Ped GI Interhospital Conference 1/2025

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History

- ผู้ป่วยทารกเพศชาย อายุ 3 เดือน ภูมิลำเนา จ กาฬสินธุ์

CC : 3 เดือน PTA หลังคลอดได้ 15 วัน มีปัญหาถ่ายอุจจาระสีซีด ตาเหลือง ตัวเหลือง ไปรพ.ใน กทม.

LFT : TB 16.6, DB 5.5 ,AST 34, ALT 9,ALP 399,Alb 3.9,

GGT 411, PT 11.6, PTT 33.1, INR 0.99 sec

- TORCH titer, RPR : negative
- US abdomen (age 2 weeks) : not well visualized GB, BA can't be excluded

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History

- DISIDA scan : only small amount of bowel activity
- IOC (1.5 mo): no macronodular seen, soft to firm consistency, patent extra hepatic bile duct

Liver biopsy : moderate intracellular with focal canalicular lobular cholestasis,patchy hepatocyte swelling, mild portal tract edema with ductular proliferation in some portal tracts

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History

- Past history : underlying preterm 31 wk AGA ,BW 1,805 gm
  Apgar 8, 9, 9 แรกคลอดมีปัญหา TTNB
- Nutrition : กินนมแม่ถึงอายุ 2 เดือน ปัจจุบันกินนมผสม 10
  onz/day
- Development : normal
- Vaccine : ครบ

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Physical examination

- GA : a male infant ,jaundice, active
- Vital signs : BT 36.6 C,PR 134/min ,RR 34/min, BP 87/46 mmHg ,BW 2.3 kg

HEENT : mild pale conjunctiva, icteric sclerae,normal head contour, no cleft lips or cleft palate

Lungs: pectus excavatum, clear and equal breath sound

Heart: split S2 and loud P2, no murmur

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Physical examination

- Abdomen : distended abdomen,soft ,no guarding, liver and spleen can not be palpated .active bowel sound
- Extremity : no edema ,no xanthoma, no petechiae
- Neuro exam : grossly intact

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Initial investigations

- CBC: Hb 8.8 g/dL , Hct 27.5% ,wbc 12700 cumm.,N 14.2, L64.2, mo 8.9,Eo 12.5,B 0.2%, plt 456,000 cumm. MCV 66.4 fL, MCH 21.3 pg, MCHC 32 g/dL
- LFT : TP 5.0,Alb 4.0,glo 1.0,TB 15,DB 13.3 g/dL , ALP 689, AST 59,ALT 37 U/L, PT 14.5 , PTT 33.9 sec ,INR 1.26
- GGT 283.3 U/L
- Electrolyte : Na 131,K 4.79 ,Cl 98, Co2 23.5 mmol/L

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Problems

- **Infantile cholestasis**

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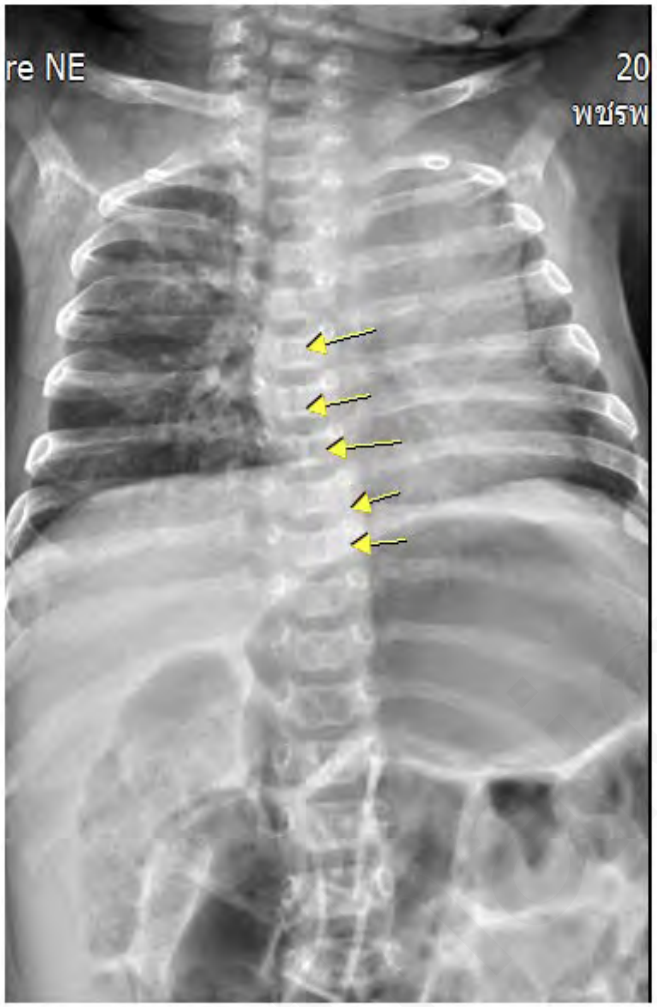

