6. Seedat F, Patel M, Phillip V, Mohamed F, Marais AD, Blackhurst DM, et al. Hyperlipidemic myeloma, a rare form of acquired dysbetalipoproteinemia, in an HIV seropositive African female. Clin Chim Acta. 2021;520:71–5.

Luis Francisco de Miguel-Rodríguez[a,*], Carla Francés-Artigas[a], María Paz Ribas-García[b], Laura Pérez-Sanchez[c], Carlos Morillas-Ariño[a]

[a] *Endocrinology and Nutrition, Hospital Universitari Doctor Peset, Av. Gaspar Aguilar 90, 46017 Valencia, Spain*
[b] *Haematology, Hospital Universitari Doctor Peset, Av. Gaspar Aguilar 90, 46017 Valencia, Spain*
[c] *Biochemistry Department, Hospital Universitari Doctor Peset, Av. Gaspar Aguilar 90, 46017 Valencia, Spain*

* Corresponding author.
E-mail address: luis.demiguel.rodriguez@gmail.com (L.F. de Miguel-Rodríguez).

Diabetes and jaundice in young patients. The importance of extrapancreatic manifestations in the typing of diabetes mellitus

Diabetes e ictericia en paciente joven. La importancia de las manifestaciones extrapancreáticas en la tipificación de la diabetes mellitus

Diabetes mellitus (DM) is a highly prevalent disease with a wide aetiopathogenesis. Type 2 DM is, by far, the most common cause of diabetes in the world, accounting for 85–95% of cases diagnosed as diabetes.[1] Among other factors, genetic factors resulting from the interaction of several genes play a role in its aetiopathogenesis. However, monogenic diabetes is a clinically heterogeneous disorder characterised by diabetes diagnosed at an early age (<30 years) with autosomal dominant inheritance and negative autoimmunity. The genes involved control the development and function of pancreatic β-cells. Prevalence studies estimate that it represents 1%–5% of all cases of DM[2] with maturity-onset diabetes of the young (MODY) the most common form. Monogenic diabetes is a diagnostic challenge given its heterogeneity and confusion with other subtypes of DM, and it is globally underdiagnosed. Clinical suspicion is essential to indicate a genetic study, and the study of possible extrapancreatic manifestations is important. The genetic study allows us to make a precise diagnosis, initiate personalised treatment and provide genetic advice to family members. Furthermore, jaundice and asymptomatic hyperbilirubinaemia are common clinical problems which can be caused by a wide variety of disorders, including excessive bilirubin production, impaired bilirubin conjugation, biliary obstruction and hepatic inflammation.[3]

We present the case of a 34-year-old male being investigated by Gastroenterology for jaundice, with no relevant history except for a self-limiting episode of hypertransaminasaemia in 2013. He did not have any toxic habits and was not on any long-term treatments. Progressive jaundice of the skin, pruritus and weight loss were notable along with choluria and acholia, with no fever or abdominal pain. Weight 82 kg, height 182 cm, BMI 24.76 kg/m^2. Blood tests showed glucose 151 mg/dL, LDH 248 IU/L (140–180 IU/L), AST 111 IU/l (8–33 IU/L), ALT 309 IU/L (4–36 IU/L), GGT 375 IU/L (6–28 IU/L), alkaline phosphatase 269 IU/L (44–147 IU/L), total bilirubin 14.8 mg/dL (0.1–1.2 mg/dL), direct bilirubin 9.6 mg/dL (<0.3 mg/dL), ferritin, alpha-1-antitrypsin and plasma copper normal, with negative hepatic autoimmunity. Complete blood count and coagulation normal. Abdominal ultrasound including the urinary tract normal. Magnetic resonance cholangiopancreatography showed normal liver and atrophy of the body of pancreas. Liver biopsy with signs of cholestasis without inflammation or fibrosis. Laboratory tests during admission showed fasting hyperglycaemia (154 and 160 mg/dL) diagnostic of DM, with HbA1c 5.5%. Given this discordance, the study was extended to two months with increasing basal blood glucose (224 mg/dL) and HbA1c also increasing (7.1%), C peptide (CP) 2.24 ng/mL (0.81–3.85), autoimmunity with negative antiGAD Ab and anti-IA2 Ab 14.1 U/mL (normal <7.5 U/mL) and low faecal elastase (103, normal >200). Elevated bile acids in the blood (>200, normal <10).

Therapy with insulin glargine was started at a rate of 0.2 IU/kg/day (16 IU) for onset of diabetes and, after having ruled out the most common causes of cholestasis (bile duct obstruction, sclerosing cholangitis, primary biliary cirrhosis), a panel of 75 genes related to cholestasis and associated syndromes was requested. Results showed a partial deletion of the long arm of chromosome 17 (17q12) which was encompassing the HNF1B gene, the gene responsible for MODY-5 diabetes and which could explain the hepatobiliary condition. Treatment was initiated with ursodeoxycholic acid 500 mg every eight hours, pancreatin 25,000 IU, eight tablets daily, and ultra-rapid insulin for corrections. At the eight-month follow-up, treated with 12 IU of basal insulin without requiring ultra-rapid insulin corrections, the HbA1c was 5.9% and CP remained normal (1.79 ng/mL).

