A novel variant HNF1A gene (HNF1A-MODY) in a patient presenting with hyperglycaemia and glucosuria

V BISBINAS[1], A SERTEDAKI[2], As GIANNOPOULOS[3], Z KARABOUTA[3]

1. University of Bristol, Bristol, United Kingdom
2. Division of Endocrinology, Diabetes and Metabolism, First Department of Pediatrics, Medical School, National and Kapodistrian University of Athens, 'Aghia Sophia' Children's Hospital, Athens, Greece
3. 2nd Paediatric Department, University General Hospital AHEPA, Thessaloniki, Greece

Topic: Diabetes and insulin

ESPE 2021 The 59th Annual Meeting Online 22-26 September 2021

INTRODUCTION

- HNF1A-MODY (MODY3) is a common subtype of the Maturity Onset Diabetes of the Young (MODY), a monogenic autosomal dominant disease presenting as a nonketotic diabetes with onset usually during adolescence, or early adulthood
- HNF1A-MODY is less common among children as the hyperglycaemia usually manifests after 10th year of life

AIM

We describe a young girl presented with hyperglycaemia and glucosuria

METHOD

Presentation: An 8.5-year-old girl presented with abdominal pain, nausea, elevated serum blood glucose(BG) 288mg/dl (16mmol/l), glucosuria (+++)

Clinical course:

- Pre-and post-prandial Bmstixs returned to normal range, urine was negative for glucose

Treatment: intravenous N/S 0.9%, no insulin

Laboratory tests on admission:

- Oral glucose tolerance tests (OGTT) (table 1)
- Blood gas: pH 7.44, HCO3, 22.4mmolL, BE -2.3mmol/L
- Urine: glucosuria, no ketones; later normal

RESULTS

Initial diagnosis: newly developing type 1 Diabetes (T1D).

Further screening:

- Autoantibody screen: Anti-GAD, IA2, ICA negative

Previous history:

- one of dizygotic twins, born at 36 wks gestation
- Unrelated parents
- Growth on the 50th percentile, prepubertal

Family history:

- Father, 51 years old, on treatment for arterial hypertension and presumed type 2 Diabetes (T2D) for the last decade
- mother and twin brother healthy

Patient was discharged home on glucose self-monitoring (BMstix), OGTT periodically (table 2), and follow up in clinic

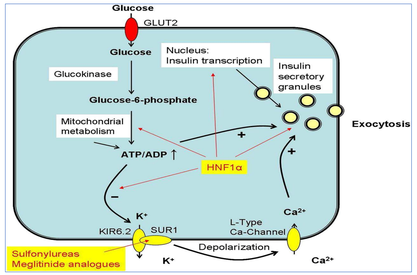
Genetic testing: both patient and her father are heterozygous in HNF1A gene for a novel variant c.454>C (p.T152P) that was confirmed by Sanger Sequencing exon 2 of HNF1A gene

Table 1. OGTT on first presentation

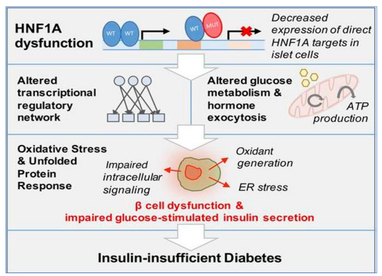
Time (mins)	0′	60′	120′
BG (65-100mg/dl) (3.6-5.5mmol/l)	84 (4.6)	191 (10.6)	230 (12.7)
Insulin (2.6-24.9μIU/ml)	5.6	21	34.4
C-peptide (1.1-4 ng/ml)	1.4	4.4	5.7
HBA1c (4-6%)	6		

Table 2. Latest OGTT

Time (mins)	0′	60′	120′
BG (74-106 mg/dl) (4.1- 5.8 mmol/l)	93 (4.6)	136 (7.5)	163 (9)
Insulin (2.6-25 μIU/ml)	3.9		
C-peptide (1.1-4ng/ml)	1.1		
HBA1c (4-6%)	6		



HNF1A is expressed in pancreatic β cells and hepatocytes. While the underlying mechanism is not well understood, the mutations relate to reduced insulin secretion in response to rising blood glucose levels.



CONCLUSIONS

- **HNF1A-MODY patients could easily be misclassified as T1D or T2D**
- **Most patients will need pharmacological treatment as they show progressive deterioration in glycaemic control**
- **Patients are extremely sensitive to sulfonylureas**
- **Molecular genetic diagnosis of the MODY subtype is of outmost importance for clinical diagnosis, disease progression, prognosis and family counselling**

REFERENCES

- Valkovicova T et al. Novel insights into genetics and clinics of the HNF1A-MODY. Endocr Regul. 2019;1; 53(2);:110-134. doi: 10.2478/enr-2019-0013. PMID: 31517624
- Ovsyannikova AK et al. A Case of Maturity Onset Diabetes of the Young (MODY3) in a Family with a Novel *HNF1A* Gene Mutation in Five Generations. *Diabetes Ther* 2018; 9;: 413–420. https://doi.org/10.1007/s13300-017-0350-8
- Delvecchio M et al. Treatment Options for MODY Patients: A Systematic Review of Literature. Diabetes Ther. 2020;11(8;):1667-1685. doi: 10.1007/s13300-020-00864-4. Epub 2020 Jun 24. PMID: 32583173; PMCID: PMC7376807
- Fantasia KL et al. Optimal Glycemic Control in a Patient With HNF1A MODY With GLP-1 RA Monotherapy: Implications for Future Therapy. J Endocr Soc. 2019; 3;3(12):2286-2289. doi: 10.1210/js.2019-00278. PMID: 31737858; PMCID: PMC6846329
- Skoczek, D et al. Maturity Onset Diabetes of the Young—New Approaches for Disease Modelling. *Int. J. Mol. Sci.* 2021; *22'*, 7553. https://doi.org/10.3390/ijms22147553
- Peixoto-Barbosa R et al. Update on clinical screening of maturity-onset diabetes of the young (MODY). Diabetol Metab Syndr. 2020 Jun 8;12:50. doi: 10.1186/s13098-020-00557-9. PMID: 32528556; PMCID: PMC7282127.

ACKNOWLEDGEMENTS

We thank the Molecular Endocrinology Laboratory, Division of Endocrinology, Metabolism & Diabetes, First Department of Pediatrics, Medical School, National and Kapodistrian University of Athens, 'Aghia Sophia' Children's Hospital for providing the genetic testing for the patient and her family

CONTACT INFORMATION

Dr Zacharoula Karabouta, MD, MSc, PhD, DCH(London), MRCP(UK), FRCPCH(UK)
Consultant Paediatrician- Paediatric Endocrinologist & Diabetologist
2nd Paediatric Department
University General Hospital AHEPA
St.Kiriakidis 1, P.O. 54636 Greece
Thessaloniki, Greece (Hellas) zkarabouta@yahoo.com