Film TL spine

Possible unfusion at mid vertebral bodies at T5-T10 levels are noted, Butterfly vertebrae are in DDX

Echocardiography (4/10/64)

- Mild LAE, LVE
- Good LV systolic function

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U/S upper abdomen (29/9/64)

- Normal size of liver with smooth surface
- Normal echogenicity and no space taking lesion
- No dilatation of IHDs or CBDs
- Gall bladder can not identify

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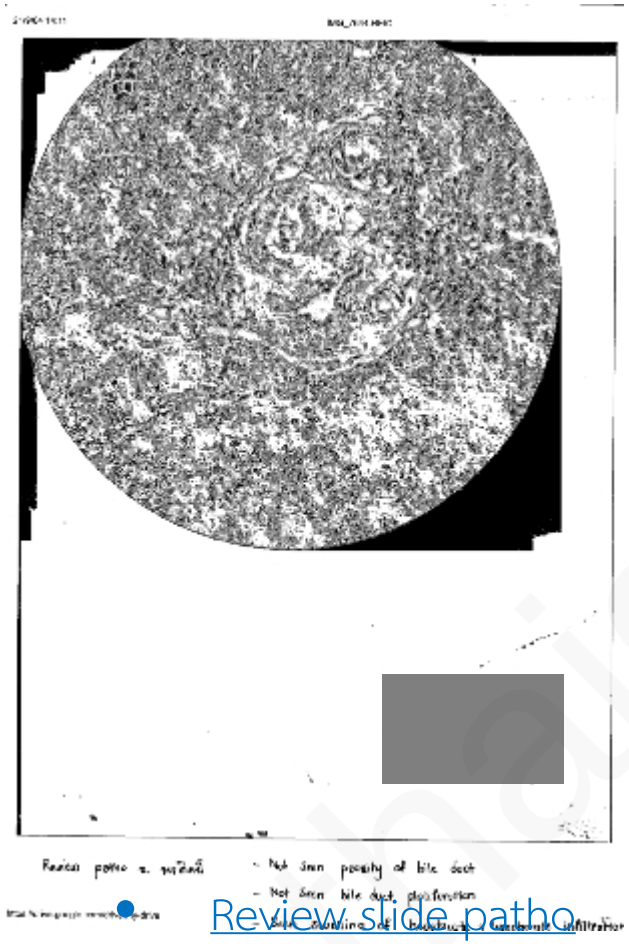
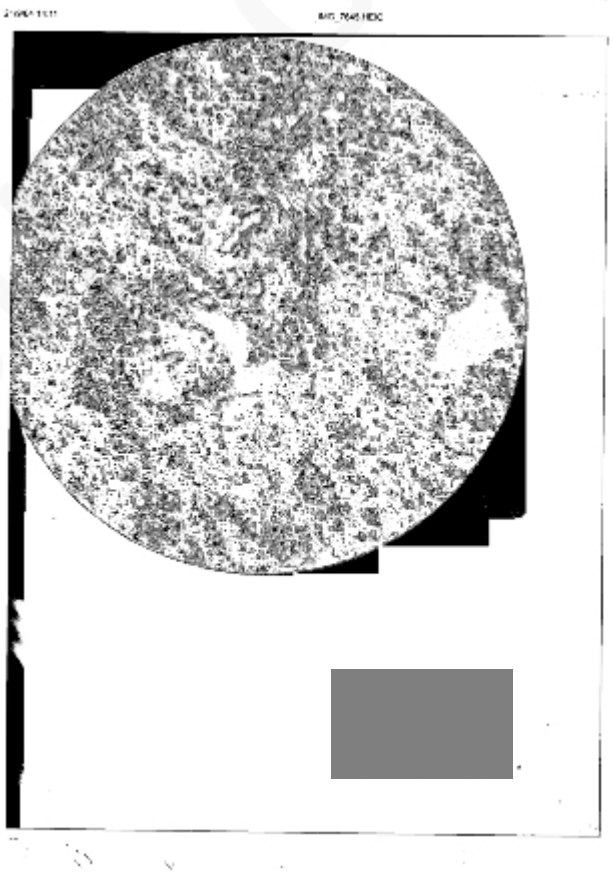
Liver pathology (review)



