# CORRESPONDENCE

## Primary Empty Sella Syndrome and the Prevalence of Hormonal Dysregulation

A Systematic Review

by Dr. med. Matthias K. Auer, Dr. med. Mareike R. Stieg, Dr. med. Alexander Crispin, MPH; PD Dr. med. Caroline Sievers, MSc; Prof. Dr. med. Günter Karl Stalla, and Dr. med. Anna Kopczak in issue 7/2018

### Rainbow Cup

A given prevalence of 2%–20% suggests very different valences of the radiological findings. I believe that the image shown in the article (*Figure 1*) supports this (1): In my opinion, the magnetic resonance image does not show an empty sella but rather a pituitary gland shaped like a rainbow cup coin, expanded (or rolled out) over the floor of the sella. Are our radiologists too often overly willing (as happens for slipped disc injuries) to present pathological or conspicuous findings, and the clinicians increasingly less trained for evaluating—and then comparing—the radiological findings with the clinical ones? Every false-positive diagnosis deeply and unnecessarily unsettles our patients, with implications not only for patient compliance but also for the physician–patient relationship. What you are reporting is a very questionable overdiagnosis. Even if the reality lies in the middle, with a prevalence of 11% (which I still believe to be overestimated), 10% of the people undergoing magnetic resonance imaging would have the burden of being misdiagnosed, at least temporarily. This is not trivial.

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**References**

1. Auer MK, Stieg MR, Crispin A, Sievers C, Stalla GK, Kopczak A: Primary empty sella syndrome and the prevalence of hormonal dysregulation—a systematic review. Dtsch Arztebl Int 2018; 115: 99–105.

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### Not an "All-or-Nothing" Principle

The discrepancy between the epidemiological data, which suggest a prevalence of pituitary insufficiency of about 50 per 100 000 people, and the estimated frequency given in the review of 1%–10% of all people, is surprising only at first glance (1). A possible explanation is indicated by the fact that the somatotropic axis appears to be the most frequently affected system, followed by the gonadotropic axis, while the systems most important for survival are only rarely affected. It cannot be assumed that damage to pituitary tissue (for whatever reason) takes the importance of functions of the corresponding cells into consideration. Rather, it seems reasonable that compensatory mechanisms are activated upon failure of the most vital substances; for instance, a more or less pronounced deficiency of adrenocorticotropic hormone (ACTH) and glucocorticosteroids leads to an increased secretion of catecholamines, which then changes the dominant symptoms accordingly.

Patients who do not present textbook symptoms of a specific hormone deficiency are referred to as "asymptomatic"; however, in fact, the symptoms of these so-called asymptomatic patients were usually at least sufficient for a referral to diagnostic imaging, even when they were not directly linked with a suspected pituitary insufficiency. As long as a (more-or-less pronounced) pituitary insufficiency is only suspected when the symptomatology for this is evident, and as long as the many countermeasures (with all of their possible side effects) taken by the human body to ensure its survival are not taken into account, it is likely that numerous cases of disrupted pituitary function that should be treated will go unrecognized.

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### Overdiagnosis is Stressful

In stark contrast to our experience, this article emphasizes that empty sella needs to be clarified (1). We thus carried out a retrospective *ad hoc* investigation of 100 patient cases from our practice (using data of scans taken from 15–26 February, 2018). The inclusion criterion was having a magnetic resonance imaging of the skull for any indication except pituitary disease. The craniocaudal heights of the sella turcica and the pituitary gland were measured on the T1-weighted sagittal images, and the percentage of the sella that was filled was calculated.

On average, the patients in this analysis were 54 years old (15–90) and 55% of them were female. The average height of the pituitary gland was 4.52 mm (95% confidence interval [CI]: [4.3; 4.8]), and on average 66% [62; 70] of the sella was filled. The height of the pituitary decreased with age (Pearson correlation coefficient –0.2; $p < 0.001$). Thirteen of the 100 patients who had no clinical signs of hormonal abnormality had a filling of less than 50% and thus would have been diagnosed with a complete empty sella, according to the definition of this article, while by definition 80 patients had a partial empty sella.

How could one explain the discrepancy between our data and the article?

1. The definition of empty sella syndrome by Auer *et al.* (1) is problematic: in our case, it would mean that 80% of our patients had partial empty sella.

2. In contrast to us, Auer *et al.* analyzed highly selected populations from departments of endocrinology at university hospitals (2, 3). However, the pretest probability (prevalence of the disease sought) influences the relevance of test results.

In summary, we consider the recommendation for intensive hormone diagnostics for the frequently occurring empty sella to be problematic, as overdiagnosis is expensive and potentially harmful to patients. DOI: 10.3238/arztebl.2018.0324c

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## In Reply:

We are grateful for the high level of interest in our systematic review. As we described, an empty sella is the radiological or pathological-anatomical imaging of an apparently empty sella turcia. Dr. Baiker is correct in stating that there is a remnant of pituitary tissue in our image. Indeed, we described this in the text: "This impression arises from the fact that the sella turcica is filled with cerebrospinal fluid (CSF), and the hypophyseal tissue at its base is flattened (*Figure 1*)." (1). The radiological definition of when an empty sella should be diagnosed is not uniform in the studies.

We support further investigations such as those from Prof. Freund and colleagues. However, the age range in the studies we included differs from that in their Correspondence letter: our systematic review referred only to adults, while the retrospective analysis of Freund *et al.* also included minors. Further, the mean age in the work of Freund *et al.* is higher than that in the studies we included. As correctly reported by Freund *et al.*, the height of the pituitary gland as measured by magnetic resonance imaging correlates with age; thus, if the criteria are not age-adjusted, a higher average age makes it more likely to observe an empty sella.

The prevalence of empty sella of 2%–20% includes both primary and secondary forms. According to a recent study, empty sella is diagnosed in 2% of all cMRT examinations as a chance finding without apparent cause. According to our systematic review of patient cases with a pooled prevalence of pituitary insufficiency of 52%, approximately 1% of all patients would have pituitary insufficiency. When interpreting the data, we also find this to be excessively high. We suspect a publication bias, as inconspicuous findings are often not published and were thus not included in our analysis.

A finding of an empty sella does not necessarily indicate a disease, and this should be clearly communicated to the patient. Our concept is based on patient education as well as collecting blood for checking the levels of basal hormones, especially as impairment of the corticotropic axis can lead to life-threatening conditions. Doctors should be aware of this from a medical point of view, but without unsettling patients. Dr. Kopka is correct in her objection that hormones do not work according to an all-or-nothing concept, and that partial insufficiencies could exist. In our meta-analysis, therefore, only studies were included in which a stimulation test had been performed. However, for everyday clinical practice, our recommendation would be to ask for specific complaints and to initiate further stimulation tests only if abnormal basal levels are detected or if the symptoms are indicative. DOI: 10.3238/arztebl.2018.0325

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1. Auer MK, Stieg MR, Crispin A, Sievers C, Stalla GK, Kopczak A: Primary empty sella syndrome and the prevalence of hormonal dysregulation—a systematic review. Dtsch Arztebl Int 2018; 115: 99–105.

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