The incidence of Crigler Najjar syndrome (CNS) is less than one case per 1,000,000 births. Only a few hundred cases have been described in world literature. CNS is elicited by a lack or deficiency of the enzyme uridine diphosphate glucuronyl transferase (UDGT). CNS is thought to affect all races equally and occurs in both sexes equally. Two distinct forms have been described type 1 and type 2. CNS type 1 is due to complete absence of bilirubin UDGT activity and the level of total serum bilirubin ranges from 20 to 50 mg/dL. CNS type 2 is due to markedly depressed activity of hepatic UDGT and the level of total bilirubin increases up to 20 mg/dL. Importantly, treatment with phenobarbitone can induce the expression of UDGT in patients with type 2 CNS, with a decrease in the serum bilirubin level of approximately 25%. If left untreated, type 1 CNS is uniformly lethal due to the development of kernicterus by age 2 years. Although much rarer, bilirubin encephalopathy can also occur in type 2 CNS, usually when patients experience a superimposed infection or stress. We present here a case of CNS type 2, by eliminating the other causes for unconjugated hyperbilirubinemia. This baby responded to phototherapy and phenobarbitone.

**Case report**

A three and half months-old male baby with yellowish discoloration of skin, sclera and mucus membrane was admitted to the pediatric ward of MVJ Medical College and Research Hospital at Bangalore, India.

On examination, the baby’s vitals were stable. Icterus was present. There was no pallor or cyanosis. The rest of the systemic examination was normal. On abdominal examination, the liver and spleen were not palpable. There was no facial dysmorphism. The eyes and ears were normal, both testes were descended and the spine and feet were normal. The posterior fontanelle was closed. No sutural diastasis or overlapping was noted. The head circumference (HC)
was 38 cm. The baby’s weight was 4.6 kg, and length: 59 cm, pulse rate: 126/min, respiratory rate: 28/min, blood pressure (BP): 80/40 mmHg, temperature: a febrile, CNS-sucking: rooting +, blood group: O+ve, birth weight: 2.3 kg. The baby was exclusively on breast feeding. Activity of the child was normal. Head control was not achieved, social smile was present.

Investigations showed that blood hemoglobin was 12.7g%, total cell count: 10,800 cells/mm², neutrophils: 29%, lymphocytes: 69%, eosinophils: 1%, monocytes: 1%, reticulocytes: 0.3%, platelet count: 5,04,000 cells/mm², Partial thromboplastin time: 33.8 seconds, blood culture: no growth, serum total bilirubin: 26.0 mg/dL, direct bilirubin: 4.0 mg/dL, indirect bilirubin: 24.0 mg/dL, total proteins: 6.5 g/dL, albumin: 3.5 g/dL, serum glutamate pyruvate transaminase: 37 IU/L, serum glutamate oxaloacetate transaminase: 35 IU/L, serum alkaline phosphatase: 160 IU/L, serum thyroid stimulating hormone: 160 IU/L, total T₄ : 2.08 μg/dL, total T₃ : 1.2 μg/dL, total T₂ : 13.3 μg/dL and thyroid stimulating hormone: 3.96 μIU/mL. Urine was negative for bile pigments. Ultrasound examination showed normal liver and gall bladder.

The child had normal hemoglobin (Hb) level, complete blood count, thyroid function and liver function tests except for a raised unconjugated bilirubin level. The baby responded well to phenobarbitone and double surfaces phototherapy. After one week, his bilirubin levels decreased by approximately 40%. The total bilirubin was 17.0 mg/dL, conjugated bilirubin: 2.5 mg/dL, and unconjugated bilirubin: 14.5 mg/dL. The baby was discharged with advice to continue phenobarbitone treatment. After one year follow-up, bilirubin levels decreased to a total of 9.8 mg/dL and direct of 1.5 mg/dL and unconjugated 8.3 mg/dL (a 60% decrease).

Discussion

CNS was first described under the title congenital familial nonhemolytic jaundice with kernicterus. CNS has been classified into two types according to the degree of unconjugated hyperbilirubinemia and response to phenobarbitone. CNS type 1 was first described in 1952 by Crigel and Najjar [1]. It is due to complete absence of bilirubin UDGT activity and the level of total serum bilirubin ranges from 20 to 50 mg/dL. Intense jaundice appears from the first days of life and persists thereafter. Some affected infants die in the first weeks or months of life from kernicterus. Others survive with little or no neurologic defect. These patients do not respond to phenobarbitone treatment. Phototherapy is the preferred long-term treatment for type 1 CNS [2, 3]. Other treatments that can reduce bilirubin in CNS type 1 are plasmapheresis [4] and orthotopic liver transplantation [5]. Other experimental methods used to reduce serum levels of bilirubin in CNS type 1 include oral calcium phosphate as adjuvant to phototherapy [6] inhibition of heme oxygenase (by tin-mesoporphyrin), bilirubin degradation by bilirubin oxidase, induction of P-450c by indoles, liver cell transplantation and gene therapy [7].

CNS type 2 (also called “Arias syndrome”) was first described in 1962 by Arias [8]. Its total serum bilirubin ranges from 6 to 20 mg/dL. CNS type 2 is caused by homozygous missense mutation in glucuronyl transferase isof orm-1. There are studies which indicate mutations in the coding region of the UDGT1A1-gene. This results in partial deficiency of enzyme activity (less than 10% of the normal activity), less severe jaundice and pigmented bile that contains bilirubin glucuronide. These patients generally survive into adulthood without neurologic or intellectual impairment. Response to phenobarbital in CNS type 2 is the most useful difference. Treatment with phenobarbitone induces the expression of bilirubin UDGT in patients with type 2 CNS with a decrease in serum bilirubin level of approximately 25% [1, 2, 8-10]. In this case, the serum total bilirubin was 26mg/dL with jaundice and normal liver function tests without neurological impairment, but the baby responded well to phototherapy and phenobarbitone [11]. These investigations and the response to the therapy suggested partial deficiency of bilirubin UDGT, which favored the diagnosis of type 2 CNS. Definitive diagnosis may be established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by a closed biopsy and in vitro expression of mutant DNA from patient fibroblast. This is too elaborate and expensive for routine use.

The authors have no conflict of interest to declare.
References