Congenital hyperinsulinism: a family case report

AMY MORRISON, DABEAN FARAJ, MARIE-FRANCE KONG

Br J Diabetes 2023;23:116-119
https://doi.org/10.15277/bjd.2023.422

Key words: congenital hyperinsulinism, neonatal hypoglycaemia, macrosomia, K-ATP channel and ABCC8

Introduction

Inappropriately elevated insulin levels in the setting of hypoglycaemia (so-called hyperinsulinaemic hypoglycaemia) is a dangerous phenomenon. It can be observed in rare and often under-recognised conditions presenting diagnostic challenges, as highlighted in patients with insulinoma.[1] In neonates, classification of hyperinsulinaemic hypoglycaemia can be divided into primary (congenital or familial) and secondary, caused by maternal diabetes, intrauterine growth restriction or birth asphyxia.[2]

Congenital hyperinsulinism is a rare genetic condition that is characterised by inappropriate insulin secretion. It manifests as persistent hypoglycaemia in neonates and children, and has a prevalence of roughly 1 in 40,000 live births.[3] It occurs as a result of mutations in the genes responsible for regulating insulin secretion; alterations in 15 genes have been identified to date. Mutations in the K-ATP channel subunits encoded by KCNJ11 and ABCC8 are the most commonly recognised defects.[4]

Congenital hyperinsulinism can develop within the first few days of life. At this time symptoms are typically severe, including seizures, apnoea, hypotonia and tachycardia, in addition to lethargy and poor feeding. In milder phenotypes children can be asymptomatic and the condition may only be identified later in life.[5,6]

We highlight the challenges in diagnosis and management of hyperinsulinism in the family of a patient referred to our outpatient diabetes clinic.

Patient information

A 66-year-old woman (Mrs X) was referred to our diabetes outpatient clinic following diagnosis of diabetes six months after a renal transplant. End-stage renal failure had developed secondary to mesangio-capillary glomerulonephritis (MSGN), requiring renal replacement therapy via peritoneal dialysis prior to transplantation. Immunosuppression post-transplant included prednisolone (10mg for six months, 5 mg ongoing), tacrolimus and azathioprine. Twelve months post-transplant her HbA_{1c} was found to be elevated at 6.9%/52 mmol/mol. Oral hypoglycaemic agents were titrated but she eventually required insulin. Her diabetes is now stably managed on linagliptin 5 mg OD and Humulin I (14 units AM and 4 units PM).

On discussion with the patient, an interesting and prominent family history of dysglycaemia emerged. Three of her four children (aged 41, 38 and 28 years, all male), and three of her six grandchildren (all female), had a confirmed diagnosis on genetic testing of congenital hyperinsulinism (gene = ABCC8) (Figure 1).

Clinical findings

Mrs X: On examination this lady is 1.78 m tall and weighs 72 kg, giving a BMI of 22.7 kg/m^2.

Children of Mrs X: All four children met criteria for macrosomia at birth (weighing 9 lb 4 oz-11 lb 15 oz or 4.1-5 kg). During each pregnancy Mrs X had negative antenatal testing for gestational diabetes.

Grandchildren of Mrs X: The three girls affected by hyperinsulinism are tall for their age and are noted to have very thick hair.

