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Letter to the Editor

Does growth-hormone treatment affect patients with and without a mitochondrial disorder differentially?

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We read with interest the article by Yokoya *et al*. on GH therapy in 2,345 Japanese patients of short stature (1). Only 0.13% developed diabetes, and only 0.56% had a neoplasm during a mean follow-up of 3.2 yr (1). We have the following comments and concerns.

Short stature is a frequent phenotypic manifestation of mitochondrial disorders (MIDs) (2). In a sample of 100 pediatric patients with a MID due to the mutation m.3243A > G, 73% had short stature (2). Among specific MIDs, short stature has been particularly reported for Kearns-Sayre syndrome, MERRF syndrome, and MELAS syndrome. Among non-specific MIDs, short stature has been reported in patients carrying mutations in the *tRNA (Lys)*, *NDUFB3*, *WARS2*, *SLC25A24*, *COX4I1*, *IARS2*, *BCS1L*, *XRCC4*, *PMPCA*, *COX10*, *SHOX*, or *COA3* gene. Thus, in pediatric patients with short stature, MIDs should be considered.

Short stature in patients with MIDs may or may not be related to GH deficiency. GH deficiency has been reported in MIDs due to mutations in the *WARS2* or *IARS2* gene, or due to the depletion/deletion of mtDNA (e.g. Kearns-Sayre syndrome) (3). We are thus interested in knowing if there were any patients with clinical presentations suggesting a MID in this study cohort. In addition to short stature, phenotypic features indicating a pediatric MID include seizures, headache, floppiness, visual impairment, hearing impairment, cardiac disease, delayed motor milestones, diabetes, poor sucking, vomiting, muscle weakness, lactic acidosis, Fanconi syndrome, and aminoaciduria (2). Cerebral imaging suggesting a MID include focal or diffuse atrophy, leukoencephalopathy, and symmetric grey matter lesions in the thalamus, basal ganglia, brain stem, or the cerebellum.

An increased frequency of neoplasms has been previously reported in adults with MIDs (4). Malignant neoplasms, such as cancers of the thyroid gland, prostate, colon, or ovaries can be found in 15% of MID patients (4). Benign neoplasms such as lipomas, thyroid adenomas, or meningiomas were reported in 10% of patients with MIDs (4). In pediatric patients with a MID, due to mutations in the *SDHx* genes, a paraganglioma or pheochromocytoma may be particularly prevalent (5). Thus, in pediatric patients with GH deficiency and a neoplasm, a MID should be considered, including in the four patients with cranio-pharyngeomas.

Overall, this interesting study could benefit

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from specifying the causes of GH deficiency, from investigations on the frequency of MIDs in the cohort, and from the provision of additional clinical data, including the rate of morbidity in these patients. In pediatric patients of short stature who also have a GH deficiency, MIDs should be considered as a differential diagnosis.

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