

# Early detection of liver disease in neonates

Liver disease is an infrequent but potentially very serious cause of morbidity in childhood. Delayed identification is common. In some cases this is due to lack of awareness by healthcare professionals and parents of the signs and symptoms of liver disease, as opposed to physiological jaundice which is common in newborn infants. This article highlights the signs of liver disease in infants and the action needed to ensure these infants get the best care possible.

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Liver disease is estimated to occur in between 2–10 per 10,000 children, if community-acquired acute infectious hepatitis is excluded<sup>1,2</sup>. Such relatively low incidence means that not all health professionals will be familiar with the symptoms and signs of paediatric liver disease in general paediatric practice. Family doctors may be exposed to only a few cases of liver disease in children during their whole career.

Approximately two thirds of children who are going to develop chronic liver disease will present during early infancy<sup>2</sup>. Therefore, the onus is on health practitioners such as midwives, neonatologists, health visitors, community nurses and general practitioners to identify early indicators of suspected liver disease and refer the children to the specialised paediatric hepatology centres, where detailed diagnostic pathways have been operational for the last 20–30 years. Timely manner of these referrals is of paramount

importance, since some children with liver disease may require immediate change in their diet, introduction of medication or urgent surgical treatment.

## Detection and diagnosis of liver disease and differentiation from mild jaundice

Clinical features of liver disease in adults and in older children are rather obvious and include jaundice, nausea, tiredness, dark urine and light stools. In newborn infants, however, the signs (jaundice, yellow urine and pale stools) can be very subtle and may go unnoticed by parents and health professionals<sup>2</sup> (FIGURES 1 and 2). Parents may not be aware that the urine of a newborn baby should be colourless. Signs may be more difficult to recognise in children with darker skin. In these infants careful examination of the sclerae of the eyes for discrete yellow discolouration is essential.

In neonates the detection of liver disease

## Keywords

liver disease; jaundice; vitamin K; pale stools; conjugated bilirubin levels; liver transplantation

## Key points

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1. Most children who are going to develop liver disease do so during early infancy.
2. Signs and symptoms can be difficult to detect and are easily confused with physiological jaundice.
3. Prolonged jaundice beyond three weeks of life and elevated conjugated bilirubin levels need urgent investigation.
4. Early detection of liver disease enables healthy growth and development to be maintained, may postpone or obviate the need for liver transplantation and could be associated with increased survival rates.



**FIGURE 1** Infant exhibiting typical signs of liver disease – yellow tinge to whites of the eyes and an enlarged abdomen.

is further complicated by the presence of physiological neonatal jaundice. This phenomenon starts soon after the baby leaves the relatively hypoxic environment of the uterus, when the antenatal requirements of an increased number of red cells to deliver oxygen to the tissues, abruptly cease to exist. The process is a result of increased degradation of the haem component of the red blood cell pigment – haemoglobin, via the biliverdin/bilirubin pathway. The increased load of bilirubin exceeds the conjugating capacities of the immature liver, resulting in an increased level of unconjugated bilirubin. In a term neonate the physiological jaundice peaks at around day 4, while in premature babies this happens between days 5–7 postnatally, and then slowly disappears. This type of jaundice is very common – up to 50% of babies will become jaundiced within 48 hours of birth.

An entirely benign phenomenon also observed at this age is so-called ‘breast milk’ jaundice. In a process that is not completely understood it appears that hormonal substances from breast milk can aggravate physiological jaundice in some infants causing it to persist for up to three months. It is important, however, not to overlook the presence of other pathological signs and symptoms, under the assumption of the presence of ‘breast milk’ jaundice in breastfed babies.

The crucial difference between physiological jaundice and pathological jaundice, often related to liver disease, is in the type of increased bilirubin. Physiological jaundice is associated with water-soluble, *unconjugated* (indirect) bilirubin – both the total and unconjugated fraction are increased, with often just a mild increase in the conjugated fraction, not exceeding 20% of total bilirubin. In contrast, in liver disease water-insoluble, *conjugated* (direct) bilirubin prevails. The pathological process occurring in the liver often affects the liver’s normal metabolic functions, including conjugation of the bilirubin, which is obligatory for its degradation. As a result normal excretion of conjugated bilirubin is often impaired. Consequently in the majority of cases of liver disease both the total and *conjugated* fraction of bilirubin are significantly elevated (normal serum values: <20 micromol/L).

