mild autonomous cortisol secretion (MACS) is typically associated with abnormal circadian cortisol production. **Aim:** To characterize the effect of MACS on cognitive performance. **Methods:** We conducted a cross-sectional analysis as part of an ongoing cohort study in patients with MACS compared to age and sex-matched referent subjects without cortisol excess. MACS was defined as serum cortisol concentration >1.8 mcg/dL after the 1 mg overnight dexamethasone suppression test (DST), in the absence of signs and symptoms of overt Cushing syndrome. We used the National Institute of Health Toolbox Cognition Battery to assess cognitive performance. A series of seven IPad-based tests were administered to evaluate five key domains: 1) executive function, 2) episodic memory, 3) working memory, 4) language, and 5) processing speed. Performance was reported using fully corrected T-scores for age, sex, education, and race with a normative mean of 50 and a standard deviation of 10. T-scores were generated for the individual components as well as three summary measures: 1) fluid cognition (includes executive function, episodic memory, working memory, and processing speed), 2) crystallized cognition (includes language), and 3) total cognition (composite of fluid and crystalized cognition). **Results:** A total of 23 patients with MACS and 23 age and sex-matched referent subjects without cortisol excess were enrolled. The median age of diagnosis was 63 years (range, 51–81), and 26 (56%) were women. In the MACS cohort, median cortisol following 1 mg DST was 2.6 ug/dL (range, 1.9–13.0) with median ACTH of 8.5 pg/mL (range, 5.0–38.0) and median DHEA-S of 37 mcg/dL (range, 5.0-141.0). On cognitive assessment, patients with MACS had lower total cognition (T-scores 50 vs. 54, p=0.05) and fluid cognition (T-scores 48 vs. 53, p=0.01) composite scores compared to referent subjects without cortisol excess. In particular, patients with MACS performed worse on tests of executive function (Dimensional Change Card Sort: T-scores 55 vs. 63, p= 0.02 and Flanker Inhibitory Control and Attention: T-scores 45 vs. 52, p=0.01). There were no significant differences observed in the remaining individual domains of language, processing speed, working memory, and episodic memory, or crystallized cognition. **Conclusions:** MACS is associated with impaired total cognition, and in particular, executive function and fluid cognition. These findings suggest that patients with MACS are susceptible to cortisol-mediated changes in the brain. Additional studies should examine the contribution of neuropsychiatric symptoms on cognition in MACS, and possible improvement following treatment for cortisol excess.

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Impaired Muscle Strength and Performance in Patients With Mild Autonomous Cortisol Secretion

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Background: Glucocorticoid-induced myopathy is well-recognized in overt Cushing syndrome (CS), but the impact of mild cortisol secretion on muscle is unclear. Recent data suggest that patients with mild autonomous cortisol secretion (MACS) are frailer and report more weakness than patients with non-functioning adrenal adenomas. We hypothesized that MACS is associated with 1) objective measures of impaired muscle strength and performance and 2) increased tissue accumulation of advanced glycation end products (AGEs), a measure of accelerated aging. **Aim:** To determine the effect of MACS on muscle mass, strength, performance, and tissue accumulation of AGEs. **Methods:** We conducted a cross-sectional analysis as part of an ongoing cohort study in patients with MACS compared to age and sex-matched referent subjects without cortisol excess. MACS was defined as serum cortisol >1.8 mcg/dL after the 1 mg overnight dexamethasone suppression test (DST), in the absence of overt signs and symptoms of CS. We measured hand grip strength with hand grip dynamometer and evaluated functional performance on the timed up and go test, 6 minute walk test, and gait speed assessment. Tissue accumulation of AGEs was measured with point-of-care AGE reader. Appendicular lean mass was calculated and adjusted for height in participants who underwent body composition scan. **Results:** A total of 23 patients with MACS and 23 age and sex-matched referent subjects without cortisol excess were enrolled. The median age of diagnosis was 63 years (range, 51–81), and 26 (56%) were women. In the MACS cohort, median cortisol following 1 mg DST was 2.6 μg/dL (range, 1.9–13.0), median DHEA-S 37 μg/dL (range, 5.0- 141.0), and median ACTH 8.5 pg/mL (range, 5.0–38.0). Patients with MACS had lower hand grip strength (median 29.3 vs. 32.5 kg, p=0.052), slower gait speed (median 1.1 vs. 1.4 m/s, p=0.001), covered less distance during the 6 minute walk test (median 453 vs. 510 m, p=0.001), and took longer to complete the timed up and go test (median 10.1 vs. 8.6 s, p=0.04) than referent subjects without cortisol excess. Accumulation of AGEs was higher in patients with MACS (median 2.9 vs. 2.4, p=0.01). No significant difference was observed in appendicular lean mass (n=19 pairs, 7.8 vs. 7.5 kg/m2, p=0.57). **Conclusions:** MACS is associated with decreased muscle strength and performance without a significant change in muscle mass, suggesting poor muscle quality. We also observed increased tissue accumulation of AGEs in MACS patients, consistent with our hypothesis of MACS-induced accelerated aging. These findings may help explain the increased frailty observed in MACS, and suggest muscle assessment be considered in all patients with autonomous cortisol secretion. Further studies should examine the impact of muscle and functional impairments on morbidity in MACS, and its possible reversal with either a structured exercise intervention or adrenalectomy.

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