Clin Genet 1993: 43: 315–317
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CLINICAL GENETICS
ISSN 0009-9163

Inheritance of intrahepatic cholestasis of pregnancy in one kindred

Hirvioja M-L, Kivinen S. Inheritance of intrahepatic cholestasis of pregnancy in one kindred
Clin Genet 1993: 43: 315–317. © Munksgaard, 1993

We report three sisters with intrahepatic cholestasis of pregnancy (ICP) and the pedigree of the family, including six generations. ICP was observed in five successive generations; most of the patients also had cholelithiasis. The uniform expression, the complete penetrance of the trait and the direct parent-to-child transmission support the Mendelian dominant mode of inheritance. Determination of HLA A, B and C haplotype was made in five ICP patients, without any findings of HLA type common to everyone. X-linked inheritance cannot be excluded in this study.

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Key words: cholestasis – intrahepatic – pregnancy, complications.

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Received 23 June 1992, revised version received 15 February, accepted for publication 18 February 1993

Intrahepatic cholestasis of pregnancy (ICP) is an abnormality in hepatic reactivity to higher circulating estrogens during pregnancy (Schreiber & Simon 1983). The pathogenesis of ICP is still unknown, but genetic factors may play a role (Reyes et al. 1976, Holzbach et al. 1983). We report three sisters with ICP, with special reference to HLA A, B and C haplotypes, and we give information about the pedigree.

Case report

Case I

The eldest sister, a 30-year-old gravida II, para 0, was admitted to the maternity clinic at 12 weeks' gestation with a short history of itching. Liver function findings were still within normal limits, but 2 weeks later serum alanine aminotransferase (ALAT) was slightly elevated, 70 U/l. At 27 weeks she was referred to hospital because of itching and elevated serum transaminases (ALAT 274 U/l, ASAT 102 U/l, AFOS 219 U/l). The serum total bile acid concentration (BA) peaked at 57.2 μmol/l, and ALAT maximum was 310 U/l. She was treated with cholestyramine 4 g three times a day and phenobarbital 100 mg daily.

The delivery was induced at 36 weeks, but suspicion of amnionitis resulted in caesarean section. A 3015-g girl was delivered with an Apgar score of 8. Itching disappeared on the third post-operative day, when BA was 9.4 μmol/l, ALAT 103 U/l, ASAT 44 U/l and AFOS 564 U/l. Eight months later, ultrasound examination of the gallbladder was normal and basal BA 3.9 μmol/l, although she had previously had biliary colic.

Case II

The second sister, a 25-year-old gravida I, para 0, was admitted due to itching at 16 weeks' gestation. She had previously suffered from liver disorders while taking an oral contraceptive. She had also suffered from biliary colic before pregnancy.

Liver transaminase concentrations were elevated at 28 weeks (ALAT 349 U/l, ASAT 153 U/l), but the BA concentration increased only slightly, 10.7 μmol/l. The patient was treated with combined administration of 100 mg of phenobarbital and 12 g of cholestyramine daily. In spite of the therapy, the BA concentration increased to 43.9 μmol/l and ALAT to 620 U/l at 33 weeks. At 38 weeks BA was 41.1 μmol/l and ALAT 460 U/l. She gave birth to a female infant weighing 3370 g with an Apgar score of 9. An ultrasound examination of

the gallbladder of the patient showed cholelithiasis 6 months after delivery, and basal BA was 0.7 μmol/l.

Case III

The youngest sister, a 24-year-old gravida II, para I was admitted due to itching at 19 weeks of gestation. During her first pregnancy 3 years earlier she had suffered from itching of palms and soles, and the transaminases were elevated.

During this present pregnancy transaminases were elevated at 28 weeks, ALAT 183 U/l, ASAT 92 U/l and BA 11.9 μmol/l. She was treated with a combination of phenobarbital and cholestyramine. The highest BA, 40 μmol/l, was observed at 35 weeks of pregnancy. The delivery was induced at 38 weeks, and she gave birth to a male infant weighing 3260 g, with an Apgar score of 8. The patient was still suffering from itching on the fourth post-partum day, when BA was 30 μmol/l. Four weeks later BA was 6.6 μmol/l and transaminases had also normalized.

The patient had typical biliary colic once during pregnancy. Ultrasound examination of the gallbladder revealed probable cholesterolosis, a "strawberry gallbladder", but cholelithiasis could not be diagnosed.

