Crigler-Najjar Syndrome

Alternative Names
Crigler-Najjar Syndrome, Type I
CN-I
CNS-I
Bilirubin Uridinediphosphate Glucuronosyltransferase Deficiency

WHO International Classification of Diseases
Endocrine, nutritional and metabolic diseases

OMIM Number
218800

Mode of Inheritance
Autosomal recessive

Gene Map Locus
2q37

Description
Crigler-Najjar syndrome type I (CN-I) is a rare and severe autosomal recessive disorder of bilirubin metabolism characterized by congenital familial nonhemolytic jaundice associated with high level of unconjugated bilirubin due to deficient uridine diphosphate glucuronosyltransferase (UDPG-T) activity in the liver. The high serum level of unconjugated bilirubin results in kernicterus and neurological sequel, which can ultimately lead to severe disability or death. A diagnosis of Crigler-Najjar syndrome type I can be arrived at by classic clinical presentation, by process of exclusion of other persistent unconjugated hyperbilirubinemia conditions in infancy and by non-responsiveness to phenobarbitone therapy. The only effective treatment for CN-I patients is orthotopic liver transplantation.

Molecular Genetics
Crigler-Najjar syndromes are familial unconjugated hyperbilirubinemias caused by genetic lesions involving a single complex locus encoding for bilirubin-UDP-glucuronosyltransferase. The UGT1A1 gene, which is mutated in Crigler-Najjar syndrome type I, is part of a complex locus that encodes several UDP-glucuronosyltransferases, with a locus that includes thirteen unique alternate first exons followed by four common exons.

Epidemiology in the Arab World

Saudi Arabia
Nazer et al. (1990) reported two children, born to first-cousin Saudi parents, with the 'fetal face syndrome.' Both of the children also had the Crigler-Najjar syndrome, as did two previously born sibs who did not have the fetal face syndrome. Both died at age 4 months. The parents lost two previous children at age 2 months with progressive jaundice but without fetal facial characteristics. Later, Nazer et al. (1998) reviewed 12 patients (8 males and 4 females) who were diagnosed with Crigler-Najjar syndrome between 1986 and 1994. Jaundice was detected in the first few days of life in all but one, in whom detection was delayed for two weeks and resulted in kernicterus. Exchange transfusions were necessary in six cases. Consanguinity was present in 11 patients, eight of whom were the offspring of first cousins. None of the patients responded to phenobarbital therapy alone, which reflected the severity of their disease. Six patients required only phototherapy while the remaining six patients required a combination of phenobarbital and phototherapy. Percutaneous liver biopsy, performed in 10 patients, showed minimal and focal cholestasis in eight, while the remaining two had a normal histological picture. Almost complete absence of the activity of UDPGT in the liver was reported in seven cases. Kernicterus developed in five cases.

In 2002, Al Shurafa et al. analyzed the outcome of six children with Crigler-Najjar syndrome type I (CNS-I) and reported the first three living-related liver transplants for this syndrome
in Saudi Arabia and the Middle East. Two of the transplanted children developed acute hepatocellular rejection, which was successfully treated with methylprednisolone pulse therapy. One patient had a biliary leak at the cut surface of the graft which was surgically repaired. Post-operative bilirubin levels returned to normal in all three transplanted children and no further phototherapy was required. One patient, who was not transplanted but received phototherapy, developed severe neurological damage, her sister is still awaiting transplantation. At the time of the study, a 14-year-old child with a bilirubin level of 420 micromol/L was undergoing phototherapy whilst awaiting orthotopic liver transplantation because of the lack of a suitable living-related donor. Six siblings of the six children in the studied series were reported dead by the families.

Tunisia
Tabarki et al. (2002) reported a 2-year-old female with Crigler-Najjar syndrome type I who presented severe cerebellar symptoms revealing bilirubin encephalopathy. The patient improved slowly with the duration of phototherapy. Tabarki et al. (2002) suggested that cerebellar symptoms can be the initial manifestation of kernicterus in children with Crigler-Najjar syndrome type I.

References

Contributors
Ghazi O. Tadmouri: 6.7.2005