- Review slide patho

- Not seen paucity of bile duct
- Not seen bile duct proliferation



- **No black pigment in hepatocyte**

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Liver histopatho (Bkk)

DIAGNOSIS : Liver, biopsy:
- Moderate intracellular and focal canalicular lobular cholestasis.
- Patchy hepatocyte swelling, moderate degree.
- Patchy extramedullary erythropoiesis.
- Mild portal tract edema with ductular proliferation in some portal tracts.

COMMENT:
- The histological findings are suspicious for early obstructive cholestasis. Please correlate with clinical and laboratory findings.
- Iron stain, PASD stain and Masson trichrome stain are recommended for excluding hemochromatosis, alpha1-antitrypsin (AAT) deficiency and evaluating degree of fibrosis.

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Hospital course and follow up

- ช่วงที่เหลืองมาก ให้ UDCA & fat soluble vitamin

- ไม่ค่อยมีคันตามตัว ไม่ค่อยนึกถึง Allagille syndrome มีแค่ T-L spine ที่อาจจะเข้าได้ ไม่มี xanthoma
- อายุ 8-11 เดือน เหลืองลดลงเอง อุจจาระสีเหลือง กินนมได้ นน. ขึ้นดี BW 7kg
- ส่ง WGS โครงการ genomic Thailand
- หลังจากนั้นผู้ป่วยได้ loss FU ไป ติดตามไม่ได้
- ผล WGS ออกหลังจากนั้น 1 ปี (DJS) ติดตามอีกหลายครั้ง ติดต่อไม่ได้

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รพ	Date	TP	alb	glo	TB	DB	ALP	AST	ALT	PT	INR
กทม.	24/6	4.9	3.9	1	16.6	7.5	399	34	9		
กทม.	30/6	4.5	3.6		18.8	10.1	473	31	10		
กทม.	20/7	5.2	3.8	1.4	17	12.5	566	35	13	12.4	1.04
ขก.	20/9	5	4	1	15.9	13.3	689	59	37	14.5	1.26
ขก.	24/9				15.6	13.3		54	29		
ขก.	2/10	5.4	4.1	1.3	17.2	14.4	601	62	30	15.1	1.34
ขก.	28/10	5.9	4.2	1.7	11.9	10.7	602	83	53	13.9	1.21
ขก.	23/12	6.2	4.2	2.0	13.6	11.7	737	102	89	13.4	1.16

มีคันตามตัว มีผื่น PE : no xanthoma , Px. ยา UDCA,fat&water soluble vit.

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Clinical course and follow up

รพ	Date	TP	alb	glo	TB	DB	ALP	AST	ALT	PT	INR
ขก.	2/2 8 mo	5.9	4.2	1.7	3.29	2.91	371	100	121	-	-
ขก.	26/5 (11 mo)	6.5	4.3	2.3	1.4	1.02	241	41	34	-	-

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Whole genome sequencing

- Homozygous C. 2201T C (p.Leu 734 Pro) (VUS) in ABCC2

- Diagnosis : Dubin – Johnson syndrome

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Dubin-Johnson Syndrome(DJS)

- A rare autosomal recessive liver disorder,inheritance of mutations in the ABCC2 gene
- First report in 1954,most in Iranian Jews 1:1,300
- Chronic, benign, intermittent jaundice, conjugated hyperbilirubinemia
- Conjugated hyperbilirubinemia
- Impaired hepatic transport of conjugated bilirubin into bile

