A Case of MODY , Difficult to Diagnose

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A 17-year-old female attended the diabetes clinic after initially presenting in primary care with dizziness and HbA1c of 75. She had no phenotypic features of type 2 diabetes. At this time, a possible diagnosis of latent autoimmune diabetes in adults (LADA) was considered and anti- GAD antibodies were requested which were later found to be negative.The patient was initiated on Metformin which was titrated up to the maximum dose. Despite this,the patient's glucose level remained high which was later switched to modified release due to GIside effects. Dipeptidyl Peptidase-4 (DPP-4) Inhibitor, Linagliptin 5mg OD was also added to optimise the blood glucose control.Despite above measures blood glucose levels remained poorly controlled and the patient began reporting recurrent episodes of thrush, therefore Sulfonylurea, Gliclazide was added as a third agent.The patient was provided with health and lifestyle advice throughout her time attending the diabetes clinic and was reviewed by a dietician. As a result, the patient lost a reasonable amount of weight. At her subsequent appointments in 9 months after diagnosis , her HbA1c was found tobe 35 therefore it was decided to stop both the sulfonylurea and DPP-4 Inhibitor.It was thought possible that the weight loss has precipitated a return to euglycemia or probably due to the oneymoon period of diabetes .After almost 1 year from diagnosis, the patient's blood glucose levels had risen again on Metformin alone and her HbA1c had drifted up as a consequence. She was re-started on Gliclazide 80mg BD. Then after a few months time , the patient's HbA1c reflected optimised glycaemic control on a combination of metformin and gliclazide.During this period a referral was made to the Genetic Diabetes Specialist for Wales and the report is as follows: 'Sequencing of RFX6/14 shows a heterozygous disease causing variant and this is causing a frame shift mutation,' showing that the patient has a genetic predisposition to diabetes. It was also noted at this time that the patient appeared to be very sensitive from the diabetes perspective to Gliclazide. In regard to family history, her father has diabetes which was diagnosed in his forties. She reports he is overweight and currently on insulin therapy. Following further genetic analysis of family members, it was found that her Mum, who does not have diabetes, has the same genetic abnormality. Her father who does have diabetes does not have the same genetic abnormality. These genetic reports resulted in a diagnosis of MODY.Eventually this patient was shifted to Insulin due to poor blood glucose control with ralglycemic agents

Maturity Onset Diabetes of the Young (MODY) is an inherited form of non-autoimmunediabetes which usually presents before the age of 25 years (Urakami., 2019). It is monogenicdiabetes that is inherited in an autosomal dominant fashion (Patel et al., 2017). Several causativemutations have been identified, the commonest of which are HNF1A, HNF4A,HNF1B and GCK (Gardner and Tai, 2012)

The RFX6 gene encodes for a transcription factor which directs islet cell differentiation in thepancreas. Studies have shown that mice without RFX6 were unable to generate any of the normalislet cell types apart from pancreaticpolypeptide-producing cells (Smith et al., 2010). This tellsus that RFX6 likely has an important role in the normal development of the pancreas.Mutations in RFX6 have been previously been associated with Mitchell-Riley syndrome, thecommon features of which are neonatal diabetes, pancreatic hypoplasia, intestinal atresia, biliaryatresia, and gallbladder aplasia/hypoplasia. (Khan et al., 2016).Mutations in RFX6 have also been previously shown to be associated with MODY. Patel et al.,(2017) sequenced the DNA of MODY patients with unknown aetiology and compared theirfindings to a control population. They found that RFX6 protein truncating variants were morefrequent in their MODY cohorts. They went on to find that RFX6 heterozygotes showed reducedpenetration of diabetes compared to other known genetic causes of MODY such as HNF1A andHNF4A mutations. This is very relevant to our case study as our patient's mother has the sameRFX6 mutation as our patient, however, the mother does not have diabetes which could beexplained by the reduced penetrance of the mutation.Other case reports further support this association between RFX6 and MODY. Levin et all,identified four generations of diabetes mellitus in one family, caused by a heterozygous mutationin the RFX6 gene (Zuckerman, 2019) Akiba et al. also report an RFX6 mutation in a family withthree generations of diabetes. (Akiba et al., 2020)MODY is often initially misdiagnosed as initially as type 1 or type 2 diabetes. Although it is arare cause of diabetes, accurate diagnosis is important for management of the patient and theirfamily. Studies have shown that those with HNF1A and HNF4A mutations show increased sensitivity to sulphonylureas therefore this will have a great impact on management (Gardnerand Tai, 2012) Identification of the genetic mutation can also guide management for other familymembers and future generations. In conclusion, this case report further supports the evidence of causative relationship betweenmutations in the RFX6 gene and MODY. It also highlights the importance of early considerationof the less common causes of diabetes such as MODY in atypical presentations. This shouldimprove diagnostic timeframes and result in tailored management for these patients, improvingoutcomes for the patients and their families.