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Letter to the Editor

HbA1c is not Suitable as a Predictor of Disease Severity in m.3243A>G Carriers

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We read with interest Saunders *et al*'s article about a study on the phenotypic presentation of 46 carriers of the variant m.3243A>G [1]. Maternally inherited diabetes and deafness (MIDD) was found to be the most common phenotype, occurring in half of patients [1]. There was a positive correlation between the number of symptoms and bowel dysmotility [1]. Neither blood nor urine heteroplasmy rates correlated with the number of symptoms [1]. It was concluded that the m.3243A>G cohort exhibits marked phenotypic heterogeneity, that HbA1c may be a novel predictor of disease severity, and that the prognosis in patients with low body mass index (BMI) and those with bowel dysmotility may be poor [1]. The study is impressive, but some points should be discussed.

We disagree with the conclusion that HbA1c could be used as a predictor of disease severity [1]. First, not all m.3243A>G carriers have diabetes. Second, HbA1c levels depend not only on the presence/absence of diabetes, but several other influencing factors such as erythropoiesis, haemoglobin type, effectivity of glycation, amount of erythrocyte destruction, and the assays used to determine HbA1c [2]. HbA1c can be increased by iron, vitamin-B12 deficiency, decreased erythropoiesis, hereditary hemoglobinopathy, alcoholism, renal insufficiency, decreased intra-erythrocyte pH, hyperbilirubinemia, carbamylated hemoglobin, large doses of aspirin, and chronic opiate use [2]. HbA1c can be decreased by erythropoietin, iron, vitamin-B12, reticulocytosis, liver disease, hereditary hemoglobinopathy, aspirin, vitamin-C, vitamin-E, increased intra-erythrocyte pH, decreased erythrocyte life span due to hemoglobinopathy, splenomegaly, rheumatoid arthritis, or drugs such as antiretrovirals, ribavirin, or dapsone, or by hypertriglyceridemia [2].

We also disagree with the conclusion that m.3243A>G carriers with bowel dysmotility have a poor prognosis [1]. The prognosis of m.3243A>G carriers may depend not only on gastrointestinal involvement, but rather on cerebral, cardiac, pulmonary, endocrine, or muscle involvement. In addition, not all m.3243A>G carriers suffer from bowel dysmotility, especially those with pure MIDD. A strong argument against poor prognosis from bowel disease is that none of the seven patients in table 2 died from gastrointestinal involvement.

One of the patients listed in table 2 died of myocardial infarction (table 2) [1]. We should know whether this patient had typical cardiovascular risk factors such as arterial hypertension, hyperlipidemia, diabetes, atrial fibrillation, or smoking. Since this patient was diagnosed with MIDD, it is very likely that at least diabetes was present. Has diabetes been well controlled? What were the HbA1c values upon admission?

One patient had an intra-ventricular thrombus at autopsy as shown in table 2 [1]. We should know the cause of intraventricular thrombus formation. Did the thrombus arise due to heart failure, atrial fibrillation, Takotsubo syndrome, or due to left ventricular hypertrabeculation, also known as noncompaction? Did this patient have a patent foramen ovale? Knowledge of the underlying pathophysiology of thrombus formation is crucial as the treatment strategy may depend heavily on the underlying pathophysiology.

In summary, the excellent study has limitations that should be addressed before drawing final conclusions. Before HbA1 is claimed as a predictor of disease severity, all factors affecting HbA1c levels must be thoroughly excluded.

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