Yanmin Zhang et al,Medicine2024

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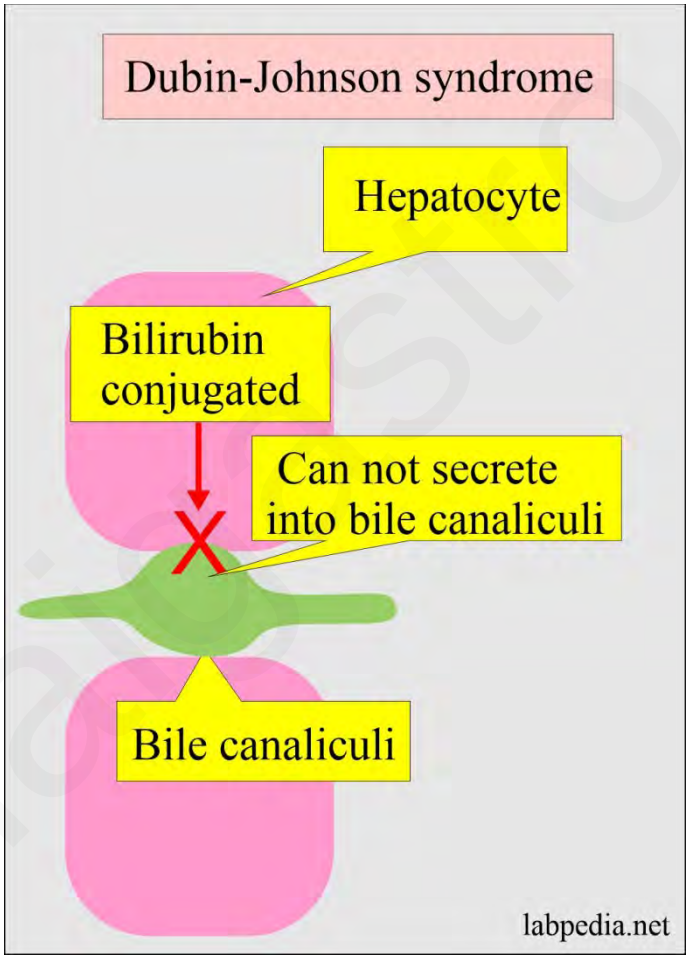
Dubin-Johnson Syndrome(DJS)



Yanmin Zhang et al,Medicine2024

Dubin-Johnson Syndrome(DJS)

- Most patients manifest as intermittent or chronic jaundice aggravated by intercurrent illness
- PE is frequently unremarkable
- Liver enzyme usually WNL,while bilirubin levels fluctuate
- Expression defects of the MRP2 gene,an ATP-dependent canalicular membrane transporter
- The diagnosis by performing the bromsulphalein,oral cholecystography,HIDA scan ,and liver biopsy