A relatively infrequent, but potentially serious symptom of liver disease in the neonatal period is susceptibility to bleeding. The liver synthesises several



**FIGURE 2** This baby with liver disease is not showing the typical visual signs of the disease, illustrating how early detection and appropriate referral can be difficult.

factors of the clotting cascade, some of them dependent on the adequate serum levels of vitamin K. Some jaundiced infants will be vitamin K-depleted as a consequence of the impaired bile flow, due to cholestasis and malabsorption. Children with liver disease secondary to PIZZ alpha<sub>1</sub> antitrypsin deficiency, but also some with biliary atresia (BA) are particularly prone to this complication, which could occasionally result in life-threatening intracranial bleeding<sup>4,5</sup>. This may be particularly true for patients where postnatal prophylaxis of haemorrhagic disease of the newborn with parenteral vitamin K has not been implemented.

### How to suspect liver disease?

In order to increase the awareness and early diagnosis rate of liver disease in the neonatal period a few simple axioms can be employed. They should be used as a guide for first-line health professionals looking after neonates and infants within the first few months of life:

- Any jaundice persisting beyond two to three weeks of life is abnormal.
- In a jaundiced baby one always needs to inspect the colour of the stools personally; second hand communication often results in misinterpretation. Persistently abnormal, pale, clay-coloured stools point in the direction of a significant hepato-biliary problem. A colour chart of normal and abnormal baby stools is available as part of an information pack provided by the Children’s Liver Disease Foundation (CLDF).

- Percutaneous tests for measurement of total bilirubin, often used in neonatology, are not helpful, since they tend not to measure the fraction of the conjugated bilirubin, which is critical in detection of liver disease.

A typical, but often misleading, feature of children with infantile liver disease, including BA, is a generally good clinical condition and appropriate weight gain at early stages<sup>3,4</sup>. In contrast, children with metabolic liver conditions will often be distressed and have feeding difficulties, manifested by irritability, persistent vomiting and failure to thrive.

Clinical examination of the jaundiced newborn is not complete unless the following questions are asked:

- Does the jaundiced baby have pale stools?
- Does the jaundiced baby have yellow urine, often staining the nappies?

If the answer to either of these questions is: ‘yes’, the child *must* have a blood test to determine the level of total and direct bilirubin in the blood (‘split’ bilirubin) (**FIGURE 3**). This should be promptly arranged at a local hospital with the results becoming available within a couple of hours. If conjugated bilirubin is elevated and represents more than 20% of total bilirubin, an urgent referral to a tertiary centre should be made. Parenteral injection of 3–5 mg of vitamin K should be given while awaiting admission, if possible. GPs are entitled and encouraged to refer the patients directly to the tertiary units since this will result in quicker assessments. There are three national paediatric hepatology centres in the UK, (King’s College Hospital, London; Birmingham Children’s Hospital; and St James’ University Hospital, Leeds) supported and funded directly by the Department of Health. These units provide surgical and medical treatment. Healthcare professionals can contact these specialist centres directly for advice. Contact details are in the CLDF Yellow Alert Jaundice Protocol.

### Advice to parents

Arrival of a newborn baby is a situation where no information could be comprehensive enough to provide answers for all possible scenarios even in the absence of any disease. The parents are often stressed and may act inappropriately. Thus, the role of the health practitioner is to provide calm and sound professional advice and genuine sympathetic reassurance, if required. Negation,

overconfidence and a patronising attitude could result in catastrophic distress for the family, but also in misdiagnosis and potentially delayed referral and treatment. Most episodes of jaundice are benign and self-limiting. Adequate hydration and establishing a feeding pattern sufficient for gradual weight gain are non-specific measures which help to reduce unconjugated bilirubin levels in the blood and this is what is needed in most cases.

In some infants the unconjugated bilirubin can rise above 350 micromol/L and at these levels can cross the blood-brain barrier causing neurological damage (kernicterus) – this requires careful monitoring of bilirubin levels and initiation of phototherapy treatment.

The health professional must make every effort not to overlook pathological conditions, including liver disease. For example, the jaundice may also be a symptom of endocrine problems such as hypothyroidism (predominantly unconjugated) or hypopituitarism (mixed pattern), infection (baby usually not well) or some genetic condition. The assessment at a paediatric hepatology centre will include all of the alternate causes for the jaundice and also pursue mutational analysis for genetic conditions if available and appropriate. This may result in genetic advice and consideration of future antenatal diagnosis if required.

