Indian childhood cirrhosis: Several dilemmas resolved

Indian childhood cirrhosis (ICC) is a chronic liver disease in 1-3 yr old children, unique to the Indian sub-continent. The Indian Council of Medical Research (ICMR) in 1983, set up a Multi-centric National Collaborative Study (MNCS) on ICC in six centres, except in Kolkata, its original home, due to total absence of cases for decades! Indeed after the 1980s there have been no cases of ICC any where in India, enhancing the erstwhile mystery. The MNCS Report on ICC1 was released in 2006, just when the disease was on the verge of extinction; in the process, apart from clarification of several longstanding dilemmas, the stage is set for the solution of the only remaining issue about its aetiology.

In October 1887, Boyle Chunder Sen2 presented the first clinical account of this condition, attributing it to some ‘inherited dyscrasia’. In the very next year, Gibbons performed the first autopsy, soon followed by three more. He designated the disease ‘Infantile Biliary Cirrhosis’, due to the presence of proliferated bile ducts, and ascribed it to some ‘endogenous chemical irritant’3 which went unchallenged for over six decades. The detailed autopsy studies revealed several new and unique features4 like ‘Peri-cellular fibrosis’ in the liver, and raised suspicions of ‘congenital syphilis’, but was ruled out on the basis of ‘negative serology’. Since cirrhosis was also accompanied by ‘phlebosclerosis’ of some of the tributaries of the hepatic vein, the causative role of some exogenous ‘plant toxins’ was invoked and a new term ‘Sub-acute toxic cirrhosis’ was introduced4. However in 1954, Bhende and Deoras described the presence of ‘hyaline’ in autopsy liver samples and also designated the condition as ‘Infantile cirrhosis’.

To clarify the prevalent issues about this unique Indian disease, the ICMR constituted an Expert Committee under the Chairmanship of Dr Khanolkar, which proposed the term ‘Infantile cirrhosis’. The presence of hyaline in liver biopsy samples was reinforced6. Incidentally, the current eponym ‘Indian childhood cirrhosis’, was actually introduced in 1957 by Jelliffe, et al7 and it acquired long lease subsequently following Achar et al8.

The ‘toxipathic significance’ of Mallory’s hyaline in liver biopsy samples was glossed over for nearly 15 years. In brief, the WHO classification of cirrhosis reveals that, while the aetiology of ICC is unknown, the morphological picture is one of ‘micro-nodular cirrhosis’, ± for copper, and +ve for Mallory’s hyaline9. Nayak and colleagues10,11 established its identity with “Mallory’s hyaline (MH)” of alcoholic liver disease. Its possible role in the development of ICC as an ‘inclusion criterion’ or a sine qua non of ICC was widely recognized12.

Yet, the pathogenesis, and aetiology of ICC, remained enigmatic, several theories were postulated, such as familial and genetic factors, community and caste-related nutritional deficiencies (vegetarian-ism)13,14, microbial15,16 and viral17,18 infections and suspected toxins10,20. Investigations at Madras (now Chennai) established that successful therapeutic regimens like γ globulin and steroids on ICC patients led to long-term survival as well as improvement of hepatic lesions, as confirmed by repeat biopsies21. However, that ICC might be due to endemic non-A, non-B viral hepatitis, was not substantiated by later studies, employing sensitive techniques to detect hepatitis due to virus infections22. Thus the aetiology remained an open issue.

Towards the end of 1970s, Tanner and associates modified the previous histochemical studies on ICC23, and reported an increase of Orcein +ve stainable hepatic Copper binding protein (CuBP)24. Finally in 1979, a new theory of ‘dietary copper toxicity’, based on elevated levels of hepatic copper, attributed to use of
‘copper yielding utensils’ was proposed\(^2\). Soon, the need to confirm the qualitative histochemical studies by ‘quantitative elemental analyses’ was felt and so the standard Atomic Absorption Spectrometry (AAS) Chemical Analysis was carried out on liver biopsy samples\(^2\). Almost simultaneously, Popper with the help of Delhi group carried out ‘AAS studies on three autopsy samples of ICC\(^2\).\(^6\)\(^7\).

The Delhi group undertook in 1981, a histochemical study on a large and wide range of cases of ICC, their asymptomatic and non-diseased siblings and matched controls, and noted that, unlike regular ICC patients, some of the “siblings” had only mild to moderate increase of hepatic Cu and CuBP. The defective copper homeostasis was not accompanied by any significant organelle damage and seemed to be spontaneously corrected\(^2\).\(^7\). Later Sundaravalli and colleagues at Chennai\(^2\), who had originally contributed to Tanner’s studies, undertook an equally comprehensive study of the copper content of liver, skin, hair and nails of ICC patients, their siblings and normal and disease controls by employing the more reliable quantitative chemo-metric analyses by AAS technique. The changes were only in the liver of established cases of ICC\(^2\).\(^8\).