Timeline

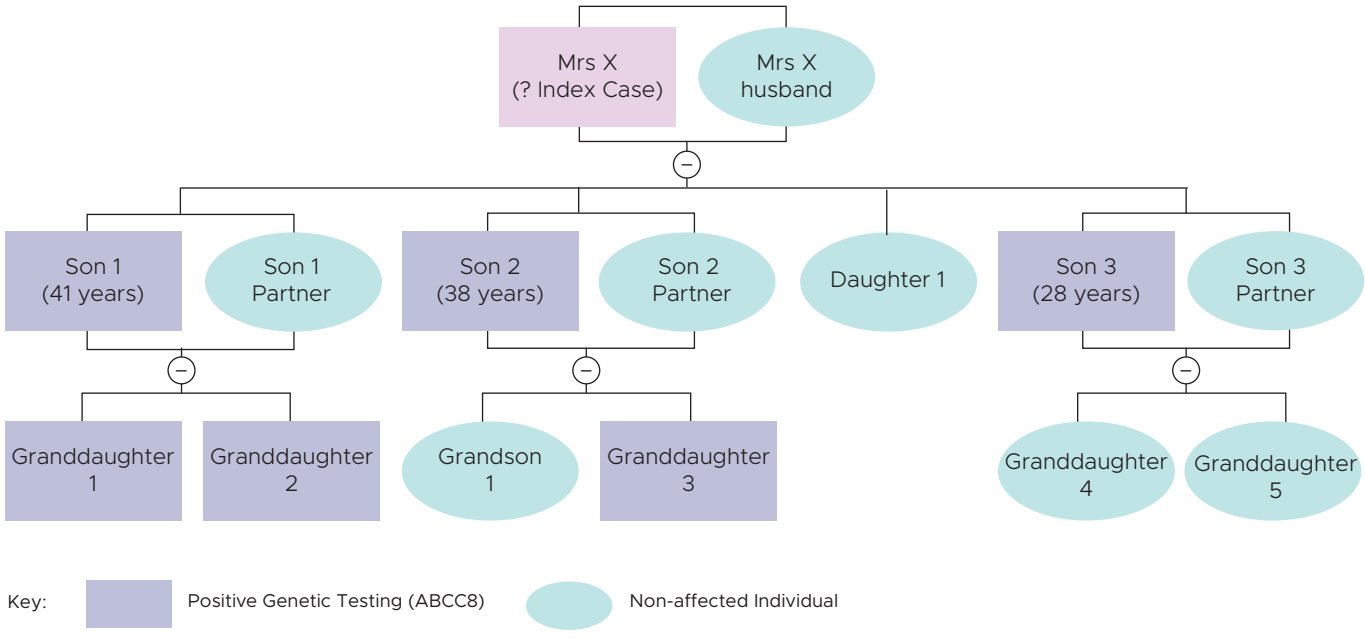
Mrs X: This lady had macrosomic pregnancies in 1979, 1981, 1984 and 1993. She was diagnosed initially with MSGN postnatally in 1981 and her renal function remained stable without intervention until she commenced peritoneal dialysis in November 2017. Just over six months later, in June 2018, she had a renal transplant. Since then MCGN has recurred in her transplanted kidney but her renal function currently remains stable, with an eGFR around 40 ml/min. Post-transplant monitoring while the patient was taking prednisolone highlighted an elevated HbA_{1c} at 6.9% (52 mmol/mol) in May 2019. Despite oral therapies, this rose to 10% (86 mmol/mol) in July 2021 and insulin was commenced. With low-dose insulin therapy (18 units per day) and DPP4 inhibitor use (linagliptin 5 mg daily), glucose levels have remained stable; her latest HbA_{1c} was 6.5% (47 mmol/mol). ICA, anti-GAD, anti-IA2 and anti-ZNT8 antibodies are negative.

Children: All four of Mrs X's children have remained well and

University of Leicester NHS Trust, Leicester, UK

Address for correspondence: Dr Amy Morrison
Department of Diabetes, University of Leicester NHS Trust, University Road, Leicester LE1 7RH
E-mail: amymorrison15@doctors.org.uk

Figure 1. Family tree identifying affected individuals with positive genetic testing for ABCC8 mutation



have not demonstrated any clinical or biochemical features of dysglycaemia to date.

Grandchildren: Mrs X's first affected grandchild, born to her eldest son, was 10 lb 5 (4.7 kg) at birth. At eight months of age she presented with a seizure secondary to hypoglycaemia. After one month in hospital she was discharged with growth hormone (GH) replacement for what was initially diagnosed as probable GH deficiency. Her sister, born two years four months later, was also large (11 lb 4 oz or 5.1 kg) at birth. She suffered from severe neonatal hypoglycaemia and required neonatal intensive care for the first three weeks of her life. A diagnosis of hyperinsulinism was suspected and diazoxide was commenced at two weeks of age.

