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Letter to the Editor

Responses to the Letter to the Editor "Does growth-hormone treatment affect patients with and without a mitochondrial disorder differentially ?"

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We would like to thank Dr. Finsterer for his comments and questions (1) regarding the possibility that the short stature in patients from our study (2) could also be a phenotypic manifestation of mitochondrial disorders (MIDs).

The GeNeSIS postmarketing research programme collected data from the routine clinical care of growth hormone-treated pediatric patients with growth disorders. Growth disorder diagnoses provided by investigators were reviewed and prioritized for impact on short stature using a predefined scheme. Based on this scheme, any diagnosis of an MID would have been noted for the affected patient and they were not excluded from the study. Although there was a possibility that some of the Japanese patients with growth hormone deficiency (GHD) included in our study had unreported MIDs, two Japanese patients from the same investigative site were definitively diagnoses for MID:

- Male (baseline age 13.8 years): This was the patient reported in our manuscript with the adverse event of insulin-dependent diabetes

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mellitus due to underlying mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). The diagnosis of short stature provided by the physician was congenital GHD due to mitochondrial tRNA mutation.

- Male (baseline age 15.0 years): No diabetes or indeed MELAS was reported for this patient, although a "cerebral stroke" was reported. However, this patient also had a short stature diagnosis of congenital GHD due to mitochondrial tRNA mutation.

In the Japanese cohort of patients with GHD, other than these two patients with MID diagnoses, there were no reports of specific phenotypic features of MID including hearing impairment, muscle weakness, lactic acidosis, Fanconi syndrome, aminoaciduria, and cerebral imaging showing focal or diffuse atrophy, leukoencephalopathy, lesions in thalamic, basal ganglia, brain stem or cerebellar; there was 1 reported event of cardiac failure in a patient with idiopathic GHD.

In relation to Dr Finsterer's comments regarding neoplastic disease and MIDs, the two patients diagnosed with MIDs were not included in the four patients with recurrent craniopharyngioma, and there were no any specific symptoms to suggest MID in these patients.

We again thank Dr. Finsterer for his interest in our paper, but given the observational nature of the GeNeSIS programme and rareness of cases of MIDs in enrolled patients, we cannot offer further insights into the frequency of MIDs and impact on GH treatment outcomes.

Sincerely,

The Authors

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