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An Adolescent with *HNF1B* Deletion. A Case Report

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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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