But, there were genuine doubts whether such changes were the “cause or consequence of the disease”. The MNCS of ICMR set out to clarify all pending issues about the disease. The MNCS was based on comprehensive and mutually agreed objectives as per standardized epidemiological, clinical, laboratory and histopathological proformas. Possible pitfalls in clinical diagnosis were circumvented by strict adherence to a mutually agreed code of pathological classification. Stress was laid on the pivotal role of single or multiple liver biopsies and clinico-pathological follow up.

Based on the large series of 748 cases, not only the early lesion, but the entire spectrum of histopathology of ICC was successfully delineated. The MNCS Report\(^1\) confirmed, with minor variations, most of the earlier epidemiological and clinical features of ICC. The clinical significance of pre-cirrhotic symptom complex (PCSC) advocated by investigators from Mumbai\(^12\) could not be substantiated. In the Madras Centre, a new feature of superimposition of keratomalacia was found in older children with ICC\(^1\).\(^2\).\(^9\). More importantly, the newly invoked theory of ‘dietary copper toxicity’ was found to be virtually untenable. Thus, in four of the six Centres, use of copper yielding utensils was reported in just 10 to 50 per cent of cases categorized as definitive ICC, a frequency not different from that in controls. In the remaining two Centres located in Mumbai, copper yielding utensils were not at all used for cooking and boiling or storing milk for any of the definitive ICC cases. Until they developed the disease, 9 children with definitive or florid ICC were found to be purely breast-fed without any supplementation by milk or weaning diets. All the other stages of ICC were also encountered in the total absence of use of copper yielding utensils for cooking the food of affected children.

In the entire series of 748 cases, Cu and CuBP were positive histologically in 91.4 per cent of definitive ICC (with Mallory’s hyaline), 24 per cent of probable ICC (without Mallory’s hyaline) and 25 per cent of mixed ‘micro-macro nodular cirrhosis’. In the other two earlier stages, with non specific milder changes, Cu positivity was seen in an extremely insignificant percentage of cases. Thereby, the basic issue of ‘dietary copper toxicity’ advocated by Tanner and associates\(^2\)\(^5\) was convincingly disproved.

Yet another fact that emerged from the MNCS Report was the dynamic transitions in liver pathology that often occurred in several cases of ICC. Thus, adjacent biopsies showed variations from a histologically mild to more severe category and vice-versa. There were also transformations amongst the three stages or sub-types of active cell damage and cirrhosis, with or without Mallory hyaline, as well as inactive cirrhosis of the micro nodular cirrhosis (mnc) type. The last type was more often found in older children with longer survival.

After completion of the MNCS work, Sriramachari and associates, undertook fresh quantitative studies in ICC. Chemometric analysis of copper and zinc content of hepatic tissue was carried out by Graphite Furnace AAS technique in 156 biopsy samples (including ten MH +ve cases), drawn from Centres 4 and 6 under their purview. In general, the values of hepatic zinc were higher than that of copper at all stages. Variable degrees of increase of both elements were found to be directly related to the pathological severity of the hepatic lesions, especially the MH +ve state of florid ICC\(^3\).\(^0\). Similar trends were observed in metallothionein immuno-histochemistry\(^3\).\(^1\). The concurrent ‘twin element response’, including non-toxic zinc, appears to represent a metabolic tissue response or consequence. Had ICC been caused by...
dietary copper toxicity, hepatic copper overload should have manifested at the initial stages of the disease, rather than towards the terminal phases.

Lastly, in order to explore the nature of exogenous toxic factors, potential causative agent(s) of ICC, a series of pilot experiments were done on rats and mice fed a diet simulating poor quality Indian vegetarian food, supplemented with domestic ‘post-puerperal therapeutic remedies’ that used to be given to mothers and infants in several Indian communities. Some of these animals have developed hepatic lesions similar to those encountered in different stages of ICC.

In conclusion, apart from bringing clarity to the century-old ICC, several misconceptions and controversies have been resolved. Establishing the early lesion, as well as the broad and dynamic pathological spectrum, with to-and-fro transitions are significant historical contributions by the MNCS. The presence of Mallory hyaline appears to be a late phenomenon, accompanied by accumulation of not only the incriminated Cu, but the non-toxic Zn as well. However, the causative role of Cu has been dispelled. In view of the subsequent disappearance of the disease in the affected castes (and communities), the hypothesis of inherited susceptibility of copper metabolism also does not appear to be valid. Instead, the possible hepato-toxic effects of post-puerperal domestic therapeutic remedies appear to be more plausible. The current efforts at identification of the incriminated compound(s) in specific herbal formulations, by appropriate animal experiment, will resolve the mystery of ICC.

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