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The profile of patients with ACTH-secreting pituitary adenomas and subclinical pituitary apoplexy
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Background: Subclinical hemorrhage or necrosis of pituitary adenomas (PAs), often defined as subclinical pituitary apoplexy (SPA), presents in up to 20% of all PAs and is more common in large prolactinomas. SPA in corticotropinomas in patients with Cushing disease (CD) is not common and the clinical and biochemical characteristics of patients with CD and SPA are not known. Subjects and methods: Pediatric patients with confirmed CD diagnosed between 2005-2021 with available MRI images before any surgical intervention were included in the study (n=171). SPA diagnosis was based on MRI findings. Although MRI sequences and machines were not same for all patients and varied over time, the results were based on possible signs of hemorrhage on the available images, but smaller areas of bleeding or necrosis may have been missed. Statistical analyses were performed with Wilcoxon signed-rank test, chi-square or Fisher’s exact test, and Cox proportional hazard as appropriate. Results are shown as median [Q1, Q3], count (percentage) and odds ratio (OR) (95% confidence intervals, 95%CI). 

Results: Out of 171 patients, 12 patients (7%) were found to have imaging characteristics of possible hemorrhage or intratumor infarct. Patients with and without SPA were similar in age (median age: 12.5 years [10.6, 15.6] in SPA group vs 13.1 years [10.6, 15.4] in non-SPA group, p=0.95) and gender distribution (n of female= 5 (41.7%) in SPA group vs 89 (56%) in non-SPA group, p= 0.51). Patients with SPA had shorter duration of disease as noted by changes in their growth chart parameters (median duration: 1.0 year [1.0, 2.0] in SPA group vs 2.5 years [1.5, 3.0] in non-SPA group, p= 0.014). Morning and midnight cortisol and 24 hour urinary cortisol levels were similar in both groups, but patients with SPA had higher levels of morning ACTH (60.8 pg/mL [43.5, 80.3]) compared to patients without SPA (39.8 pg/mL [28.5, 53.4], p=0.017). Change of cortisol and ACTH levels during CRH stimulation test were similar between the two groups, but patients with SPA had lower suppression of cortisol after overnight high dose (8mg or weight-based equivalent) dexamethasone suppression test (58.0% [-85.4, -49.7]) compared to patients without SPA (85.8 [-90.5, -76.8], p= 0.035). Specifically, patients with SPA had lower chance of passing the threshold of 69% that it suggestive of pituitary source of hypercortisolemia compared to patients without SPA (OR: 0.18, 95%CI: 0.03-0.95). The odds of remission after surgery and the risk of recurrence after initial remission did not differ based on the presence of SPA. 

Conclusion: Patients with CD and signs of hemorrhage or necrosis in their tumor may present with different characteristics on their biochemical evaluation which should be considered during their diagnostic workup, especially in the setting of a discordant dexamethasone suppression test.

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