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Abstracts

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An adolescent with *HNF1B* deletion. A case report

Aikaterini Vourdoumpa[1,2], *Diamanto Koutaki*[1,2], *Ioannis-Anargyros Vasilakis*[1], *Ioanna Bacopoulou*[1], *Amalia Sertedaki*[1], *Evangelia Charmandari*[1,2], *George Paltoglou*[1]

[1]Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, 'Aghia Sophia' Children's Hospital, Athens, Greece. [2]Division of Endocrinology and Metabolism, Center of Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

Introduction: Mutations in hepatocyte nuclear factor 1B (*HNF1B*) gene (chromosome 17q12), lead to monogenic diabetes (*HNF1B*-MODY or MODY5, OMIM 137920) accompanied by multisystem disorders. *HNF1B* gene encodes HNF1B protein, a member of the homeodomain-containing superfamily of transcription factors, expressed early in embryogenesis, contributing significantly to organogenesis and the function of many systems (kidneys, liver, pancreas, bile ducts, gut, urogenital tract, lung, and thymus).

Methods: A 14.3-year-old adolescent boy was referred to our Outpatient Obesity Clinic for investigation and management of impaired fasting glucose and unhealthy dietary habits. Elevated concentrations of fasting glucose (maximum 112mg/dL) and HbA1c (maximum 5.7%) alternating with normal values for 3 years were noted. The past medical history revealed unilateral nephrectomy due to polycystic kidney, a femoral fracture and hypertransaminasemia. Family history was unremarkable. At initial evaluation, our patient was pubertal (Tanner staging: G3, P4, A3, Testicular volume: 6-8mL) with normal weight (BMI z-score: - 0,07) and a right hydrocele. The OGTT was diagnostic of diabetes mellitus (plasma glucose 200 mg/dL at 120´), with maximum insulin concentration 96.94 ng/mL at 120´ (HbA1c: 5.5%, fasting c-peptide: 0,401 nmol/L, autoantibodies for Type I diabetes: negative). He also had hypomagnesemia, hypertransaminasemia, hyperparathyroidism with normal vitamin D levels, and hyperuricemia. Clinical genetic evaluation set a possible diagnosis of *HNF1B*-MODY. DNA from peripheral blood was obtained from the patient and his parents and MLPA methodology was implemented to evaluate the possibility of *HNF1B*, *GCK, HNF1A,* and *HNF4A* gene deletions or duplications.

Results: Genetic testing revealed a *de novo* heterozygous deletion of *HNF1B*, confirming the diagnosis of *HNF1B*-MODY. Further investigation with abdominal elastography, MRCP and MRI showed pancreatic hypoplasia and steatosis, liver fibrosis, a cystic formation in the epididymis and right hydrocele. A multidisciplinary management plan was introduced that included dietary consultation, a structured diabetes training program (glucose monitoring, carbohydrate counting, and insulin therapy), as well as monitoring of parathormone and magnesium concentrations and pediatric nephrological and gastroenterological care, to early detect and manage other multisystemic defects.

Conclusion: A child with impaired glucose metabolism or diabetes and multisystem (extrapancreatic or exocrine pancreas) involvement is of paramount importance to be investigated early towards monogenic forms of diabetes. *HNF1B* mutations lead to multisystemic manifestations, presenting with a heterogenous and broad phenotype. Such patients benefit from early diagnosis and require an integrated follow up by a multidisciplinary team, even in the absence of overt diabetes, to prevent and manage complications and comorbidities in time.

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Outmoded by MODY? A Case Report of HNF1A-MODY in Paediatric Stroke

Thomas Siese[1], *Hannah Hickingbotham*[1], *Anne Eggers*[1], *Yolanda Alins-Sahun*[2], *Philippa Bowen*[1], *Julian Hamilton-Shield*[1]

[1]University Hospitals Bristol and Weston, Bristol, United Kingdom. [2]University Hospitals Plymouth, Plymouth, United Kingdom

Background: The association between HNF1A-MODY and vascular complications including stroke has previously been identified in adults but to date there have been no reported paediatric cases published.

Description: We present the case of an Eritrean 13-year-old girl, who was admitted with an acute ischaemic stroke, on a background of Diabetes Mellitus (presumed Type 1) diagnosed the previous year. Aside from being on multiple dose injections (MDI) of basal-bolus insulin at 0.9Units/kg/day, she had no other regular medications. There was a history of vitiligo (longstanding, with negative adrenal antibodies) with no history of acanthosis nigricans or clinical features of insulin resistance. On acute presentation, she was normoglycaemic (7.2mmol/L), normotensive (122/90mmHg) with normal body habitus (weight 46kg) and no other known cardiovascular risk factors (non-smoker, normal lipid profile). She was confirmed to have an anterior spinal artery infarct and multiple small cerebellar infarcts on MRI and underwent extensive investigations to identify the cause. In view of her acute presentation on a background of negative islet cell autoantibodies at diagnosis and first degree family history of diabetes, a broader screen for mitochondrial and monogenic diabetes was performed. This identified a missense mutation in the HNF1A gene, (Ch12:g.121432011G>A). Of note, her father was mosaic for the mutation with 7% of his cells affected. She was diagnosed with Maturity Onset Diabetes of the Young (MODY) HNF1A, and her diabetes treatment was altered accordingly, enabling her to be switched from MDI insulin to sulphonylureas.

Discussion: Glycaemic control correlates poorly with cardiovascular risk in HNF1A-MODY, instead the increased risk may be related to wider metabolic dysfunction. HNF1A variants have been associated with changes to cholesterol homeostasis, lipid profile and endothelial factor dysfunction. Populations of Black African Heritage have an increased risk of stroke from a younger age, and a recent study identified the HNF1A variant (rd55931441) as a significant stroke-associated locus in this population. This clinical case supports the current evidence that single nucleotide polymorphisms at the HNF1A locus may be implicated in metabolic dysregulation and cerebrovascular injury, particularly in young black patients. Further genomic research is needed in this patient cohort. Aggressive cardiovascular risk reduction and primary prevention from adolescence may be implicated.