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Letter to the Editor

In response to: “Involvement of the endocrine system is common in mitochondrial disorders and requires long-term comprehensive investigations”

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Dear Editor,

In response to Josef Finsterer's letter, we would like to thank him for his interest in our study, and give a chance to us to emphasize and clarify a few points.

If we consider the first point in this letter regarding this article (1) we focused on all endocrinological problems in mitochondrial patients. We specifically mentioned pituitary imaging findings in patients with pituitary hormone deficiency. Two patients with central adrenal insufficiency and central hypothyroidism showed no abnormalities on their pituitary imaging. We provided detailed information about patients no. 20 and 21 under the subheadings of central adrenal insufficiency and central hypothyroidism in the results section of our article, stating that their pituitary magnetic resonance (MRI) imaging was normal.

Patient no. 20 had normal sella turcica contours and dimensions. Neurohypophysis showed normal hyperintensity. The infundibulum is in the midline, and its thickness werenormal. We observe widespread t2-flair pathological signal increases in both periventricular deep white matter and cortical deep white matter in brain MRI. This localization clearly identifies perivascular areas. Corpus callosum was thin. In the last control, there was no other hormone deficiency, especially pituitary hormones, and the annual growth rate was normal. Patient no. 21 has passed away. The brain MRI of the patient with global developmental delay revealed minimal hypoplasia in the brain stem and mild hypoplasia in the vermis. We observed variation in the cavum septum pellucidum et vergae. Both occipital localizations showed signal increases in FLAIR sequences in cortical-subcortical areas.

Secondly, our patient group includes different types of mitochondrial diseases, and their ages and follow-up periods were also variable. Our priority was to determine the current status in our group. This study is a preliminary study, and the follow-up of the patients is ongoing. Our studies targeting specific endocrine problems, including imaging, will continue in the future.

Lactic acidemia does not necessarily indicate the presence of mitochondrial diseases, a low value does not rule out mitochondrial disease, and a high value is a supportive finding (2). Lactate elevations in 5/26 patients were just above the limit (21-82.56 mg/dL). Laboratory reference values were 4.5-20 mg/dL. Lactate levels were normal in 1/26 patients during follow-up, with a maximum of 10.3 mg/dL (patient no. 18). Although lactate levels in the remaining 20 patients decreased during treatment, basal lactate levels at diagnosis were 1.5 times higher than the upper limit. (30.6-82.56 mg/dL).. Among our two patients with pituitary hormone deficiency, patient no. 20 had a significant lactate elevation. Patient no. 21 also had a slightly elevated lactate level.

22 of our patients were in pubertal stage 1, and ten of them were female. These patients did not exhibit polycystic ovarian syndrome. There were two female patients in pubertal stage 5, one of whom had hypergonadotropic hypogonadism, and pubertal development and regular menstruation was achieved with pubertal hormone replacement therapy. To date, the other patient has no menstrual abnormalities and no clinical or biochemical hyperandrogenemia findings.

The hypothalamic-pituitary and adrenal axes play an important role in the stress response. Centrally activated hypercortisolism is considered the cornerstone of the human endocrine stress response. Adrenal insufficiency due to a critical illness does not develop in every patient, and although it is not a true hormone deficiency, we included it in this group because it developed in our patient with mitochondrial disease. Since critical illnesses and severe infections intensify the current energy crisis, leading to increased oxidative stress and decreased ATP synthesis, and obstruct the synthesis pathways, this situation is also regarded as evidence supporting mitochondrial insufficiency. In adrenal insufficiency due to a critical illness, the cortisol response, cortisol clearance, and cortisol receptor shift change within days. Although cortisol production is low, the cortisol value in circulation is high. We believe it is important to report this situation, as it indicates a functional cortisol deficiency. We conducted a retrospective study in our hospital's pediatric intensive care unit, examining data from 1956 patients followed up in the tertiary intensive care unit for various reasons over a 5-year period, and found that only 79 patients developed critical illness-related adrenal insufficiency (3).

Laboratory reference values, primarily FSH, LH, estradiol, IGF-1, and IGFBP-3, vary according to age and gender. Therefore, they are given as standard deviations. For other parameters, average values that can be used for children aged 4–10 are added to the Table below (Table-1).

Patient no. 26, who carries the 16519 T>C mutation in MT-CR, is diagnosed with mitochondrial disease and exhibits the Kearns-Sayre syndrome phenotype. The number of confirmed variants in MitoMap is only 96. Variants reported as disease-related but not yet confirmed form a large group of nearly a thousand variants. MitoMap classifies the variant in question as disease-related and possibly pathogenic in silico, leading to its inclusion in the publication (4). However, it is important to remember that deletion-type mutations, another potential cause of the disease, are present in muscle tissue but not in peripheral blood.

We also agree with you that endocrine system involvement in mitochondrial diseases can affect all endocrine organs and may not occur at the beginning of the disease but may develop as the disease progresses, requiring long-term follow-up.

We thank you for your interest and suggestions in our study.

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Table-1:Biochemical and hormonal profiles of the study population.

	Number of Patients (%)	Mean ±SDS or Median (min-max)
TSH (mIU/mL) (0.6-4.84)	26 (100)	2.49 ±1.27
Free T4 (ng/dL)* (median,IQR) (0.97-1.67)	26 (100)	1.25 (0.85-4.09)
Free T3 (pg/mL) (2.53-5.22)	19 (73)	3.97 ± 0.95
ACTH (pg/mL)* (median,IQR) (7.2-63.3)	26 (100)	35 (4-365)
Cortisol (µg/dL)* (median,IQR) (6.2-22.6)	26 (100)	14.95 (5-68)
Calcium (mg/dL) (8.4-10.2)	26 (100)	9.79 ±0.56
Phosphorus (mg/dL) (2.9-5.1)	26 (100)	4.57 ±0.91
Magnesium (mg/dL) (1.7-2.2)	26 (100)	2.1 ±0.18
ALP (U/L) (57-254)	26 (100)	203.5±71.52
PTH(pg/mL) (15-65)	26 (100)	38.63 ±23.59
25 OH vitamine D (ng/mL)* (median,IQR) (20-80)	26 (100)	20 (4.71-94.2)
HbA1c %* (median,IQR) (4-6)	26 (100)	5.2 (4.7-7.25)
FSH (mIU/mL)* (median,IQR)	6 (23)	9.5 (3.05-280)
LH (mIU/mL)* (median,IQR)	7 (26.9)	8.3 (0.85-66)
IGF-1 (ng/mL) SDS* (median,IQR)	23 (88.5)	0.6 (-2.1-9.03)
IGFBP-3 (mg/L) SDS* (median,IQR)	22 (84.6)	-0.25 (-2.38-7.07)

*Nonparametric disturibition according to Kolmogorov-Smirnov test
Normal values for laboratory parameters are indicated in parentheses beneath the parameter.