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Brief Clinical Observation

Clinical expression of co-inherited Dubin–Johnson and thalassaemic heterozygous states

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Abstract

Dubin–Johnson syndrome is a worldwide prevalent familial conjugated hyperbilirubinaemia. The identification of multidrug resistance-associated protein 2 provided an understanding of the complex metabolic impairment involved in this syndrome. We report the first family with modified clinical expression of Dubin–Johnson heterozygous state due to genotypic interaction with co-inherited β and δβ thalassaemia, an interaction that has never been described.

Keywords: Bilirubin; Dubin–Johnson syndrome; Familial hyperbilirubinaemia; MRP2 gene

1. Introduction

A genetic syndrome, consisting of benign, chronic, often intermittent predominantly conjugated, mild hyperbilirubinaemia and characterized by the deposition of a dark pigment within the otherwise functional normal liver cells, has been ascribed to Dubin and Johnson (DJS; OMIM No. 237500) [1]. The DJS, inherited in an autosomal recessive manner with reduced penetrance, is often an occult entity until various factors and situations accentuate hyperbilirubinaemia, resulting in clinically apparent disease [2]. Obligate heterozygotes of the underlined genetic defect do exhibit subtle manifestations rendering some indices to vary from normal to grossly deviated values [3].

We herein present a family in which the expression of DJS heterozygous state was influenced, on clinical and functional grounds, by co-inherited heterozygous β and δβ thalassaemia, an interaction that has never been described.

2. Case report and family study

A three-year and three-month old male of Greek descent was first seen at the outpatient clinic because, since the age of 2 years, he had been intermittently passing coloured urine, attributed to bilirubinuria.

Upon admission to the hospital, physical examination revealed icteric sclerae, hard palate, pale skin and moderate hepatosplenomegaly. Body measurements (weight 18 kg, height 107 cm) were at the 97th percentiles for age.

The patient was the first child of non-consanguineous parents; his sibling is an apparently healthy 3-month-old girl. He was born at term after an uncomplicated pregnancy by normal delivery with body measurements in the 50th percentile. Jaundice, first appeared on the 3rd day of life with total bilirubin reaching maximum concentration of 12.5 mg/dL (213.75 μmol/L), was considered as transient neonatal bilirubinaemia. On day 30, sclerae were still obviously icteric with a serum total bilirubin level of 6.2 mg/dL (106.02 μmol/L) with a conjugated fraction of 4.6 mg/dL (78.66 μmol/L) which was incautiously attributed to breast feeding, and no further investigation was attempted (Fig. 1).

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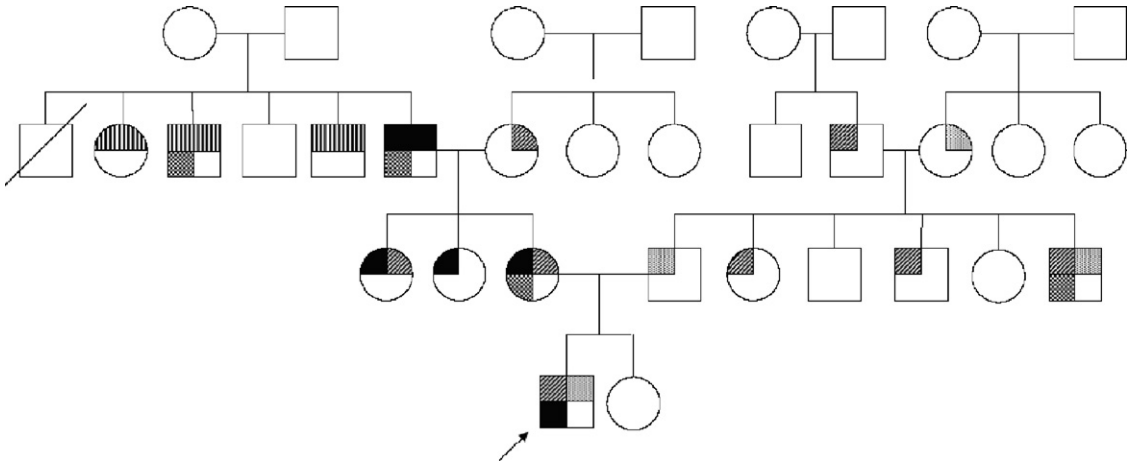

