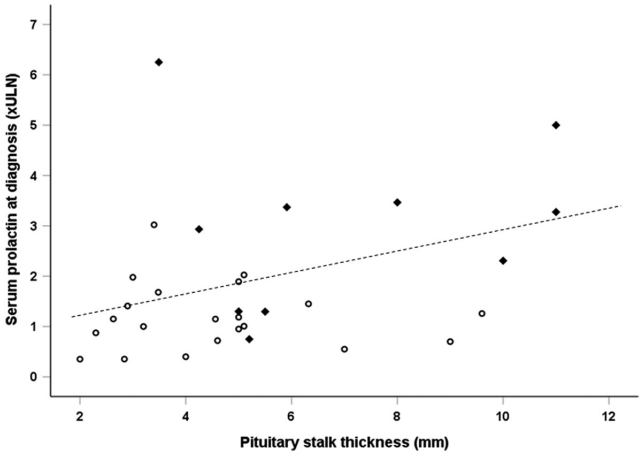

Figure 1
Correlation between pituitary stalk thickness (maximal diameter measured on a sagittal T1-weighted view on magnetic resonance imaging) and serum prolactin concentration at diagnosis, expressed as a multiple of the upper limit of normal (ULN). Diamonds represent patients with a neoplastic disease while circles represent patients with a benign etiology. The correlation was not significant between the two parameters (n = 31; r = 0.363, $P = 0.063$).

Finally, we also agree with Wang and colleagues that further studies are needed to validate our findings and to define the best serum prolactin cut-off that will differentiate malignant from benign PST with CDI.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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