

## Indian Childhood Cirrhosis – A Forgotten Entity

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The March 1967 issue of *Indian Pediatrics* published four original research articles, amongst which we decided to review a study on Indian Childhood Cirrhosis (ICC) [1]. Through this communication, we present the changes in epidemiology, and new insights into the etiopathogenesis and natural history of ICC over the last 50 years.

### THE PAST

The article by Mohan, *et al.* [1] is a retrospective review of records of 116 cases of ICC from Department of Pediatrics, Maulana Azad Medical College and associated hospitals, New Delhi from August 1965 to September 1966. This study was conducted with the objective to evaluate the role of heredity and other factors in the etiology of ICC. The cases were diagnosed as ICC based on the criteria laid down by the Liver Disease subcommittee of the Indian Council of Medical Research (ICMR) in 1955 [2]. Besides studying the socio-demographic profile of the cases, a detailed assessment of the familial predisposition to ICC was done by interviewing one or more family members and developing pedigree charts.

Of 116 cases of ICC reviewed, 91.6% of children were <3 years with the maximum proportion (58.6%) in the age group 13-24 months. There was a male preponderance (69%), especially in first born; no evidence of a sex-linked inheritance was found. A strong familial incidence (38.8%) was observed among the cases, the commonest being affliction of another sibling. A positive family history from maternal, paternal or both sides were present in 11 (9.5%), 9 (7.8%) and 2 (1.7%) patients, respectively; while in 14 families, successive born children were affected. In addition, a peculiar susceptibility of the disease was noted among the Hindus with maximum proportion in Aggarwal (42.2%), followed by Brahmin (18.1%) and Khatri (14.6%) communities. The cases of ICC were primarily

seen in the upper- and middle-class families. The authors failed to elicit any evidence of past viral hepatitis in the child, mother or family, except in one case. They did not find a hepatotoxic factor (nutritional or environmental) that could possibly be responsible in the etiology of ICC.

The authors considered ICC to be a genetically transmitted metabolic defect with a likely autosomal recessive inheritance. They proposed inheritance as a possible etiological factor for ICC rather than nutritional and toxic factors, based on a strong familial incidence with susceptibility for certain castes.

*Historical background and past knowledge:* The infantile and childhood variety of Cirrhosis was first described by Sen from Bengal in 1887 [3]. Earlier, it was known by the name ‘infantile

cirrhosis’ or ‘infantile biliary cirrhosis’, based on a few clinicopathological accounts of the disease. In 1950s, the disease gained public health importance on account of its high prevalence, unique clinical features and high mortality. The pioneer treatise on the clinicopathological spectrum of the disease was compiled and published by a group of expert panellists constituted under the ICMR in mid-fifties [2]. In 1960, Achar and colleagues from Chennai proposed a change in name to ‘Indian Childhood Cirrhosis’ denoting its affliction in young children rather than infants [4]. The etiology of ICC remained unknown, although the role of a toxic injury to liver was hypothesized.

### THE PRESENT

ICC became recognized as a distinct clinical entity ever since the landmark identification of its peculiar histological feature: hepatocellular injury accompanied with deposition of intracellular Mallory hyaline similar to that observed in alcoholic liver disease [5]. The quest for its etiopathogenesis gained momentum, when excessive deposits of Orcein positive copper (Cu) and copper-binding protein (CuBP) were seen in the liver of index



cases, siblings and close family members [5,6]. ICC is known for being endemic and unique to India, but there are accounts of published case reports of ICC and ICC-like disease in other parts of the world [7,8].

Till the beginning of the 21st century, there existed uncertainty over the etiological role of Cu in the pathogenesis of ICC. Studies suggested the hepatotoxic effect of Cu from either domestic water supply or the diet cooked in Cu-yielding utensils [7-9]. Around this time, the evidence for the causal role of Cu in ICC was questioned in a study by Sethi, *et al.* [10], who reported no use of Cu utensils in 46% of children with ICC. In a yet another study to explore the association of Cu with liver injury, the authors postulated that an unknown external toxic agent catalyzes hepatocyte injury in genetically predisposed individuals for aberrant Cu homeostasis in infancy [11]. A review of the pedigree charts of families of index cases along with the age-matched controls suggested multifactorial inheritance of the disease [12].

A large prospective multicenter study in six centers in India was carried out under the ICMR in 1980's. The results of this research were published nearly two decades later [13]. The authors did not find a significant difference in the use of Cu-yielding utensils among cases with definitive ICC as compared to cases where ICC was ruled out on pooled data analysis. The possible role of an exogenous toxic agent in initiating and perpetuating the hepatocyte injury was suggested instead. The theory behind the toxic insult to the liver originated from the histological presence of Mallory hyaline, which is characteristically observed in cases of toxic injury (like alcohol) to hepatocytes. The authors concluded that Cu deposition is seen as an association with established hepatocyte injury, and hence refuted the role of Cu in triggering ICC. This finding was complemented by epidemiological research from Massachusetts, USA and Germany that failed to find an etiological role of exogenous/dietary Cu (domestic water supply) in incriminating ICC/ICC-like disease [14,15].

Over the last three decades, there has been a sharp fall in the number of ICC cases and ICC-like diseases. The decline in cases can possibly be either due to a true decline in incidence related to sociodemographic and economic growth or the clinicians are probably unaccustomed to diagnose ICC in the present era. The latter can be explained by an epidemiological upward shift in age of presentation of ICC observed over a period of time [16]. Some of the ICC cases presenting late could have been unrecognized because of the diagnosis of cryptogenic liver disease.

Till date, the etiopathogenesis of ICC remains a mystery. The exogenous toxic agent that activates the

hepatocyte injury in genetically predisposed individuals is still obscure. There are no definitive clinical criteria to diagnose ICC, and the diagnosis primarily lies on characteristic histopathological features on liver biopsy.

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