Mrs X's second oldest son has two children; an older boy who has not been affected by hyperinsulinism and a younger daughter who presented with hypoglycaemia at two days old. Following glucose level stabilisation with IV replacement and feeding she was discharged without further investigation at nine days, but later presented aged nine months, unresponsive secondary to severe hypoglycaemia (1.2 mmol/L). Mrs X's youngest son has two daughters, neither of whom has been affected.

Diagnostic assessment

Diagnosis of hyperinsulinism was first made in Mrs X's second affected granddaughter, through clinical assessment in the presence of hypoglycaemia with elevated insulin levels. Genetic aetiology was confirmed via genetic testing at eight months of age under the guidance of Great Ormond Street Children's Hospital. This led to testing of her sister, who until this point had been on GH replacement for presumed deficiency.

All of Mrs X's children have undergone genetic screening, and three of the four have had an ABCC8 gene mutation identified. She herself has not yet undergone genetic testing, but has had an invitation and plans to do so.

Prior to the birth of Mrs X's youngest granddaughter (born to her youngest son), antenatal genetic testing was offered and carried out. This informed the family that this unborn baby did not have the identified gene mutation (ABCC8) for congenital hyperinsulinism.

Therapeutic intervention

Medical management of hypoglycaemia associated with hyperinsulinism has been required in all three affected grandchildren. Diazoxide was commenced at two weeks of age in her second granddaughter. Several attempts have been made to discontinue this, but hypoglycaemia recurs, and she therefore continues on a low dose (2 mg/kg, split into two doses daily). She is currently aged 11 years. Her sister has never taken diazoxide. She was initially treated with GH until the age of three years. The GH was stopped at the time of her sister's congenital hyperinsulinism diagnosis. Mrs X's third affected granddaughter commenced diazoxide at nine months of age and continues to take this now, aged seven years (Table 1).

Follow-up and outcomes

Mrs X is a 66-year-old woman diagnosed with steroid-induced diabetes following a renal transplant for MCGN. Her glycaemic management has been optimised with low-dose insulin therapy (0.25 units per kg). A personal history of macrosomic babies and a family history of hyperinsulinism has been explored. Symptomatic hyperinsulinism in two of her three affected granddaughters has been controlled through therapeutic

Table 1. Phenotypes and clinical management of family members with positive genetic testing for ABCC8 mutation

Family member	Age (years)	Presenting features	Current management
Mrs X*	66	Current BMI 22.7 kg/m^2. All four children met criteria for macrosomia at birth (9 lb 4 oz-11 lb 15 oz or 4.1-5 kg). In each pregnancy Mrs X had negative antenatal testing for gestational diabetes. Diagnosed with steroid-induced diabetes following a renal transplant for MCGN	Linagliptin and Humulin I
Son 1	41	No clinical features	Nil
Son 2	38	No clinical features	Nil
Son 3	28	No clinical features	Nil
Granddaughter 1	13	10 lb 5 oz (4.7 kg) at birth; at 8 months presented with a seizure secondary to hypoglycaemia. Commenced growth hormone (GH) replacement for what was initially diagnosed as probable GH deficiency	Nil
Granddaughter 2	11	11 lb 4 oz (5.1 kg) at birth, severe neonatal hypoglycaemia and required neonatal intensive care for the first three weeks of her life. A diagnosis of hyperinsulinism was suspected and diazoxide commenced at two weeks of age	Diazoxide
Granddaughter 3	7	Hypoglycaemia at 2 days old. Discharged without further investigation at 9 days, but later presented aged 9 months, unresponsive secondary to severe hypoglycaemia (1.2 mmol/L). Developed epilepsy, with refractory seizures requiring brain surgery. Damage to the right hippocampus was identified secondary to this episode of prolonged hypoglycaemia aged 9 months	Diazoxide

*Genotype currently unknown

intervention with diazoxide.