Yanmin Zhang et al,Medicine2024

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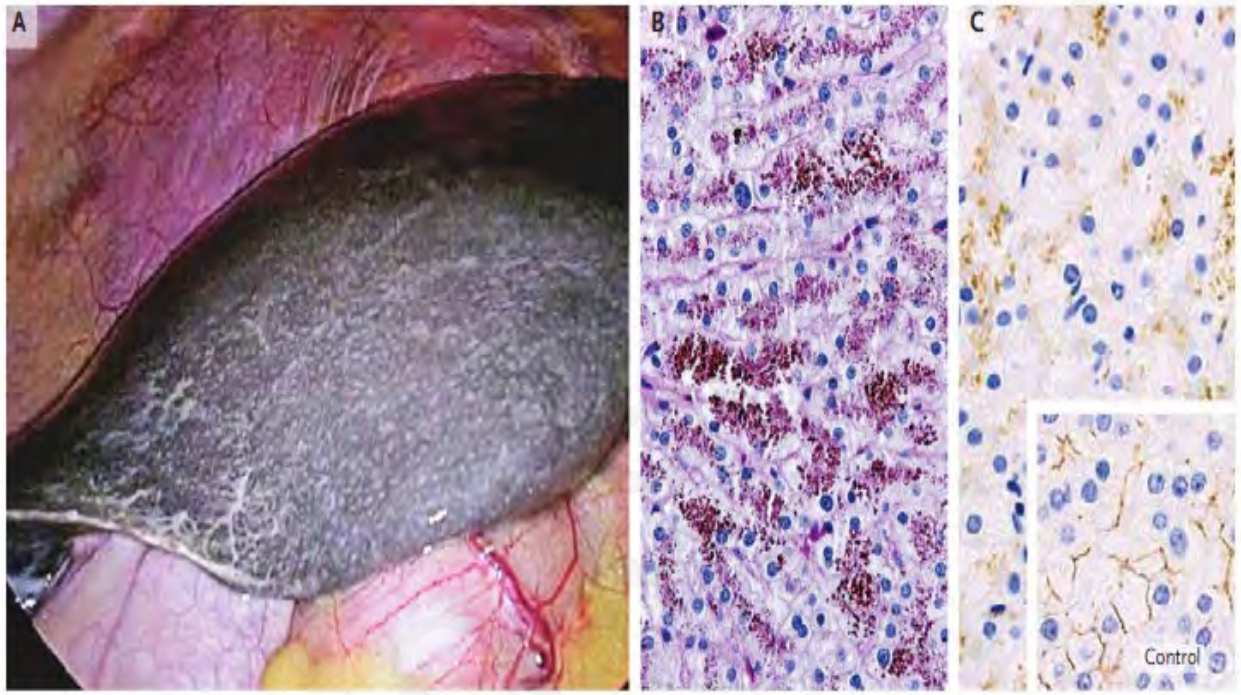
Dubin-Johnson Syndrome(DJS)



Liver biopsy : grossly black appearance and coarse ,deep brown, pigmented granules in the centrilobular hepatocytes “ gold standard”

Dubin-Johnson Syndrome(DJS)

- Molecular genetic testing of the ABBC2 gene is the definitive diagnosis

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DJS Presenting With Infantile Cholestasis: An Overlooked Diagnosis in an Extended Family

- A 14-year –old female child born to consanguineous Saudi first-degree cousins
- Pesistent hyperbilirubinemia at 4 days with normal AST ,ALT
- Unresolved jaundice at 40 days and mild abdominal distension with no organ enlargement
- Mild direct hyperbilirubinemia (TB 5,DB3.5),normal GGT,coagulogram and US
- CBC,reti ,Coombs,hemoglobin electrophoresis,urine and blood culture,TORCH screening,serum bile acids,TFT,metabolic screening, non-glucose-reducing substance in urine, were normal

Kamal NM et al,Frontiers in Pediatrics,2022

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DJS Presenting With Infantile Cholestasis: An Overlooked Diagnosis in an Extended Family

- HIDA scan and MRCP not available
- Liver biopsy was refused by the parents,and againt medical advice (TB 4.8/DB 4)
- At age of 14 years,parents used to visit different health care facilities when their child's jaundice deepened with intercurrent illness
- PE : tinge jaundice,normal VS,no organomegaly
- LFT: TB 3.2,DB 3.1 with normal in other parameters

Kamal NM et al,Frontiers in Pediatrics,2022

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DJS Presenting With Infantile Cholestasis: An Overlooked Diagnosis in an Extended Family

- HIDA scan reveals impairment of excretory function in absence of obstruction
- Urine coproporphyrins were not done (not available in hospital)
- The diagnosis was confirmed genetically with c.2273G > T, p.G758V mutation in exon 18 of the ABCC2 gene.
- The 2nd patient is a 7-day-old baby, the son of the 1st patient who gave birth to him at the age of 21 years old.
- He was diagnosed with DJS at the age of 2 weeks based on normal clinical and laboratory workup apart from direct hyperbilirubinemia.
- He had the same mutation as his mother in homozygous status. The husband was heterozygous for the same mutation.