### What can go wrong when counselling new parents?

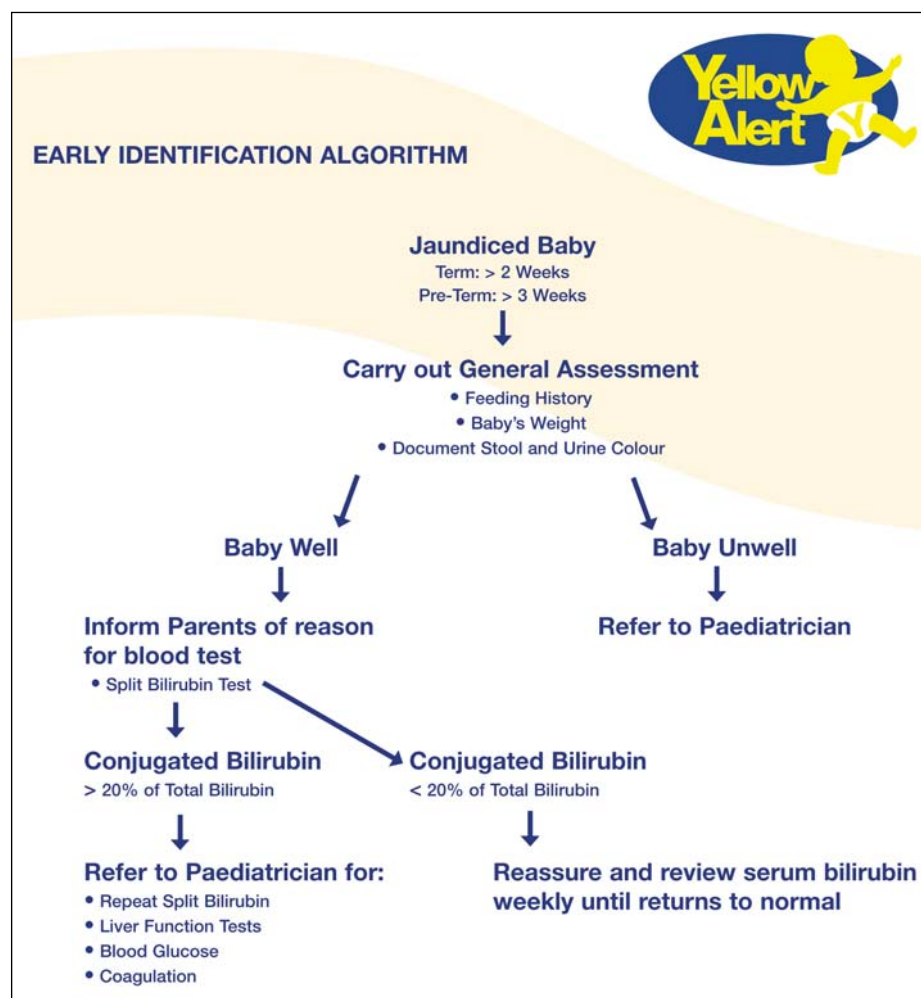
At late referrals to the tertiary centres commonly observed scenarios include:

- false reassurance about physiological jaundice by health professionals
- wait-and-see strategy
- perceived over-anxiety of the parents
- unprepared and uninformed parents
- social and logistical difficulties.

Referral centres always provide feedback to the referring health professionals, but their role is difficult to ascertain given the relative low incidence of liver conditions in the community. Increasing general public awareness appears to be a more logical way of helping early diagnosis of liver disease.

### Consequences of undetected liver disease

Most liver diseases are of a quiescent nature, due to the phenomenal reserve capacities of this organ<sup>1,3</sup>. Failure to identify the liver disease will result in ongoing progression of the pathological process.



**FIGURE 3** Algorithm for early detection of liver disease – part of the Yellow Alert Campaign Pack from the Children's Liver Disease Foundation.

For example, continuing a galactose-containing diet in galactosaemia will lead to worsening of coagulopathy, possible infections, and increased likelihood for formation of cataracts in the eyes. Belated introduction of 2-(2-nitro-4-3 trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) medication in tyrosinaemia type 1 will leave production of toxic and potentially carcinogenic metabolites unabated. However, the most illustrative example of the significance of early referrals to expert centres is in those liver conditions requiring surgical intervention, such as BA<sup>6</sup>. This is the commonest cause of chronic liver disease and liver transplantation in childhood, estimated to occur in around 1:16,000 live births in Europe<sup>7,8</sup>. Detailed pathogenesis has not been fully elucidated yet, but it is thought that in the majority of infants this obstructive cholangiopathy develops shortly after birth and progresses to cirrhosis, end stage liver disease and death during infancy, if left untreated<sup>4</sup>. Around one-eighth of the infants with BA will have abnormalities of

other organs (spleen, heart, intestine, large blood vessels) and the condition may originate early in pregnancy. This subgroup is termed embryonal (congenital) or biliary atresia splenic malformation (BASM) syndrome<sup>9</sup>. At least 50-60% of children with BA will require liver transplantation (LT) during their lifetime<sup>5</sup>. Nevertheless, in 11% of children operated on for BA, where the surgery was performed in a timely manner, there were no clinical signs of liver disease after at least ten years of follow up<sup>10</sup>.