Fig. 1. A pedigree of a Greek family with homozygous DJS in the paternal grandfather (generation II) and heterozygous DJS in his three daughters and his grandson—proband (two consecutive generations, III and IV) along with coexistence of thalassaemia in both sides of the family. (■) DJS homozygous; (◴ and ◪) DJS heterozygous; (▥ and ✋) reported jaundiced; (▨) β/δβ thalassaemia; (◪ and ◔) β thalassaemia heterozygous; (◧ and ◔) δβ thalassaemia heterozygous; (◪ and ◔) choledocholithiasis.

The mother has also had intermittently scleral jaundice since childhood (Fig. 1). At the age of 20, she was investigated due to recurrent episodes of abdominal pain. Her total and fractionated bilirubin as well as haemoglobin electrophoresis pattern at that time are shown in Table 1. Liver function tests were all within normal limits, whereas sonography revealed choledocholithiasis. A liver biopsy specimen, taken during the cholocystectomy, was interpreted as normal without pigmented cells under light microscopy. During pregnancy, her jaundice exacerbated and bilirubin reached the value of 4 mg/dL (68.4 μmol/L) with a conjugated fraction of 3.4 mg/dL (58.14 μmol/L). Icteric sclerae were also evident on her re-examination during the hospitalization of the proband. Bilirubin measured at that time was 2.2 mg/dL (37.62 μmol/L) with a direct fraction of 1.6 mg/dL (27.36 μmol/L).

Maternal grandfather has been known to have "yellow eyes" since adolescence (Fig. 1). Because of being otherwise healthy, no diagnostic investigation has ever been attempted. At the age of 55, following an episode of colic upper abdominal pain, he was admitted to hospital for further investigation. The serum bilirubin values and haemoglobin fraction along with relevant measurements observed in the maternal grandmother are shown in Table 1. Ultrasound examination revealed gallbladder sludge mixed with stones without dilatation of the biliary tree. During cholocystectomy, the liver was moderately dark in appearance. A wedge biopsy specimen examined under light microscopy showed no evidence of cholestasis. The liver cells were laden with coarse, pigment granules with centrilobular distribution characteristic of DJS.

Clinical examination of two older sisters of the patient's mother, both considered as obligate DJS heterozygotes, revealed icteric slcerae in association with β thalassaemia trait in one of them. Interestingly, in the other one, without co-inheritance of β thalassaemia, total bilirubin measurement was within normal range (Fig. 1, Table 1).

The patient's father has never experienced bouts of jaundice or abdominal pain (Fig. 1). His total bilirubin value was all unconjugated within the normal range. Blood film showed microcytosis and haemoglobin electrophoresis revealed a heterozygous pattern of δβ thalassaemia. His younger brother, aged 25, was diagnosed as having β/δβ

Table 1
Bilirubin fractions and haemoglobin electrophoresis pattern

Family members	Bilirubin (mg/dL)			Haemoglobin fractions (%)	
	Total[a]	Conjugated	Unconjugated	A2	*F*
Grandfather	1.8	1.4	0.4	2.4	<1
Grandmother	0.8	0.2	0.6	5.12	1
Mother	2.6	1.8	0.8	5.4	0.8
First sister	3.8	3.1	0.7	4.8	<1
Second sister	0.6	0.2	0.4	2.8	<1
Father	0.8	0.0	0.8	1.6	4.2
Brother	3.5	0.5	3.0	1.4	94
Proband	2.4	1.9	0.5	1.8	71.4

[a] Normal values <1 mg/dL (17.1 μmol/L).