Sulphonylurea responsive monogenic diabetes in an Insulin treated 8-year old child in West Africa; of more than academic interest and one of many?

Abstract: We describe the case and identification of monogenic diabetes mellitus in a Togolese girl at the age of eight years, previously treated as Type I Diabetes following diagnosis at the age of two months. She has since been transitioned from insulin to oral sulphonylurea therapy, with improved glycaemic control and greater therapeutic security. We believe many more such cases must exist in Africa amongst those with a history of neonatal diabetes. Free genomic testing is available (see below) in suitable cases. The case highlights the value of personalized medicine and international cooperation.

Key Words: Neonatal Diabetes Sulphonylurearesponsive monogenic diabetes

Introduction

Neonatal diabetes mellitus (NDM), characterised by the onset of diabetes in the first six months of life, is rare with a reported incidence of 1 in 160,000.1,2 NDM is monogenic in aetiology, arising most often from inherited or sporadic mutations in single genes which are critical for the regulation of pancreatic β-cell function.3 NDM may be transient, resolving within a median of three months, or it may be permanent.4 Activating het- erozygous mutations of the KCNJ11 and ABCC8 genes which encode subunits of the pancreatic β-cell KATP channel are the most common causes of permanent NDM.5 Identification of the underlying genetic mutation in these patients is fundamentally important as they are often able to transition to oral sulphonylurea therapy. Therefore, referral for genetic testing has important clinical implications and is essential for the guidance of appropriate and cost-effective treatment.

Cellular Pathophysiology

Mutations in the KCNJ11 and ABCC8 genes encoding for the Kir6.2 and SUR1 subunits of the pancreatic β-cell inward rectifying KATP channel account for 30% to 58% of permanent NDM diagnosed in patients under six months of age.6 The pancreatic KATP channel is essential for the regulation of insulin secretion which is initiated by closure of the KATP channels and inhibited by the opening.7 Glucose metabolism within the pancreatic β-cell generates increased intracellular ATP levels. Under normal circumstances, increased intracellular ATP exerts inhibitory effects leading to the closure of the KATP channels, allowing for cell membrane depolarization and the opening of voltage-gated calcium channels. This in turn results in calcium-induced insulin release as part of a coordinated cellular response to glucose metabolism. Patients with NDM caused by heterozygous activating KCNJ11 mutations have KATP channels which are less sensitive to inhibitory ATP. As a direct consequence, their channels remain in an inappropriate open configuration, despite the presence of glucose, resulting in cell membrane hyperpolarization and impaired insulin secretion leading to dramatic hypoglycaemia. Sulphonylureas act to close KATP channels in an ATP-independent manner, thereby inducing insulin secretion. They therefore represent the optimal therapy for patients with NDM caused by KCNJ11 mutations.

Case Report

AE, an 8-year-old girl from Lomé, Togo, West Africa was diagnosed with NDM at the age of two months. She was being managed on a twice daily “mixed-split” insulin regimen requiring in excess of thirty units per day.
Her diabetes control was suboptimal with marked glycaemic variation on capillary blood testing. Height 127cm at 33rd centile, weight 25kg at 33rd centile and BMI 15.5 at 39th centile. HbA1c was not available.

Given the age of initial presentation, an underlying genetic diagnosis was sought. However, genetic analysis proved challenging in the setting of limited local resources, laboratory facilities, postal services and transport networks. Thus, it became clear that international collaboration would be required. An EDTA sample was obtained, carried by hand back to Ireland and forwarded to the Genomics Laboratory at the University of Exeter, UK, who offer free genetic analysis for individuals diagnosed with diabetes before the age of nine months.

Sanger sequencing analysis of the ABCC8, KCNJ11, and INS genes was carried out on the sample as previously described, which identified a novel heterozygous KCNJ11 missense variant p.(Phe333Val). Evaluation of this variant using the ACMG Guidelines classified this variant as being of uncertain significance. Parental salivary DNA was then obtained and transported for analysis which confirmed that the p. (Phe333Val) variant had arisen de novo in AE, allowing for variant reclassification as likely pathogenic with a predicted positive response to oral sulphonylurea therapy.

A modified version of the therapeutic transfer protocol available at https://www.diabetesgenes.org/about-neonatal-diabetes/su-transfer-in-patients-with-kcnj11-and-abcc8-mutations-pndm/ was implemented in order to allow safe transition from insulin to oral glibenclamide, with careful monitoring of response. AE successfully transitioned to twice daily oral glibenclamide initially but required 5mg once daily to achieve optimal control. Blood glucose levels ranged between 4.0 – 7.6 mmol/L post transition allowing for the complete withdrawal of subcutaneous insulin.

Discussion

Patients diagnosed with diabetes in the first six months of life are likely to have an underlying genetic anomaly rather than autoimmune Type1 Diabetes. Approximately 40% of patients with NDM have a potassium channel mutation identified, up to 90% of whom may be able to switch to low cost oral sulphonylurea therapy. This should result in improved glycaemic control. Available data suggests a significant average reduction of 1.7% in HbA1c, 12 weeks following sulphonylurea commencement, with sustained improvement after one year. A further recent multi-center study on 90 patients with NDM caused by KCNJ11 mutations showed that sulphonylurea therapy is safe and provides excellent glycaemic control for at least 10 years. Thus, a simple once daily oral therapy can provide significant quality of life benefits, decreased intensity of care required, removal of risk from insulin supply chain disruption in resource poor areas and have a welcome life-altering impact for both the child and their family. Furthermore, cost benefits have been calculated to be in the region of US$ 12,000 after 10 years following transition from subcutaneous insulin.

Conclusion

This case exemplifies the importance of early molecular genetic analysis in patients with a diagnosis of diabetes arising in the first 6-9 months of life. Identification of a de novo KCNJ11 mutation in this case had significant therapeutic implications, illustrating an example of personalized medicine where genetic information from the patient was translated into optimal treatment for her. The positive outcomes could not have been achieved without healthcare professionals in different countries and even continents working together. We are pleased to demonstrate the importance of teamwork and collaboration in overcoming difficulties in the delivery of optimal patient care.

The Genomics Laboratory at the University of Exeter currently offers free genetic screening for patients with neonatal diabetes (diagnosed at <9 months of age). For further information see https://www.diabetesgenes.org/about-neonatal-diabetes/genetic-testing-for-neonatal-diabetes/

Acknowledgements

Free genetic testing for neonatal diabetes was funded through a Wellcome Trust Senior Investigator Award to Professors Andrew Hattersley and Sian Ellard. Elisa De Franco is a Diabetes UK RD Lawrence fellow (19/005971).

AE is under the ongoing care of KT and MS in the children’s and young person’s clinic in Lomé, Togo, which is supported by the “Life For a Child” programme of the International Diabetes Federation.
References