In our patient, the development of cholestasis coinciding with the diagnosis of diabetes is an uncommon manifestation, with very few cases described in the literature,[4] but which must be taken into consideration in order for correct typing. For this reason, we have included in the differential diagnosis genetic cholestasis associated with DM (Fig. 1), such as benign recurrent intrahepatic cholestasis type 1, although none of the genes involved were mutated in our patient. As in this case, the aetiopathogenesis of diabetes may not be evident at onset. The presence of positive anti-IA2 Abs points to an autoimmune origin, the genetic study to a monogenic aetiology and pancreatic atrophy with exocrine pancreatic insufficiency (EPI) and the recent onset

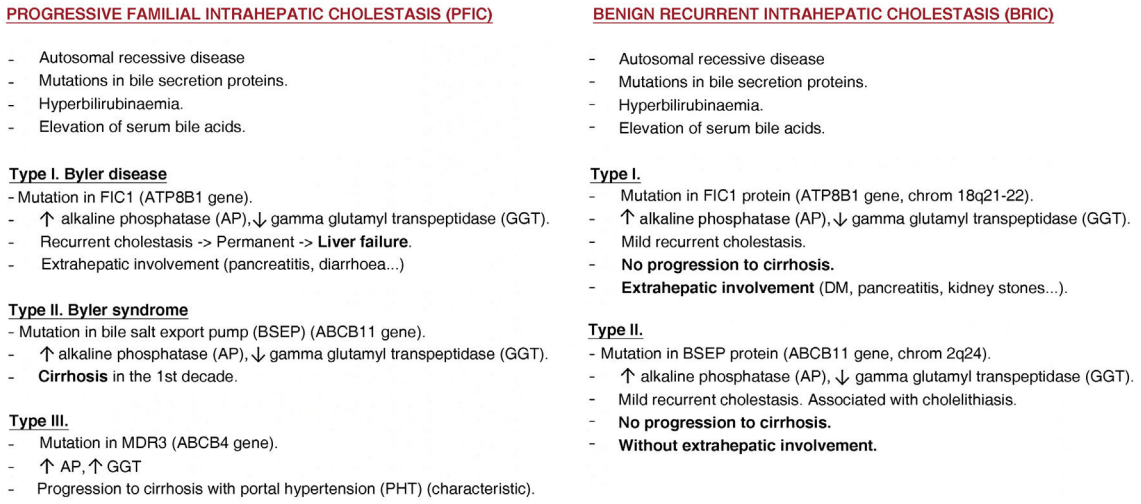

Figure 1 Cholestatic disease of genetic origin: differential diagnosis.
Source: modified from Jansen et al.[6]

of diabetes to diabetes of the exocrine pancreas. The identification of the predominant pathogenic mechanism will be marked by the clinical-analytical progress of the patient over time and will guide therapeutic management. In this case we decided to maintain the insulin treatment on a basal regimen given the good metabolic control obtained, the recent onset of diabetes, the patient's good adaptation to the therapy and considering the uncertain outcome given the multiple aetiopathogenesis.

The mutation of the HNF1B gene located on chromosome 17 is associated with MODY-5 diabetes. The deletion of 17q12, which encompasses the HNF1B gene, causes a phenotype called renal cysts and diabetes (RCAD) syndrome, characterised by a congenital abnormality in renal development which can manifest from the prenatal period with large and hyperechoic kidneys, associated with chronic tubulointerstitial nephritis, which manifests with slowly progressive renal failure with non-pathological urinary sediment. However, our patient did not have renal manifestations. This syndrome can also involve renal cystic dysplasia, pancreatic atrophy with EPI, MODY-5 type DM, neurodevelopmental disorders (particularly speech) and autism spectrum disorders, genitourinary and biliary tree malformations causing cholestasis, Müller aplasia in women, macrocephaly, mild dysmorphic facial features (high forehead, sunken eyes and full cheeks) and transient hypercalcaemia.[5]

Our aim with this case was to highlight the importance of making a broad differential diagnosis of diabetes based on the patient's characteristics. The possible associated extrapancreatic manifestations should increase our suspicion of monogenic diabetes.

References

1. Federación Internacional de la Diabetes. Atlas de la Diabetes. Octava edición. Update 2017. [Accessed January 2018]. Available in: http://www.diabetesatlas.org/resources/2017-atlas.html.
2. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med [Internet]. 2001;345(13):971–80.
3. García-Romero R, Morlan-Herrador L, Ros-Arnal I, Miramar MD, Molera-Busons C. Intrahepatic cholestasis, sometimes benign recurrent. Gastroenterol Hepatol. 2021;44(10):719–20, http://dx.doi.org/10.1016/j.gastre.2021.10.001.
4. Kettunen JLT, Parviainen H, Miettinen PJ, Färkkilä M, Tamminen M, Salonen P, et al. Biliary anomalies in patients with HNF1B diabetes. J Clin Endocrinol Metab [Internet]. 2017;102(6):2075–82.
5. Roehlen N, Hilger H, Stock F, Gläser B, Guhl J, Schmitt-Graeff A, et al. 17q12 deletion syndrome as a rare cause for diabetes mellitus type MODY5. J Clin Endocrinol Metab. 2018;103(10):3601–10.
6. Jansen PL, Müller M. The molecular genetics of familial intrahepatic cholestasis. Gut. 2000;47:1–5, http://dx.doi.org/10.1136/gut.47.1.

Víctor José Simón Frapolli*, Miguel Damas Fuentes, María José Picón César, Andrea Fernández Valero, Francisco José Tinahones Madueño

Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen de la Victoria, Málaga, Spain

* Corresponding author.
E-mail address: victorsimonfrapolli.med@gmail.com (V.J. Simón Frapolli).