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A Renal Cysts and Diabetes (RCAD) Syndrome Associated with a Hepatocyte Nuclear Factor 1β (*HNF1β*) *De Novo* Mutation: A Case Report on the Challenges of the Diagnostic during Childhood

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Abstract

Renal cysts often represent a diagnostic challenge in pediatric age, given the range of disorders they may be associated to. They can be either congenital (due to non-hereditary fetal malformations or genetic mutations) or, more rarely, acquired.

The Hepatocyte Nuclear Factor-1beta (*HNF1β*) gene is known to play an essential role in the embryonic development of several organs (such as kidneys, pancreas, liver and parathyroid glands). Molecular genetics has allowed the identification of new mutations occurring in this gene and *HNF1β*-associated disease is now recognized as a clinical entity of variable and multisystemic phenotype.

We present the case of a male child, referred to a pediatric nephrology unit at age 4, after presenting the first signs of nephropathy. Abdominal ultrasonography had shown cortical renal cysts. The patient had a stage 2 Chronic Kidney Disease (CKD). He later presented an insulin-dependent diabetes, at age 7. The combination of early onset diabetes and renal cystic disease was suggestive of an *HNF1β*-associated condition. Genetic testing of the patient and his parents confirmed a *de novo* nonsense mutation on heterozygosity at *HNF1β* (c.301G>T (p.E101*), exon 1).

Even though a strictly renal phenotype may occur, the association of renal disease and diabetes at a young age should particularly alert nephrologists and pediatricians to the possibility of an *HNF1β*-associated disease. Furthermore, the early detection of this genetic mutation will warrant screening of other potential extrarenal disorders or malformations and allow appropriate genetic counseling to patients and their families.

Keywords: Hepatocyte nuclear factor 1-beta; Cystickidneys; Maturity-onset diabetes of the young; Type 5

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Introduction

Hepatocyte Nuclear Factor-1Beta (*HNF1β*) gene is located on chromosome 17 and encodes a widely spread transcription factor, with a known major role in endodermal development, thus explaining the frequent multiorgan involvement in affected patients [1]. Even though *HNF1β* mutations translate into a large phenotypic spectrum, affected individuals commonly present with isolated renal disease (including hypoplastic glomerulocystic kidney disease, multicystic renal dysplasia, horseshoe kidney, hypoplasia and hydronephrosis), isolated diabetes (maturity-onset diabetes of the young-MODY), or both (namely, the Renal Cysts And Diabetes syndrome, RCAD) [2,3]. Nevertheless, not all patients with an *HNF1β* mutation actually have renal cysts and/or diabetes and other disorders have also been described, such as agenesis of the pancreas, urogenital malformations, hyperparathyroidism, hyperuricemia/gout, cognitive delay, autism spectrum disorders and hepatic disorders [4]. *HNF1β*-associated disease is currently recognized as a

clinical entity of variable and multisystemic phenotype, even though, at the same time, it remains the most common monogenic cause of Congenital Anomalies of the Kidney and the Urinary Tract (CAKUT) [4]. Noteworthy is also the fact that, although the *HNF1β* was initially associated with MODY type 5 diabetes (MODY5) [5], renal involvement is more prevalent than diabetes in *HNF1β* mutation carriers, particularly in pediatric cases [6].

Case Presentation

A 4-year-old male child was initially admitted to the hospital for an acute gastroenteritis, complicated with impairment of renal function. Since the latter persisted after correction of the fluid balance, a renal ultrasound was performed and revealed signs of renal disease (diffuse hyperechogenicity, absence of corticomedullary differentiation), as well as bilateral multiple small (<12 mm) cortical renal cysts (even though both kidneys were normal in size) (Figure 1). The patient was then referred to the pediatric nephrology unit, with the suspicion of Autosomal Recessive Polycystic Kidney Disease (ARPKD).

The patient was not obese, and the physical examination was unremarkable. The systolic and diastolic blood pressure profile remained under the 90th percentile for age, height and gender. The urine sediment examinations were normal. No urinary tract infections were diagnosed during the follow-up period. The renal function remained stable, despite a stage 2 Chronic Kidney Disease (CKD) (with an eGFR around 75 ml/min/1.73 m^2).

