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Kernicterus

Synonym: bilirubin encephalopathy

What is kernicterus?[1] [2]

Kernicterus is a bilirubin-induced brain damage most commonly seen in infants. Regions of the brain most commonly affected are the basal ganglia, hippocampus, geniculate bodies and cranial nerve nuclei, especially the oculomotor, vestibular and cochlear. The cerebellum can also be affected.

Kernicterus is a complication of neonatal jaundice. The following terms are used to describe the neurological consequences of hyperbilirubinaemia:[3]

- Acute bilirubin encephalopathy occurs when there is severe hyperbilirubinaemia. Features include lethargy, irritability, poor suck, abnormal muscle tone and posture (opisthotonus), high-pitched cry, apnoea, and eventually seizures and coma.
- Chronic bilirubin encephalopathy results from acute encephalopathy, and includes athetoid cerebral palsy, seizures, developmental delay, learning difficulties, vision and hearing problems, and dental dysplasia.
- Kernicterus is used to describe the clinical features of acute or chronic bilirubin encephalopathy and the pathological findings of deep yellow staining in the brain.

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).

Bilirubin induced encephalopathy may be permanent, chronic and lifelong, with symptoms including visual (upward gaze palsy), auditory (sensory neural hearing loss), dental dysplasia abnormalities, and extrapyramidal disturbances (choreoathetosis, cerebral palsy).

The risk of developing kernicterus increases considerably in infants with bilirubin levels above 250 mg/L while levels above 300 mg/L are associated with extremely high risk and irreversible damage. Any event that leads to increased bilirubin production or decreased elimination can lead to hyperbilirubinaemia and thus kernicterus.

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.

How common is kernicterus? (Epidemiology)

- The exact incidence of kernicterus is unknown; however, most recent data from the United Kingdom and Canada suggests kernicterus occurring at a rate of 1-2 per 100,000 live births.[1]
- Universal access to rhesus immunoprophylaxis, co-ordinated perinatal-neonatal care, and effective phototherapy has virtually eliminated kernicterus in many countries.[4]

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.[5] 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:[6]

- 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.

Symptoms of kernicterus (presentation)[7]

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.

Acute bilirubin encephalopathy encompasses the acute illness caused by severe hyperbilirubinaemia. Presenting signs and symptoms include decreased feeding, lethargy, abnormal tone (hypotonia and/or hypertonia), high-pitched cry, retrocollis and opisthotonus, setting-sun sign, fever, seizures, and possibly death. Seizures usually resolve several weeks after the acute insult.

The so-called ‘kernicteric facies’ in acute bilirubin encephalopathy includes a combination of the setting-sun sign (paresis of upward gaze) with eyelid retraction, which together comprise the Collier sign, and facial dystonia. These findings make the infant appear stunned, scared, or anxious. Some infants may also exhibit disconjugate or wondering eyes. This kernicteric facies persists for at least 2-3 weeks after acute bilirubin encephalopathy.

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.[8]

Diagnosing kernicterus (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.[9]
- 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 hypernatraemia and elevated bilirubin.

Brain MRI is the best imaging modality for the confirmation of the diagnosis. [2]

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 of kernicterus [7]

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

Established treatment strategies for acute bilirubin encephalopathy include phototherapy and exchange transfusion.

Management of patients with kernicterus is directed towards neurodevelopmental sequelae, such as physical, occupational, speech, and audiological therapies, as well as complications including nutritional difficulties, gastro-oesophageal reflux, sleep disturbances, hypertonicity, and muscle cramps.

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 sensory-processing disabilities. [4]

Prevention of kernicterus

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

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

Further reading

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