National Metabolic Biochemistry Network Best Practice Guidelines
Neonatal & Infant Jaundice in Inherited Metabolic Disorders

Introduction

Jaundice is the most common clinical sign in the neonate, arising from either overproduction or undersecretion of bilirubin. There are many causes, but only a small proportion will be the result of an inherited metabolic defect. These guidelines are limited to the investigation of these metabolic causes only and provide guidance for the local laboratory and clinical teams managing patient care. However, non–metabolic causes have been briefly described below so that they can be put in context and appropriately considered in any differential diagnosis of a jaundiced neonate and infant. This guideline provides more detailed information regarding specific laboratory investigations and the supporting clinical findings relating to investigation of inherited metabolic disorders than contained in NICE Clinical Guideline 98 Neonatal Jaundice (2010).

When should neonatal and infant jaundice be investigated?

The pattern of appearance of the jaundice may help in deciding when to investigate. It is important to note that two thirds of healthy term infants and almost all premature infants, develop jaundice in the first week of life due to the immaturity of bilirubin conjugation in the liver. Typically these infants will not develop jaundice in the first 24 hours and the increase in total plasma bilirubin will be less than 85 µmol/day. Monitoring of the plasma total bilirubin may be the only investigation required. Jaundice appearing within three days of birth is most likely to be due to haemolytic causes. Jaundice which persists after 10 – 14 days should be investigated, including consideration of inherited metabolic defects.

- Early Onset Jaundice

Haemolytic causes of neonatal jaundice tend to be associated with an early (within the first 24hr) and more exaggerated increase in plasma bilirubin concentration. By 5 days of age only 10 % neonates have a plasma bilirubin concentration > 200 µmol/L and the median concentration at that age is variously reported between 70 - 170 µmol/L. Marked and early increases in plasma bilirubin should lead to the investigation of inherited causes of haemolytic jaundice, once common causes such as blood group incompatibilities and infection, have been eliminated.

- Prolonged Jaundice

By 10 days of age 90 % of neonates will have bilirubin concentration < 150 µmol/L. If the total bilirubin concentration is persistently > 50 µmol/L after 14 days, then a cause should be sought. The majority of term infants presenting with prolonged jaundice will have an unconjugated hyperbilirubinaemia secondary to breast feeding.

Measurement of conjugated bilirubin in prolonged jaundice is important and it is abnormal in the neonate if it is > 20 μmol/L. This finding taken in conjunction with pale or acholic stools and dark bile-stained urine are markers of established cholestatic disease and require urgent follow up.

With developing maturity of bilirubin uridine glucuronyl transferase in the latter parts of gestation and early neonatal life bilirubin glucuronide can be increasingly formed and retained. In prolonged jaundice the absence of conjugated bilirubin may suggest undersecretion because of deficient conjugation. Conversely a particularly increased proportion of conjugated bilirubin is compatible with a cholestasic contribution to the persisting jaundice.

However, there are no hard and fast rules as conditions such as Galactosaemia, Fructosaemia (Fructose-1-6-Bisphosphatase Deficiency) and Cystic fibrosis may present with a mixed feature of unconjugated and conjugated hyperbilirubinaemia.

Supporting information to suggest an inherited metabolic disorder includes consanguineous parents, previous unexplained deaths in the family, dysmorphic features, hyperammonaemia, hypoglycaemia, association of symptoms with intake of milk and failure to thrive.

Which investigations for IMD should be considered in babies with early presenting jaundice ?

Blood group incompatibilities, infection and drug induced haemolytic processes must be included in the differential diagnosis, Investigations to exclude these causes of jaundice are not included in this guideline.

Disorder	Laboratory Investigations	Supporting Clinical findings
Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency 305900	G6PD screen (RBC)	Mediterranean, Asian or African race, antimalarial drug related, family history
Pyruvate kinase (PK) deficiency 266200	FBC, blood film, PK (RBC)	Anaemia, splenomegaly
Galactosaemia 230400	Reducing substances (U) if lactose in diet. Galactose-1-phosphate uridyl transferase (RBC) Note transfusion will invalidate result.	Vomiting, diarrhoea, failure to thrive, hypoglycaemia, hepatocellular damage, cataracts

Which investigations should be considered for Prolonged Jaundice?