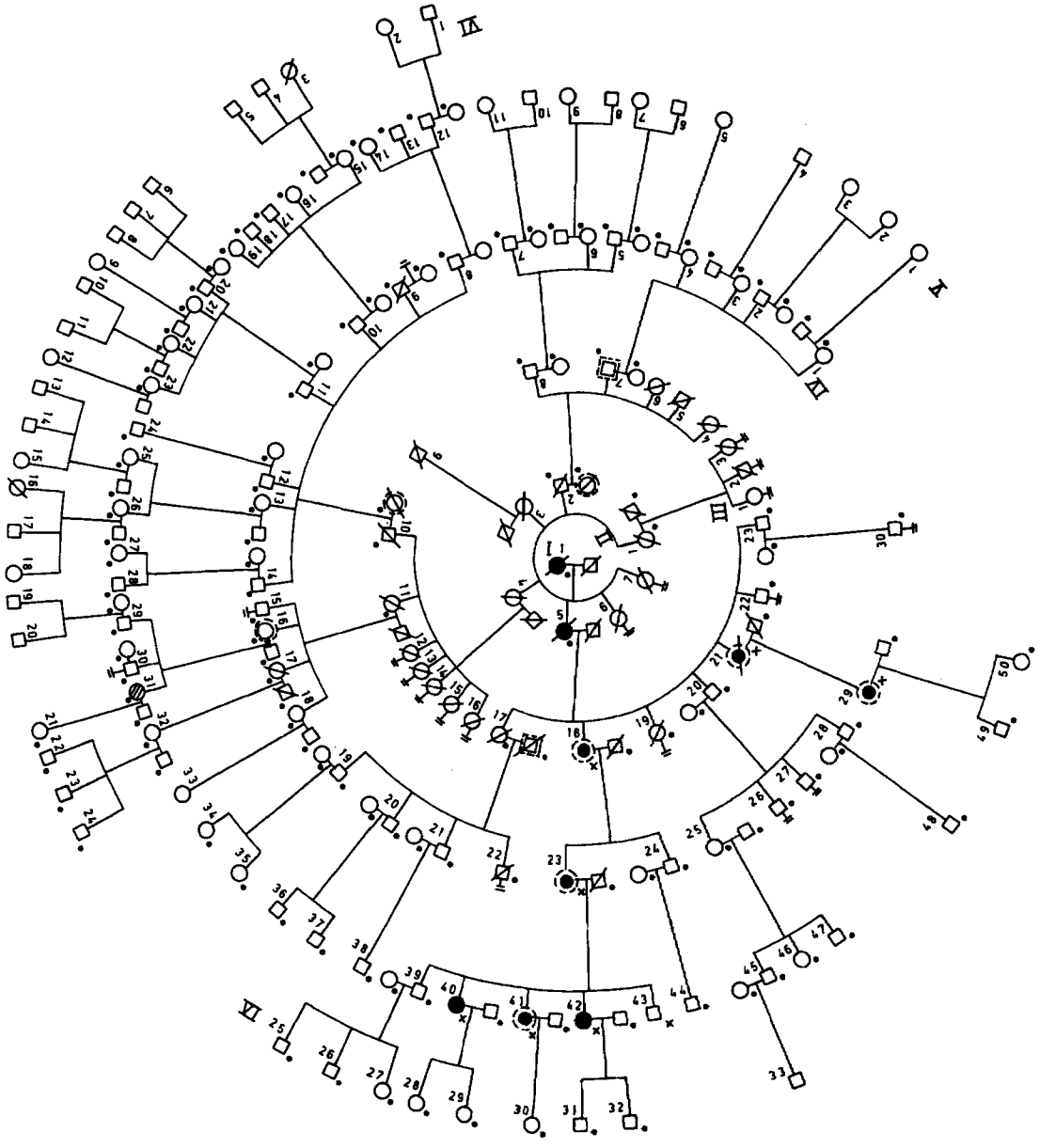

Fig. 1. Inheritance of ICP and cholelithiasis in the reported kindred.
●=ICP, ◌=cholelithiasis, ◍=status post hepatitis, ⊥=no children, •=anamnestic knowledge, ×=examined.

Table 1. HLA A, B and C haplotypes in five ICP patients in the reported kindred

Case no.*	Generation	Haplotype A	B	C
–	III 18	1,3	8,35,w6	w4
–	IV 23	3,28	12(44),35,w4	–
I	V 40	9,28	12(44),15(w62)w4,w6	w3
II	V 41	3,9	15(w62),35,w6	w4
III	V 42	9,28	12(44),15(w62)w4,w6	w3

* see Fig. 1.

Results

Obstetric cholestasis (ICP) was observed in five successive generations in the reported family (Fig. 1). Early onset of itching, before 20 weeks of gestation, was typical of these three sisters as well as their mother and grandmother. All deliveries of both mother and grandmother were pre-term, but there were no miscarriages, stillbirths or disabled children in the kindred. In each case ICP complicated every pregnancy and also occurred while one patient was taking oral contraceptives (Case II).

Cholelithiasis has been diagnosed in most patients with recurrent ICP (III-18, III-21, IV-23, IV-29, V-41, Fig. 1), and apart from V-41 they have undergone cholecystectomy. One of these three sister (V-42, Fig. 1) had a possible "strawberry gallbladder", which is associated with a high cholesterol concentration of bile. Only one male in the reported kindred had cholelithiasis, and none of the males had other hepatic diseases.

Determination of HLA A, B and C haplotype was made in five of the ICP patients (Table 1).

Discussion

It was known previously that ICP is often familial. Also, ethnic differences in its incidence support the role of genetic factors in the pathogenesis of ICP. In our hospital the incidence is 1.35%, while in Scandinavia it is 0.5–1.8% (Heikkinen 1982, Berg et al. 1986), in Chile 12–22% (Reyes et al. 1978), and in Canada and Western Europe 0.1–0.2% (Vore 1987).

Two large kindreds have previously been described (Reyes et al. 1976 and Holzbach et al. 1983), in which the uniform expression, the complete penetrance of the trait and the direct parent-to-child transmission support the inheritance mode of Mendelian dominant type, either autosomal or X-linked.

Reyes reported an unusually high incidence of cholelithiasis in an ICP kindred (Reyes et al. 1976). Our findings are analogous, and the condition seems to be associated with a high cholesterol concentration of bile.

Holzbach (Holzbach et al. 1983) found that six out of seven ICP patients among the same kindred had HLA type Aw31B8. One member of the same kindred had HLA haplotype Aw31B8 without ICP. In this study we found no HLA type common to all subjects, and none had the haplotype Aw31B8. This does not support the possibility of the trait being connected with chromosome 6. We did not find any case of father-to-son transmission of the gene, either in the reported kindred or in the literature (Reyes et al. 1976, Reyes et al. 1982, Holzbach et al. 1983), which would exclude X-linked inheritance. DNA-analysis may be useful to study the possible connections between ICP and X-chromosome.

Acknowledgements

We are most grateful to Prof. Albert de la Chapelle for his encouragement and help in working out the family tree, and to the members of the family, who have been very cooperative in helping us to carry out this investigation.

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