Her third granddaughter affected with congenital hyperinsulinism, despite a known family history of the condition (symptomatic in two cousins), was not diagnosed until she became unresponsive with severe hypoglycaemia aged nine months. Following on from this she developed epilepsy, with refractory seizures requiring brain surgery. Damage to the right hippocampus was identified secondary to an episode of prolonged hypoglycaemia aged nine months. Fortunately, her seizures have resolved since this surgery.

Discussion

This case highlights the profound impact that a delay in diagnosis of neonatal hypoglycaemia secondary to congenital hyperinsulinism can have. It raises awareness of this uncommon condition, the clinical features to be aware of, the diagnostic pathway and the therapeutic options available.

The diagnosis of congenital hyperinsulinism requires confirmation of hypoglycaemia with associated hyperinsulinism and exclusion of other clear causes, including maternal diabetes, perinatal asphyxia, intra-uterine growth restriction, rhesus haemolytic disease and insulinoma. Genetic testing can be utilised to confirm the aetiology of this condition. Genetic testing involves blood test screening for the presence of the currently identified causative mutations: *ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF1A, HNF4A, HK1, PGM1, PMM2, FOXA2, CACNA1D* and *EIF2S3*.[7] There is an overlap in phenotypes for most genetic subgroups. Almost half of congenital hyperinsulinism cases occur as a result of loss- of-function mutations in K-ATP channel genes ABCC8 and KCNJ11. Genetic variants impact clinical severity and responsiveness to treatment.[7]

As highlighted in the case of Mrs X's youngest granddaughter (born recently to her youngest son), antenatal testing to assess for the presence of these known causative mutations is now additionally available. This enables the clinical team to prepare for the likelihood of neonatal hypoglycaemia, with prompt appropriate management, and for the parents to prepare psychologically. Antenatal testing aims to prevent complications associated with hypoglycaemia, such as hypoglycaemic brain injury inducing refractory seizures as seen in this report. Genetic testing is, however, a matter of personal choice. It is an investigation which can be associated with both benefits and challenges. Various modes of inheritance are observed and despite these currently identified genes almost half of all cases of congenital hyperinsulinism remain genetically unidentified.[7]

The first symptomatic family member (one of Mrs X's granddaughters) was initially treated as having growth hormone deficiency, and given growth hormone replacement. Growth hormone deficiency typically presents in childhood with short stature and poor growth velocity and can be associated with hypoinsulinaemic hypoglycaemia.[8] Whilst on this therapy this child did not have any further episodes of symptomatic hypoglycaemia, and these episodes have not recurred since she stopped taking growth hormone.

Avoidance of recurrent hypoglycaemia has now been achieved following correct diagnosis in her other two granddaughters through the implementation of diazoxide therapy. Diazoxide is a potassium channel activator which enhances cell membrane permeability to potassium ions. This results in calcium channel inactivation and prevention of ATP generation and therefore insulin release.[9] It is prescribed based on body weight, usually 5-15mg/kg/day in the treatment of congenital hyperinsulinism. The main recognised side effects include fluid retention, weight gain and excessive body hair

Key messages

- Congenital hyperinsulinism is a rare but recognised cause of neonatal hypoglycaemia.
- A family history may be key in the consideration of this diagnosis.
- Genetic testing, of the currently recognised causative genes, is helpful to confirm this rare diagnosis and can aid in prediction of severity and treatment responsiveness.
- Antenatal testing for those with a family history can enable pre-emptive management and reduce morbidity.

growth. Rarely, respiratory decompensation and pulmonary hypertension can be seen in neonates, with risk factors including pre-term infants, low birth weight and intra-uterine growth restriction.[10] Response to diazoxide in congenital hyperinsulinism is dependent upon the genetic variant of the causative mutation. Individuals with hyperinsulinism unresponsive to diazoxide can require near-total pancreatectomy in order to control symptoms.[7]