A plasma total and conjugated biliurbin must be measured. Non-metabolic causes should be included in the differential diagnosis, such as:

- biliary atresia
- use of total parenteral nutrition
- breast milk jaundice
- congenital hypothyroidism
- septo-optic dysplasia and hypopituitarism
- viral infection
- choledochal cysts

Investigation of these differential diagnoses is not included in this guideline.
Laboratory investigations should be one component of the structured investigation protocol for neonatal cholestasis. Supporting clinical signs and symptoms should be considered when prioritizing the laboratory investigations necessary – if there is doubt this should be discussed with your Metabolic Laboratory.

Disorder (McKusick Index number)	**Laboratory Investigations**	**Supporting Clinical Findings**
Crigler-Najjar syndrome type I and II 191740, 191743	DNA testing Bilirubin components (bile) Glucuronyl transferase (L)	Unconjugated hyperbilirubinaemia No liver dysfunction, type II responds to phenobarbitone.
Galactosaemia 230400	Sugar Chromatography (U) if lactose in diet. Galactose-1-phosphate uridyl transferase (RBC) Note transfusion may invalidate result	Symptoms after start of milk feed Vomiting, diarrhoea, failure to thrive, hypoglycaemia, hepatocellular damage, cataracts
Tyrosinaemia type 1 276700	Aminoacid profile (HB); Organic acids including succinyl acetone (U) PBG synthase screen (HB)	Ascites, steatorrhoea, hypoglycaemia Raised alkaline phosphatase Coagulopathy
Alpha-1-antitrypsin deficiency 107400	Alpha-1-antitrypsin level and protease inhibitor (pheno-)typing (P)	Cholestasis, hepatomegaly
Neonatal haemochromatosis 231100	Ferritin (HB)	Congenital cirrhosis Severe liver failure from birth

Niemann-Pick disease type C (NPC) 257220	Foam cells in bone marrow; cholesterol esterification (FB) and NPC gene mutations	Hepatomegaly, splenomegaly, fetal ascites
Zellweger syndrome 214100	Very long chain fatty acids (HB)	Hypotonia, dysmorphic features, neurological, renal and liver dysfunction
Wolman's disease 278000	Abdominal X-ray of adrenal glands, acid esterase (EDTA)	Hepatosplenomegaly, anaemia, enlargement and calcification of adrenal glands.
Alagille syndrome 118450	DNA testing	Hepatomegaly, dysmorphic features, congenital cardiac anomalies
Byler disease (Progressive Familial Intrahepatic Cholestasis) PFIC-1: 211600 PFIC-2: 601847 PFIC-3: 602347	Low/normal γ- glutamyl transpeptidase (GGT) (HB) in type 1/2, ↑GGT in type 3, cholesterol (HB), total bile acids (HB, U) DNA testing	Pruritis, pancreatitis, diarrhoea, hepatomegaly, growth retardation
Bile acid synthesis defects 213700, 235555	Bile acids (U, HB)	Steatorrhoea, pruritis, diarrhoea, Neonatal hepatitis
Cystic fibrosis 219700	Sweat test, Immunoreactive trypsin (dried blood spot) (if < 8 weeks of age), DNA testing (as part of newborn bloodspot screening programme)	Meconium ileus, family history
Hereditary fructose intolerance 229600	Sugar chromatography if lactose/sucrose in diet(U); DNA testing; Fructaldolase B (L)	Hypoglycaemia, hepatomegaly only presenting after weaning
Fructose 1,6 bisphosphatase deficiency 229700	Fructose 1,6 bisphosphatase (WB)	Metabolic acidosis, hypoglycaemia, hepatomegaly
Citrin deficiency 605814	DNA testing Amino acid profile (HB) Sugar chromatography (U)	Hepatic steatosis, mild hepatomegaly, cholestatic jaundice hypoglycaemia, FTT

Mitochondrial DNA deletion syndrome (Hepatocerebral) Type 3 251880 Type 6 256810	DNA testing	Hepatomegaly, acute/progressive hepatic failure, sensorimotor neuropathy, lactic acidosis, hypoglycaemia, neurological abnormality
ARC syndrome 208085	DNA testing Aminoacids (U) Low/normal GGT (HB)	Arthrogryposis, renal tubular dysfunction, cholestasis, FTT, dysmorphia, hypotonia

U = urine; RBC = red blood cells; FB = fibroblasts; HB = heparinised blood; S = serum
L = Liver; EDTA blood

Numbers are references to the McKusick Index Phenotype "Mendelian Inheritance in Man".

