The saga of neonatal cholestasis syndrome (NCS) continues ever since Dr John Cooke in 1769 referred to mortality occurring in infants due to jaundice. The presenting clinical features of NCS are jaundice, dark urine, with or without passage of pale stools. The major stumbling block in the management of these babies is the varied etiology of this condition. This includes biliary atresia, choledochal cyst, giant cell hepatitis, intrauterine infections, ductal paucity, and metabolic defects. The final outcome of many of these causes is dependent on early diagnosis and timely management, while the presenting clinical features are usually alike.

More than 80% of cases with extrahepatic biliary atresia (EHBA), one of the major causes of NCS, who undergo Kasai portoenterostomy before 60 days of age become jaundice-free, as compared to 20%-35% operated on later. Of the infants with successful biliary drainage, a 15-year survival of 87% has been shown.

Subgroups of NCS other than EHBA also need early and targeted management. Timely treatment of metabolic causes like galactosemia and tyrosinemia, choledochal cyst, and infections, and early recognition of disorders like ductal paucity and progressive familial intrahepatic cholestasis will decrease the morbidity due to late presentation.

The consequences of infantile cholestasis are profound, resulting in malabsorption, failure to thrive, and deficiencies of fat-soluble vitamins. NCS babies are at special risk for life-threatening bleeding due to vitamin K deficiency. These babies need more calories to maintain growth, as also supplementation of vitamins A, D, E and K at diagnosis and thereafter.

In this issue of the Journal, Bazlul Karim and Kamal from Bangladesh, in their study of 62 infants with cholestatic jaundice, highlighted the etiology, delay in presentation of cases with EHBA, importance of acholic stools, and investigative modalities to diagnose EHBA. In their study an identifiable cause for neonatal hepatitis was seen in 35.5% of cases, EHBA in 25.8%, idiopathic neonatal hepatitis in 24.2%, choledochal cyst in 6.5%, and miscellaneous disorders in 8%. In a report we published earlier based on pooled data from eight medical centers in India, among 1008 analyzed cases of NCS, hepatocellular causes were seen in 53% (neonatal hepatitis 47%, metabolic 4%, and 2% other causes), obstructive etiology in 38% (biliary atresia 34%, choledochal cyst 4%), ductal paucity in 3%, and 6% were idiopathic. Among those with neonatal hepatitis (n=468), idiopathic giant cell hepatitis constituted 64%, TORCH infections 22% (including cytomegalovirus in 58% of these, toxoplasma in 23%, hepatitis B in 10%, rubella in 4.5%, syphilis in 4%, and herpes in 1%), sepsis 8%, and other causes like malaria, urinary tract infection 6%. Among the metabolic group (n=43) 35% were due to galactosemia, 33% tyrosinemia, 4% had storage disorders, and 2% had hemochromatosis. Ductal paucity (n=29) was due to non-syndromic variety in 83%.

There is considerable delay in presentation of NCS cases, both in India (average delay of 3 months in referral centers) and Bangladesh (3.5 months). EHBA comprises a significant proportion of cases of NCS in India (34%) and Bangladesh (25.8%). If treatment of EHBA is delayed beyond the first 90 days of life, the only option thereafter is liver transplantation, which is not presently feasible on a large scale in developing countries. This delay contributes to increase in morbidity and mortality and also to poor outcome in several disorders other than EHBA grouped under NCS.

Why this delay in referral? Babies with NCS by and large look well, feed well, develop normal social smile, giving a false impression of well-being to parents, with the exception of being dressed up in yellow. Other factors contributing to the delay are lack of awareness at the primary and secondary levels of health care to prioritize referral and also lack of clarity in the clinical approach to diagnose the underlying cause. The 1999 Indian “Consensus Report on Neonatal Cholestasis Syndrome” recommended several corrective measures including adoption of a uniform management protocol to improve the outcome of NCS cases in India.

At our institute we initiated an awareness campaign in the state of Uttar Pradesh and adjoining states that form the referral base for our patients. Awareness was imparted through interactive lectures, CMEs, and circulation of NCS consensus brochures. We compared our earlier data (January 1992 to July 1995; period A) with those obtained after the national consensus and during our continued awareness campaign (May 1999 to August 2002, period B; and September 2002 to May 2004, period C). NCS constituted 60, 70 and 68 cases during periods A, B and C, respectively. The number of NCS cases per month steadily increased from 1.5 to 1.8 to 3.2 during the corresponding periods. Mean age at presentation of EHBA to our center also showed a trend to earlier referral (132, 122 and 97 days, respectively). The delay in referral of EHBA cases decreased from 121 days to 107 days to 78 days. These data emphasize a positive impact on earlier referral in EHBA apart from increased frequency of NCS referral.

The Children’s Liver Disease Foundation launched an educational program in the United Kingdom in May 1993 with the help of the Department of Health, to im...
prove the outcome of infantile hepatobiliary diseases. The aim of that campaign was to make certain that all babies who remain jaundiced after 2 weeks of age are tested for conjugated hyperbilirubinemia and referred for timely management. Pilot programs have also been developed in Japan and Taiwan, wherein color cards are given to mothers for early recognition of acholic stools. In India continued efforts are required to achieve the final goal of timely referral. We are shortly launching an “NCS Yellow Alert” poster campaign for creating awareness among referring pediatricians throughout the country. An awareness campaign is urgently required to improve the outcome in Bangladesh and other countries observed to have such a delay in NCS referral.

The management protocol of NCS in developing countries should be cost-effective, quick and appropriate for a given clinical setting. The key point is that babies with conjugated jaundice with or without acholic stools have NCS. Observing stool color on three consecutive days by the doctor is mandatory. This step helps in prioritizing the direction of investigations. Passage of yellow stools after 4 weeks of age almost rules out the possibility of EHBA. We recommend administration of fat-soluble vitamins, particularly vitamin K, as the first step in the treatment of all babies with NCS. NCS babies looking sick (refusal of feeds, irritability, fever, altered sensorium, coagulopathy, abdominal distension, etc.) should be managed promptly, as these are the cases likely to have galactosemia, malaria, intrauterine infections, tyrosinemia and congenital hemochromatosis. NCS babies not looking sick and passing pale stools should undergo ultrasonography to rule out choledochal cyst followed by liver biopsy to diagnose EHBA.

Newer dimensions of genetic cholestatic syndromes have been identified. Alagille syndrome has been linked to the JAG-1 gene on chromosome 20. Three different forms of progressive familial intrahepatic cholestasis have been related to mutations in the hepatocellular transport system genes involved in bile formation. The etiopathogenesis of EHBA is unknown. Phillips and colleagues have described absence of villin (protein and mRNA) in three cases of NCS leading to atresia of extrahepatic ducts.

In summary, there is urgent need to create greater awareness about neonatal cholestasis syndrome in countries where referral is delayed. This effort will salvage a number of infants and may help reduce the infant mortality rates that bother our health-care planners.

Surender K Yachha
Department of Gastroenterology (Pediatric GE), Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 014

References

E-mail: skyachha@sgpgi.ac.in