Treatment response in the first Emirati patient with diabetes associated with the A3243G mitochondrial point mutation

Alshafi Mohammad1, Najeef Waheed2, Ahmed EL-Laboudi2, Adam Buckley1
1 Research Institute, Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates
2 Diabetes and Endocrinology, Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates

Background: Maternally Inherited Diabetes and Deafness (MIDD) is estimated as the cause of 1% of cases of diabetes. Due to the small patient population, it is not clear which diabetes treatments are most effective in MIDD.

Aims: We discuss the response to different classes of hypoglycaemic agents in the first Emirati patient reported with mitochondrial diabetes.

Method: A 23-year old male presented with hyperglycaemia and features atypical for Type 1 Diabetes including retinal changes at diagnosis. MIDD was confirmed by presence of an A to G point mutation in the tRNALeu(UUR) gene at base pair 3243 (A3243G) of the mitochondrial genome using targeted next generation sequencing. We report his management and his clinical features at 3.8 years of follow-up.

Results: At diagnosis, anti-GAD and anti-IA2 antibody titres were not elevated and insulin secretory reserve was maintained, with C-peptide of 0.631nmol/L and simultaneous plasma glucose of 11.6mmol/L. No objective hearing loss was detected at presentation. Microvascular disease was detected at 39 days after onset of diabetes with background retinopathy (R1) and maculopathy (M1), and elevated albumin-creatinine ratio (ACR) (3.7mg/mmol, with subsequent microalbuminuria of 3.1, 4.1, 3.1, and 5.6mg/mmol at 12, 14, 17, and 19 months, respectively). Pinhole visual acuity (VA) was 0.8 (left) and 0.7 (right). BMI, HbA1c, and triglycerides were 27.3kg/m2, 8.5%, and 1.34mmol/L, respectively. MIDD was confirmed by genetic analysis in the patient’s mother, who had an established diagnosis of diabetes mellitus; his brother declined screening. He was initially managed with insulin and metformin (HbA1c from 8.5% to 6.9%). He was switched to sulphfonylurea (gliclazide) after diagnosis of MIDD (HbA1c from 6.9% to 7.7%), with canagliflozin added at 12 weeks (HbA1c from 7.7% to 6.2%, subsequently to 9%) and sitagliptin combined at 48 weeks (HbA1c from 9% to 8.7%). Dulaglutide was added at 73 weeks, leading to a dramatic improvement in his HbA1c from 8.7% to 6.5% and BMI from 28.4 to 25.4kg/m2 within 4 months and cessation of insulin, canagliflozin and sulphphonylurea treatment. Dulaglutide was discontinued due to intolerance with subsequent deterioration of glycaemic control (HbA1c 9.4%). At 3.8 years of follow-up, he progressed to pre-proliferative retinopathy (R2, M1); his ACR was 7.0mg/mmol. Pinhole VA reduced to 0.4 (left) and 0.3 (right). He remained overweight (BMI, 27.6kg/m2). LDL was elevated at 3.5mmol/L, and triglycerides were 1.3mmol/L while taking atorvastatin 20mg.

Discussion: The use of glucagon-like peptide-1 (GLP-1) analogues in patients with MIDD has been shown to effectively improve HbA1c within 6 months in three recent case reports. In this case, a GLP-1 induced a dramatic improvement in HbA1c within 4 months with cessation of several concomitant medications, sustained until the GLP-1 was discontinued due to lack of tolerability, with subsequent deterioration in glycaemic control. Although a full case series is lacking, accumulating evidence from case reports suggests that GLP-1 treatment may be particularly effective in people with MIDD.