### Management of liver disease and outcomes

It has been unequivocally observed that the success of corrective surgery for BA – Kasai portoenterostomy (KPE) – is in direct proportion with age at the surgery<sup>6</sup>. The likely explanation is a timely removal of the biliary tree affected by the progressive inflammatory process and replacement with effective biliary drainage via a new Roux-en-Y loop constructed from the patient's own small bowel segment and anastomosed to the jejunum. The best



results from KPE are expected if the operation is performed within two months of life<sup>6</sup>. Children diagnosed late and undergoing KPE after four months of age are unlikely to benefit due to the already established hepatic cirrhosis and portal hypertension and should be considered for early primary LT. The surgery at a later stage is still possible, but could be associated with an increased number of postoperative complications affecting the final outcome and should be deemed as palliative or a "bridge to transplantation"<sup>11</sup>. Another important element of the management of BA is the individual expertise of the surgeon and comprehensive medical, nursing and nutritional support provided by the tertiary centre<sup>8</sup>. This combined management approach in treating BA, including KPE and early consideration for LT if and when indicated at the same tertiary centre, offers an impressive five-year survival rate of around 95% for children with BA<sup>11</sup>. A number of studies have reported superior results from the centralised referral pathways in managing BA as an exemplary paradigm for overall management of chronic liver disease in children<sup>8,11</sup>.

Before advent of LT the options for effective impact on the natural history of liver disease were limited. The non-transplant measures that remain relevant at present include aggressive supplementation of fat soluble vitamins and high calorie nutrition regimens with special medium chain triglyceride-based or semi-elemental milk formulas, often including auxiliary modes of feeding such as additional nasogastric or overnight tube feeding and gastrostomy. Medications such as bile flow enhancers (ursodeoxycholic acid), diuretics and beta-blockers may be required. The aim of the management of chronic liver disease is to provide conditions for unaffected growth, uninterrupted development and appropriate educational and academic progress during infancy and childhood. Failure to achieve any of this will represent one of the softer indications for consideration for LT. More robust medical reasons for LT include persistent conjugated jaundice, uncontrolled portal hypertension with risk of repeated gastrointestinal bleeding, decompensated chronic liver disease with signs of synthetic liver failure such as ascites, coagulopathy or re-emergence of jaundice, repeated life-threatening infections of the biliary tree, intractable itching and unresectable malignant and benign neoplasms of the

liver. Indications for LT following acute liver failure are beyond the scope of this review.

Over the last 20 years, since LT has become an established option of treatment for terminal and acute liver failure, its success rate has been constantly improving. For elective LT required for end stage chronic liver disease, one-year survival rate in the majority of paediatric transplant centres in Europe and North America is between 90-95%<sup>12</sup>. BA represents the most common indication for LT in children worldwide. Though LT has dramatically changed the outcome of chronic liver disease in children it should not be regarded as a panacea for all liver and metabolic conditions. LT carries significant intraoperative and postoperative risks short term, but also long term complications such as increased rate of infections, chronic nephrotoxicity, vascular complications and increased risk for malignancies (post-transplant lymphoproliferative disease), related to the indefinite anti-rejection treatment which is required. Moreover, there is a chronic cadaveric organ shortage in the community, which has been somewhat ameliorated recently by advents of split organ transplantation (one liver graft into two recipients) and living related donor transplantation (use of a part of the liver from a relative, often a parent). Therefore, risk and benefits of LT for each patient with advanced chronic liver disease have to be carefully and critically considered by a team of different specialists involved in this formidable medico-surgical intervention, which remains at the forefront of medical practice more than 40 years after its original description.

Hepatocyte transplantation is emerging as a potential option for bridging intervals when formal liver grafting is not possible. It is hoped that better understanding of modes of preserving and extending the function and life span of transplanted hepatocytes would broaden our knowledge about hepatic biological processes, including growth and regeneration. Further progress may be hampered by the limited availability of organs from brain-

dead donors and the concept of voluntary organ donation needs to be more firmly embedded in the community.

## Conclusion

Identifying infants with liver disease can be difficult. For community healthcare professionals it is only one of many diseases of which they need to be aware. The Children's Liver Disease Foundation has launched the Yellow Alert aimed at highlighting the signs of liver disease in neonates to healthcare professionals and parents.

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Free copies of the Yellow Alert Pack can be obtained from the Children's Liver Disease Foundation.

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