References

- Green A, Morgan I, Gray J. Neonatology and Laboratory Medicine, ACB Venture Publications 2003, Chapter 6: 89-106.
- Kelly D. Diseases of the Liver and Biliary System in Children. Second edition, 2004, Chapter 4: 35-73.
- Grompe M. The pathophysiology and treatment of hereditary tyrosinaemia type 1. Semin Liver Dis. 2001; 21 (4): 563-71.
- Valaes T, Severe neonatal jaundice associated with glucose-6-phosphatase dehydrogenase deficiency : pathogenesis and global epidemiology. Acta Paed Suppl 394 (1994): 58 – 76.
- Shapira R, Hadzic N, Francavilla R, Koukulis G, Price JF, Mieli-Vergani G. Retrospective review of cystic fibrosis presenting as infantile liver disease. Arch Dis Child. 1999 Aug;81(2):125-8.
- Wilson G.N, Holmes R D, Hajra A.K. Peroxisomal Disorderes: Clinical commentary and future prospects. Am J. Med. Genet. 1998;30:771-792.
- Deleuze J.F, Dhorne-Pollet S, Pollet N, Meunier-Rohwal M. Hadchouel M. Allagille Syndrome in 1995. Clinical and genetic data. Gastroenterologie Clinique et Biologique. 1995;587-596.
- Cohen YH, Merlob P, Marcus-Eidlists T, Amir J. Dubin Johnson syndrome as a cause of neonatal jaundice: the importance of coproporphyrins investigation. Clinical Pediatrics (1998) 37 (8) 511 – 513
- Gissen P, Tee, L, Johnson CA, Genin E, Caliebe A, Chitayat D, Clericuzio C, Denecke J, Di Rocco M, Fischler B, Fitzpatrick D, Garcia-Cazorla A, Guyot D, Jacquemont S, Koletzko S, Leheup B, Mandel H, Sanseverino MTV, Houwen RHJ, McKiernan PJ, Kelly DA, Maher ER. Clinical and Molecular genetic features of ARC syndrome. Hum. Genet (2006) 120:396-409
- Bin T. Citrin deficiency: Learn more, and don't forget to add it to the list of neonatal cholestasis and the NASH trash bin. J. Ped. Gastroenterol. Nutr. (2010) 50 (6): 578-579

- Dimmock D, Kobayashi K, Iijima M, Tabata A, Wong L-J, Saheki T, Lee B, Scaglia F. Citrin deficiency: A novel cause of failure to thrive that responds to a high-protein, low-carbohydrate diet. Pediatrics (2007) 119 (3):e773-e777
- Spinazzola A, Santer R, Akman OH, Tsiakas K, Schaefer H, Ding X, Karadimas CL, Shanske S, Ganesh J, Di Mauro S, Zeviani M. Hepatocerebral form of mitochondrial DNA depletion syndrome; novel MPV17 mutations. Arch. Neurol. (2008);65 (8):1108-1113
- Mancuso M, Ferraris S, Pancrudo J, Feigenbaum A, Raiman J, Christodoulou J, Thorburn DR, DiMauro S. New DGK gene mutations in the hepatocerebral form of mitochondrial DNA depletion syndrome. Arch. Neurol (2005) 62:745-747

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Version Number/ date of origin: v3 July 2012

Suggested review date: July 2015

Disclaimer: These are laboratory guidelines reflecting current best practice in specialist metabolic laboratories the UK. They are not evidence based but reflect expert opinion. The network cannot accept any responsibility for use of these guidelines.

The National Metabolic Biochemistry Network (www.metbio.net) is a professional network funded by the Department of Health Genetic Services