Kernicterus

Synonym: bilirubin encephalopathy

Kernicterus is a complication of neonatal jaundice. The word kernicterus means yellow kern, kern being the structures of the brain that are most commonly affected. They are the basal ganglia, hippocampus, geniculate bodies and cranial nerve nuclei, especially the oculomotor, vestibular and cochlear. The cerebellum can also be affected.

Acute bilirubin encephalopathy is an acute clinical manifestation of bilirubin toxicity. There is hypotonia followed by hypertonia, opisthotonus (hyperextension of the spine causing backward arching of the neck and back) or retrocollis (backward arching of the neck).

Premature babies are at risk of kernicterus. Kernicterus rarely affects a term infant unless bilirubin levels are exceptionally high. A high level of physiological jaundice, especially in breast-fed babies, seems benign and resolves spontaneously without complications.

Epidemiology

- Universal access to rhesus immunoprophylaxis, co-ordinated perinatal-neonatal care, and effective phototherapy has virtually eliminated kernicterus in many countries.\(^1\)
- Seven incidence studies conducted internationally between 1988 and 2005 identified an estimated incidence of kernicterus at 0.4-2.7 per 100,000 births.\(^2\)

Risk factors

Risk factors for hyperbilirubinaemia neurotoxicity include isoimmune haemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, asphyxia, sepsis, acidosis and albumin <3.0 mg/dL.\(^3\) Other risk factors include:

- Rapidly rising level of bilirubin
- Galactosaemia
- Hypothyroidism
- Crigler-Najjar syndrome

However, those at recognised risk may well be treated so that kernicterus occurs more often in those of lower risk in whom the process was not recognised.

Babies with hyperbilirubinaemia are at increased risk of developing kernicterus if they have any of the following:\(^4\)

- Serum bilirubin level greater than 340 µmol/L in babies with a gestational age of 37 weeks or more.
- A rapidly rising bilirubin level of greater than 8.5 µmol/L per hour.
- Clinical features of acute bilirubin encephalopathy.

Presentation

There may be known risk factors such as prematurity, rhesus incompatibility or a family history of G6PD deficiency or spherocytosis. ABO incompatibility rarely causes severe problems.

Kernicterus usually presents in the first week of life, but may first present until the third week.

- Early features within the first few days include severe jaundice, hypotonia, poor sucking and feeding, and absent startle reflex.
- The affected baby may then develop a high-pitched cry, hypertonia of extensor muscles with arched back and hyperextended neck, bulging fontanelle and seizures.
- Later neurological features include sensory hearing loss, intellectual disability, muscle rigidity, speech difficulties, seizures and movement disorder.

Chronic bilirubin encephalopathy

This develops over the first few years of life. The first phase occurs in the first year of life with hypotonia, hyperreflexia and delayed physical milestones. The tonic neck reflex can also be present. In children aged over 1 year, the classical features develop, which include abnormalities in the extrapyramidal, visual and auditory systems. Minor intellectual deficits may be present.

Extrapyramidal signs

These may occur and the most common and most severe is athetosis, although chorea can also occur. Upper extremities are more severely affected than the lower ones and bulbar nerves may also be involved. Chronic bilirubin encephalopathy causes damage to the basal ganglia.
Visual problems
These most commonly affect ocular movements, resulting in upward gaze, although horizontal gaze abnormalities and gaze palsies can also occur. They are due to damage to the cranial nerve nuclei in the brain stem.

Hearing problems
These are the most consistent feature of chronic bilirubin encephalopathy and can occur in the absence of any other characteristic features. The most common problem is high-frequency hearing loss, ranging from mild to severe. Both the cochlear nuclei in the brain stem and the auditory nerve appear to be very sensitive to bilirubin, even at relatively low levels. This may present as delayed language and so any baby at risk must have hearing assessed. The presenting feature of kernicterus may be childhood deafness.

Cognitive defects
These do not feature prominently in kernicterus but athetosis or chorea along with hearing defects may give the false impression of learning disability.

Dental enamel
Shows some hypoplasia and some may show green staining of teeth.

