Abstract citation ID: bvaf149.1357

Neuroendocrinology and Pituitary

MON-025

Diagnostic Utility Of Machine Learning In Central Adrenal Insufficiency Due To Pituitary Disorders

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Disclosure: M.R. Bitencourt: None. **F.C. Araújo:** None. **I.P. Biscotto:** None. **V.H. do Nascimento:** None. **A. Carvalho:** None. **R. Bonidia:** None. **L.R. Silveira de Carvalho:** None.

Introduction: Central adrenal insufficiency (CAI) results from deficient ACTH or CRH stimulation of the adrenal glands, impairing cortisol and androgen secretion. Diagnosis is often challenging due to nonspecific symptoms and limitations of basal cortisol and dynamic tests such as the insulin tolerance test (ITT), especially when hypoglycemia is not achieved or contraindicated. Aim: To evaluate the use of machine learning to improve the diagnosis of CAI in patients with congenital hypopituitarism (CH) and acquired pituitary disorders undergoing ITT. Patients and **Methods:** We retrospectively analyzed 420 cases from a tertiary academic center: 220 patients with confirmed CH (with or without CAI) and 200 patients undergoing ITT

for suspected CAI. Inclusion criteria were basal cortisol and DHEA-S measurements within 12 months before testing and no glucocorticoid use in the preceding 6 months. A DHEA-S ratio was calculated using age- and sex-specific lower reference limits.Patients were grouped as follows: Group 1: CH with ACTH deficiency; Group 2: CH with preserved ACTH; Group 3: Acquired pituitary disease undergoing ITT (the ITT cohort). The experiments using the CatBoost machine learning algorithm were conducted in three stages: Stage 1: Gold-standard cohort using Groups 1 and 2 (n=62); Stage 2: Expanded cohort using Groups 1, 2, and 3 (n=148) and Stage 3: Real-world simulation using 30 patients random chosen from stage 2 (Group 1, 2 and 3) with classification filtered by confidence level. **Results:** Among CH patients with ACTH deficiency (Group 1), 29 had confirmed CAI, and 19 had available DHEA-S data. These were compared with 43 CH patients with preserved ACTH (Group 2). In the ITT cohort (Group 3), 92 patients met criteria for analysis. In Stage 1 (group 1), information gain ranking showed: basal cortisol (0.48), DHEA-S ratio (0.34), followed by TSH (0.22), LH/FSH (0.17), and GH (0.10), achieving 93.5% balanced accuracy. In Stage 2 (80% training, 20% testing), balanced accuracy was 75% in training and 83% in testing. In Stage 3, patients were randomly chosen from stage 2 (groups 1, 2 and 3), where 10 of 30 patients had model confidence <80% and were referred for ITT. Among the 20 high-confidence cases, above 80%, the model reached 90% accuracy, correctly classifying 18 patients (1 false positive, 1 false negative). **Conclusion:** Machine learning combined with biochemical profiling—especially the DHEA-S ratio—can enhance CAI diagnosis when conventional tests are impractical. These findings support the DHEA-S ratio as a promising screening biomarker and justify its prospective validation.

Presentation: Monday, July 14, 2025