Three years later, the patient was again admitted to the hospital, this time for the first clinical presentation of diabetes (without ketoacidosis). He was started on insulin therapy, with good glycemic control. An abdominal CT scan performed at this point confirmed the abovementioned echographic signs and revealed an atrophy of the body and tail of the pancreas. The patient also presented increased levels of parathormone (up to 108 pg/ml). A RCAD syndrome was suspected.

There was no family history of renal disease or diabetes. Parents were non consanguineous. There had been no complications during pregnancy, delivery or the postnatal period. The ulterior ophthalmological, gastroenterological and cardiological evaluations revealed no anomalies. No learning disability had been detected.

In order to confirm the diagnosis of RCAD, genetic testing from peripheral blood leukocytes was carried out by Sanger sequencing of the *HNF1β* gene. The variant c.301G>T (p.E101*), on exon 1, was identified in heterozygosity. Parental segregation study was normal and proper genetic counseling was given to the patient and his family.

Discussion

In our case, although Autosomal Recessive Polycystic Kidney Disease (ARPKD) was a possibility, the kidneys were normal in size, the cysts were numerous and confined to the cortical region. These characteristics, associated with the diabetes later diagnosed, made us suspect another genetic syndrome.

Germline heterozygous mutations in the *HNF1β* occur relatively frequently [7] and can arise *de novo* or be inherited [3] (at least 100 different mutations have been identified) [8]. This autosomal dominant disorder is associated with a wide clinical spectrum [2,3], but it is particularly known for producing the RCAD syndrome [9]. In fact, *HNF1β* mutations were detected in 9% to 24% of adult patients with chronic renal failure of unknown origin [10,11] and

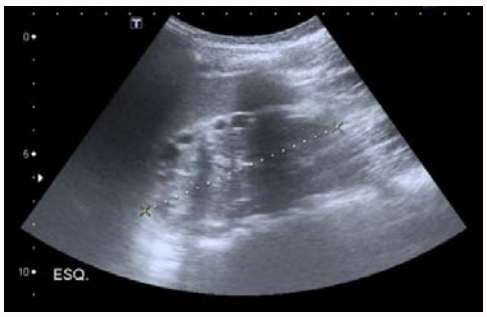

Figure 1: Patient's kidney ultrasound, showing multiple cortical cysts.

the renal function has been found to be impaired in 86% of *HNF1β*-associated disorder cases [12] (with eGFRs widely ranging from 8 ml/min/1.73 m^2 to 113 ml/min/1.73 m^2) [13]. MODY, on the other hand, accounts for 1% to 2% of cases of diabetes and the reported prevalence of diabetes in *HNF1β* mutation carriers (characterized by the fact that the C-peptide is persistently detectable and there are no pancreas autoantibodies) is about 45% (the diagnosis of diabetes occurring after the onset of renal failure in the vast majority of cases) [14]. Other relatively common extrarenal phenotypes include genital tract malformations, gout and disturbed liver function [1,3,15], but there was no evidence of these in our case.

What makes our case unusual and noteworthy is, on one hand, the age at which the renal disease was detected (most cases being diagnosed at the beginning of adulthood) [14] without any previous clinical warning signs and, on the other hand, the fact that neither parent presented any mutation for the *HNF1β* gene (which made his a *de novo* mutation in a case where no particular risk factors were identified). Nevertheless, it is important to note that only a minority of children with *HNF1β* mutations has diabetes and that not all their renal malformations contain evident cysts on ultrasound [13] (even though renal cysts are usually detected in over 80% of cases) [12].

To the best of the authors' knowledge, this is the first report of a RCAD syndrome in a Portuguese child presenting an *HNF1β de novo* mutation. This is an important diagnosis that clinicians should consider when non-diabetic nephropathy, particularly renal cystic disease, is diagnosed in a patient with early-onset diabetes, or *vice-versa*. This case also highlights the point that testing for such mutations should not be discouraged by the absence of a family history of renal disease or diabetes. A timely diagnosis is not only important in preventing avoidable complications, but it will also prompt screening for other medical conditions that it may be associated to (such as hyperparathyroidism or hypomagnesaemia) [3]. In addition, it will allow screening of other family members and genetic counseling about future offspring (among other reasons, because there can be variability in the renal tract manifestations between generations, in the RCAD syndrome). For such reasons, we suggest that this screening is undertaken with pediatricians, nephrologists and clinical geneticists working closely together, in order to better guide the choice of treatment and to inform carriers about how they can avoid exacerbating or complicating factors (such as obesity).

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