Individuals with congenital hyperinsulinism as a result of K-ATP channel mutations (ABCC8 and KCNJ11) who have achieved symptomatic control through medical management with diazoxide therapy are reported to have a reduction in symptom severity over time. It is therefore imperative that periodic assessment of medication dose and requirement should take place to optimise this therapy and minimise unnecessary adverse effects.[7]

Conclusion

Congenital hyperinsulinism is a rare but recognised cause of hyperinsulinaemic hypoglycaemia in neonates and children, with vast heterogeneity in clinical presentation. Screening for known genetic defects and prompt treatment with diazoxide may prevent morbidity and mortality resulting from severe hypoglycaemia in these individuals.

Conflict of interest None.
Funding None.
Informed consent This patient and her family consented for this case report to be published. All details have been kept anonymous.
Patient perspective The key outcome of discussions with Mrs X revealed how important it was to her and her family that clinicians in the field have an awareness of hyperinsulinism, its presentation, diagnosis and prompt appropriate management.
A welcome introduction to their family has been the use of antenatal genetic diagnosis, enabling the family to prepare both psychologically and medically prior to the time of delivery and post-natal period.

References

1. Gillis D. Familial hyperinsulinism 2003, updated 2019. In: Adam MP, Everman DB, Mirzaa GM *et al,* eds. *Gene Reviews* Seattle (WA), University of Washington, Seattle, 1993-2023. Available from hhtp://www.ncbi.nlm.nih.gov/books/NBK1375/
2. Demirbilek H, Rahman SA, Buyukyilmaz GG, Hussain K. Diagnosis and treatment of hyperinsulinaemic hypoglycaemia and its implications for paediatric endocrinology. *Int J Pediatr Endocrinol* 2017;**2017**:9. https://doi.org/ 10.1186/s13633-017-0048-8. Epub 2017 Aug 29.
3. Senniappan S, Arya VB, Hussain K. The molecular mechanisms, diagnosis and management of congenital hyperinsulinism. *Indian J Endocrinol Metab* 2013;**17**(1):19–30. https://doi.org/10.4103/2230-8210.107822
4. Inagaki N, Gonoi T, Clement JP, *et al*. Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor. *Science* 1995;**270**(5239):1166–70. https://doi.org/10.1126/science.270.5239.1166
5. Arya VB, Guemes M, Nessa A, *et al*. Clinical and histological heterogeneity of congenital hyperinsulinism due to paternally inherited heterozygous ABCC8/KCNJ11 mutations. *Eur J Endocrinol* 2014;**171**(6):685-95. https://doi.org/10.1530/EJE-14-0353
6. Rozenkova K, Nessa A, Obermannova B, *et al*. Could a combination of heterozygous ABCC8 and KCNJ11 mutations cause congenital hyperinsulinism? *J Pediatr Endocrinol Metab* 2017;**30**(12):1311-15. https://doi.org/10.1515/jpem-2017-0163. PMID: 29127764.
7. Guemes M, Rahman SA, Kapoor RR, *et al*. Hyperinsulinemic hypoglycemia in children and adolescents: recent advances in understanding of pathophysiology and management. *Reviews Endocrine Metabolic Disorders* 2020;**21**(4):577-97. https://doi.org/ 10.1007/s11154-020-09548-7
8. Gan HW, Katuganpola H. Growth hormone deficiency in children. *BMJ Best Practice* 2022. Available at Growth hormone deficiency in children – Symptoms, diagnosis and treatment | BMJ Best Practice, last accessed 8th April 2023.
9. Doyle ME, Egan JM. Pharmacological agents that directly modulate insulin secretion. *Pharmacol Rev* 2003;**55**:105-31. https://doi.org/ 10.1124/pr.55.1.7
10. Desia J, Key L, Swindall A, *et al*. The danger of diazoxide in the neonatal intensive care unit. *Therapeutic Advances in Drug Safety* 2021;**12**:20420986211011338. https://doi.org/10.1177/204209862111011338