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Original article

Serum unbound bilirubin as a predictor for clinical kernicterus in extremely low birth weight infants at a late age in the neonatal intensive care unit

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Abstract

Background: This study aimed to evaluate peak serum total bilirubin (TB) and unbound bilirubin (UB) levels in preterm infants with clinical kernicterus (KI) who were diagnosed by clinical findings during infancy.

Design/subjects: For this multicenter retrospective study, 18 Japanese extremely low birth weight (ELBW) infants with clinical KI were included. Clinical KI was diagnosed based on the presence of motor developmental impairment with/without athetosis, and abnormal magnetic resonance imaging or brainstem auditory evoked potential findings during infancy. High and low TB or UB levels were defined as serum TB levels $\geqslant$ and $<$15 mg/dL or serum UB levels $\geqslant$ and $<$0.8 μg/dL, respectively. The clinical characteristics of KI preterm infants were analyzed. The proportion of infants with high or low serum TB levels and with high or low serum UB levels was then investigated. Sensitivity and specificity were calculated.

Results: In 18 KI infants, the median age when serum TB levels peaked was 28 days after birth. In eight KI infants with low serum TB levels, 88% of them had high serum UB levels. For comparison of the number of infants who had high or low serum TB and UB levels, the sensitivity was 90% and specificity was 13%.

Conclusions: Serum TB and UB levels peak at a later age than expected. Chronic serum UB monitoring may be helpful for identifying ELBW infants at risk for developing KI, even when they do not have high serum TB levels.

Keywords: Athetosis; Brainstem auditory evoked potentials; Jaundice; Magnetic resonance imaging; Motor impairment

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1. Introduction

Kernicterus (KI) in term infants is extremely rare in Japan because of the widespread use of a management guideline for hyperbilirubinemia and the initiation of phototherapy (PT) on the basis of guideline. However, some preterm infants have been diagnosed with KI, as shown by the presence of motor impairment with athetosis, abnormal magnetic resonance imaging (MRI) and/or brainstem auditory evoked potential (BAEP) findings during infancy (clinical KI) [1–4]. Most importantly, preterm infants with KI do not always have severe hyperbilirubinemia during their stay in the neonatal intensive care unit (NICU) [1–3,5–7]. A better predictive biomarker than serum total bilirubin (TB) is required to prevent the development of KI in preterm infants.

Clinical studies have suggested that serum unbound bilirubin (UB), which is a measure of bilirubin not bound to albumin, is a more sensitive predictor of low birth weight infants with "at risk" KI, infants with auditory impairment due to bilirubin-induced neurotoxicity, and extremely low birth weight (ELBW) infants with death or adverse neurodevelopmental outcomes than serum TB levels [8–12].

Our study aimed to evaluate peak serum TB and UB levels during the NICU stay in Japanese ELBW infants with clinical KI who were diagnosed by clinical findings during infancy, not autopsy.

2. Patients and methods

2.1. Subjects

For this multicenter retrospective study, we collected preterm infants <30 weeks' gestational age (GA), who were diagnosed with KI in their infancy from 2002 to 2012, and were measured both serum TB and UB levels during their NICU stay at Kobe University Hospital, Kobe Children's Hospital, Kakogawa West Municipal Hospital, Takatsuki General Hospital, Yodogawa Christian Hospital, Chibune General Hospital, and Juntendo University Hospital. Serum TB and UB levels were measured once a day until 7 days after birth, once every 2–3 days between 7 and 14 days of age. Indications for measurements of serum TB and UB levels, and treatment of phototherapy, intravenous albumin administration, or exchange transfusion were decided at the discretion of the responsible neonatologists after 14 days of age.

Clinical KI was diagnosed by criteria based on physical and neurological examinations, and laboratory findings during infancy, including the presence of motor impairment (dystonia, hypertonia, motor developmental delay, and/or disturbance of coordination or muscle tone) with/without athetosis, abnormal bilateral high intensity signals in the globus pallidi seen on T2-weighted images of brain MRI, and/or abnormal BAEP, such as bilateral no response or abnormal interwave separation at 90 dB [1,4]. Clinical KI infants were classified into three subtypes proposed by Shapiro [4]: classic KI, auditory KI, and motor KI. Classic KI refers to individuals with auditory neuropathy with/without hearing loss, neuromotor symptoms ± athetosis, oculomotor pareses, or dental enamel dysplasia. Auditory or motor KI refers to individuals with predominantly auditory symptoms with relatively minimal motor symptoms or predominantly motor symptoms with minimal auditory symptoms, respectively. Motor impairment and athetosis were diagnosed by a pediatric neurologist and brain MRI images were analyzed by a radiologist in each hospital.

2.2. Study methods

Clinical and laboratory findings in all of the enrolled infants were collected from medical charts. The clinical characteristics of preterm infants with KI were analyzed, including GA, birth weight (BW), the age when serum TB levels peaked, and serum TB and UB levels when serum TB levels peaked during the NICU stay. The cause and treatment of their hyperbilirubinemia were also analyzed. The number of infants with high or low serum TB levels and with high or low serum UB levels was determined in all KI infants, as well as KI infants who had peak serum TB levels at <28 days of age or ⩾28 days of age. Sensitivity and specificity were calculated in each group and values were compared between the <28 days of age and ⩾28 days of age groups. The collection and use of clinical data for this study were approved by the Ethical Committee of Kobe University Graduate School of Medicine.

2.3. Definitions of high and low serum TB and high and low serum UB levels

At the age when serum TB levels peaked in infants, high and low TB levels were defined as serum TB levels ⩾ and <15 mg/dL, respectively. High and low UB levels were defined as serum UB levels ⩾ and <0.8 μg/dL, respectively. These values are recommended for exchange transfusion based on our previous report [8].

2.4. Assay methods

Serum TB and UB levels were measured at the same time using a Food and Drug Administration-approved analyzer (UB Analyzer; Arrows Co., Ltd, Osaka, Japan) by spectrophotometry and the glucose oxidase–peroxidase method, respectively, as previously described [8,13–16]. Serum UB levels were measured using the single peroxidase concentration method, as recommended