More subtle alterations - bilirubin-induced neurological dysfunction (BIND) - occur with a chronic state of mild BIND, which may include neurological, learning and movement disorders or isolated hearing impairment.[5]

Investigations

Bilirubin levels
- Jaundice can be detected clinically, although this is more difficult in babies with dark skin. Clinical assessment is not enough and estimation of serum bilirubin is required, although a technique of transcutaneous measurement of bilirubin has shown value in preventing unnecessary re-admissions to hospital.[6]
- Transcutaneous bilirubinometry is a non-invasive technique that is currently being explored.
- Both direct and indirect bilirubin should be measured. This gives an indication of the level of free bilirubin, although direct measurement of this is not possible. It is free bilirubin that crosses the blood-brain barrier. The test may need repeating with a frequency dependent upon the levels found, gestational age and age since birth. Nomograms have been produced to try to anticipate maximum levels.

Other blood tests
- Both mother and baby should have blood tested for ABO and rhesus groups as well as minor groups.
- Neonates have a slightly higher reticulocyte count than older children but an elevated level for age suggests an ongoing problem of haemolysis.
- The direct Coombs’ test detects antibody on the surface of the erythrocyte. A positive result indicates that antibody is on the red cells and so they are at risk of immune haemolysis. This is a qualitative test that does not indicate the amount of antibody or the degree of haemolysis, although the reticulocyte count may indicate this.
- A differential white count may indicate sepsis. If there is any suggestion of infection, a full septic screen (including swabs, urine culture, blood cultures and lumbar puncture) should be performed.
- A blood smear should be examined for spherocytosis or elliptocytosis.
- Check U&E. Dehydration seems a risk factor for kernicterus and may be a feature in babies re-admitted with hypomatrema and elevated bilirubin.

Imaging of the brain does not help in the diagnosis, except by excluding other causes. Ultrasound is portable and useful. CT does not provide so much information as MRI. There may be some subtle changes in the MRI scan in kernicterus but the value of this is uncertain.

Brainstem auditory evoked response (BAER) can be used to assess hearing at a very early stage and long before the presentation of delayed language.

Management

Management is aimed at preventing neurotoxicity. The management of hyperbilirubinaemia by both phototherapy and exchange transfusion is discussed in the separate article Neonatal Jaundice.

Babies who are thought to have neurological damage should be referred early for neurodevelopmental assessment and remedial help.

Management of kernicterus will include management of neurological complications, including seizures and sensory nerve deafness.

Prognosis

Bilirubin-related neurotoxicity can result in neonatal death or multisystem acute manifestations and long-term impairments, including irreversible athetoid cerebral palsy, and speech, visual, auditory and other sensori-processing disabilities.[1]
Prevention

Prevention of kernicterus is based on the identification and adequate treatment of hyperbilirubinaemia in neonates.

Attention needs to be paid to any baby with hyperbilirubinaemia, but particularly to those who are premature, to those who are known to have a family history of G6PD deficiency or other disorders that may produce neonatal haemolysis, and to any baby seeming to develop rapid and unexpected jaundice. The Newborn Jaundice and Kernicterus Meeting in Siena called for a global expansion of neonatal G6PD screening. [7]

Breast-feeding increases levels of bilirubin but should not be discontinued.

If the size of a population at low risk is very much larger than a high-risk group, then the total number affected may contain more individuals from the low-risk than the high-risk group. This is especially likely if the high-risk group is carefully monitored and treated but the low-risk group is ignored.

- It is very important that if there are signs of abnormality in the low-risk group, investigation with a view to treatment should not be overlooked.
- With early discharge it has been suggested that bilirubin should be checked and a nomogram used, as discharge is before the peak of physiological jaundice and this may help to identify those who will have problems. [8] Neonatal jaundice is common but kernicterus is rare.
- Questions have been raised about the cost-effectiveness of routine predischarge serum or transcutaneous bilirubin screening and one study concluded that it could be falsely reassuring. [9] Predischarge bilirubin does, however, have a greater predictive value than a clinical risk factor score. [10]
- When jaundice is deeper than expected it must be taken seriously, as the consequences of kernicterus are devastating and lifelong. Infection also needs to be excluded. Breast-feeding might increase levels of bilirubin but it should be encouraged with a regime for identifying babies at risk. [11]
- A synopsis report from the American register suggested that the incidence of kernicterus could be reduced if families had better access to healthcare in the early stages of neonatal jaundice. [12]
- Some babies develop kernicterus with unexpectedly low levels of bilirubin.

Further reading & references

4. Jaundice in newborn babies under 28 days; NICE Clinical Guideline (released 2010, updated Oct 2016)

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<th>Author: Dr Colin Tidy</th>
<th>Peer Reviewer: Dr Adrian Bonsall</th>
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<td>Document ID: 2355(v23)</td>
<td>Last Checked: 12/03/2014</td>
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