Kamal NM et al,Frontiers in Pediatrics,2022

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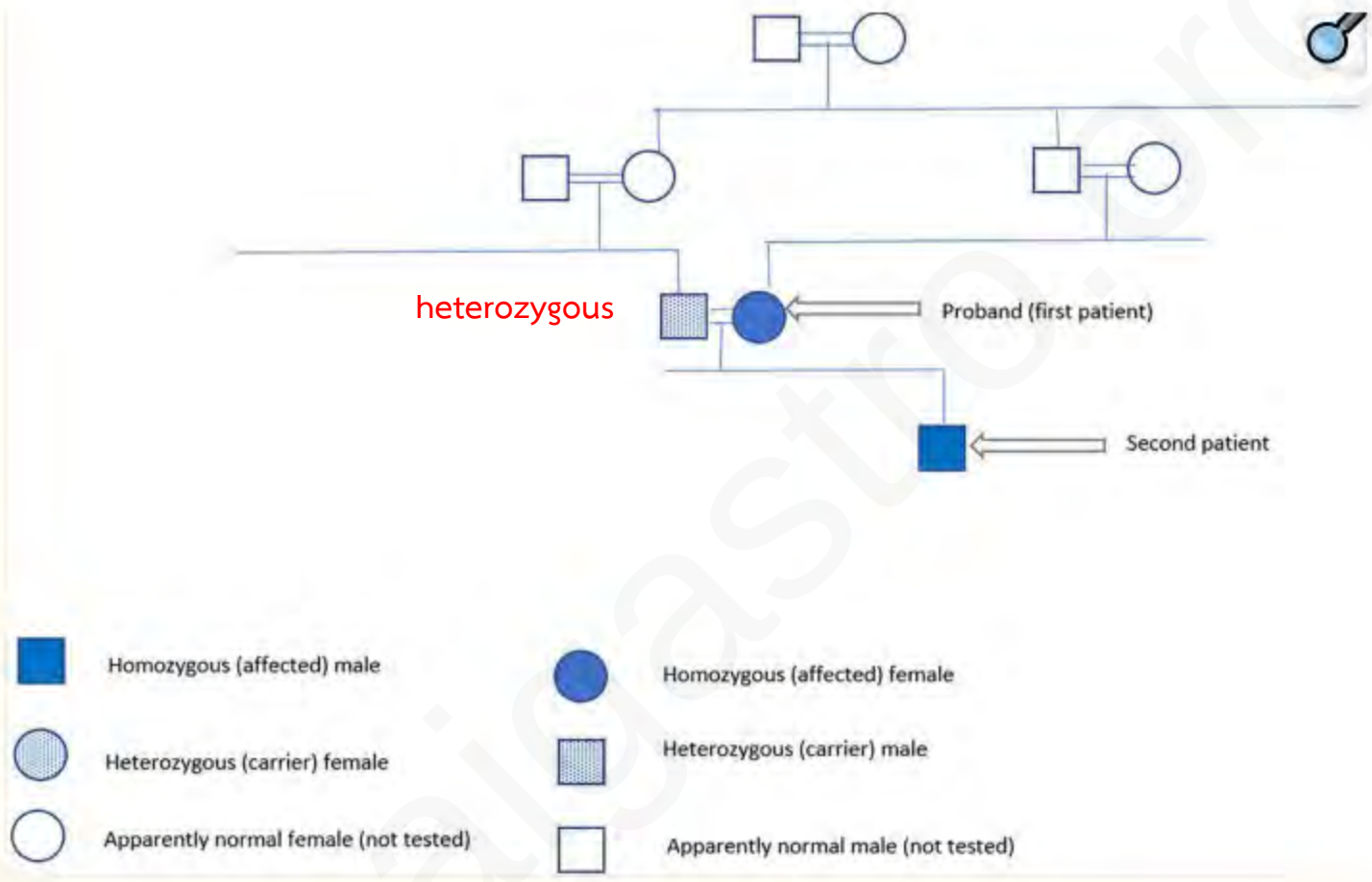

Family Pedigree

DJS : conclusions

- DJS is very rare and is one of the often-missed differential diagnoses of neonatal cholestasis.

- It should be suspected in patients of infantile cholestasis, who have an, otherwise, normal physical examination, and laboratory investigations to avoid unnecessary lengthy, invasive, and expensive workups.

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Thank You for Your Attention

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