Correspondence

Urgent need of experimental model for Indian childhood cirrhosis

Sir,

The century-old Indian Childhood Cirrhosis (ICC) worldwide is known as a disease unique to India. In October 2006, the ICMR released a landmark historical document/publication, based on a Multicentric National Collaborative Study (MNCS) conducted earlier in 1980s, just before it virtually vanished. The Report has indeed clarified several long-pending issues.

Firstly, based on a large series of around 750 cases, including 120 with Multiple Biopsies follow up the MNCS Report successfully delineated the entire histopathological spectrum of ICC. It was shown that a “Cirrhotic triad of lesions”, with or without presence of Mallory hyaline, was indeed preceded by a “Precirrhotic triad”, comprising of the much sought-after “early stages of the disease”. This triad showed transitions from a normal stage through the acute and subacute or chronic phases of non-specific toxic hepatitis.

From the days of discovery of ICC by Sen in 1887, there has been a divergence of views on the nature and causation of the disease. He advocated the theory of “inherited dyscrasia”, whereas Gibbons proposed on a pathological basis, the possible role of “some chemical irritants”. Although based on infrequent autopsies, subsequent pathologists like Green-Armytage (1926) and Radhakrishna Rao (1935) upheld the toxicity theory. Soon after the advent of the era of Liver Biopsy, the Liver Diseases Subcommittee of the Indian Council of Medical Research (ICMR) echoed similar views in its classical report of 1954.

In spite of the rapid progress of clinical and experimental medical research in India during the last century, the aetiology of ICC remained an enigma. In the past, there were several speculations as to the aetiology of ICC, notably the following: (i) Ethnic or racial; (ii) Familial; genetic or nutritional due to vegetarianism; (iii) Infections, bacterial or viral; (iv) Toxic factors like castor oil, dietary copper toxicity of culinary or ecogenic origin, etc.

The MNCS clearly ruled out any viral aetiology, and supported the erstwhile theory of sub-acute toxic cirrhosis. The epidemiological data failed to substantiate the theory of dietary copper toxicity, in both the early pre-cirrhotic phases as well as the later triad of cirrhotic phases of ICC. On the contrary, the pathological data revealed that there was elevated hepatic copper only in the late or advanced stages, suggestive of a tissue response or consequence, rather than initiating the disease. Subsequent chemometric studies on material from two of the Centres confirmed increased hepatic copper accompanied by much higher levels of non-toxic Zn. Immuno-histochemical demonstration of metallothionein provided further proof of intracellular accumulation of bivalent cations, especially Cu and even Zn. Thus the MNCS concluded that the then prevalent theory of dietary copper toxicity, propagated by Tanner and the Pune Group, was not tenable.

It is indeed unfortunate, that no attempts were ever made to explore other potential causes of toxic cirrhosis. It is strange and inexplicable that no formal inquiries seem to have been made about the several indigenous or regional domestic therapeutic remedies, commonly used in Indian homes during the last trimester of pregnancy, childbirth and post-puerperal/neonatal periods and during lactation, which often extended into the subsequent pregnancy. Similarly, the possible risks due to indigenous herbals such as galactagogues, emmenagogues, and abortifacients/ecbolics for the mother and antipyretics, antispasmodics/laxatives, expectorants and anthelmintics to the child during...
infancy and early childhood, could also have been examined.

While completing the MNCS project-related work in the late 1980’s, I was intrigued by the rapid transformations in the nature and course of ICC over the last five decades in different parts of India, starting with Kolkata, West Bengal. Perhaps, rapid changeover in key socio-cultural customs and practices promoted the rapid decline, if not extinction of ICC. Every effort should be made to resolve the baffling issues related to the enigma of aetiopathogenesis of ICC. Amongst the above mentioned indigenous ‘Ayurvedic & Siddha medicines’ which are frequently used during maternity, infancy and early childhood might be potentially toxic. Thus, they could be useful in the development of an experimental model of ICC.

With this objective, all the available information on the cumulative effects of the foregoing toxipathic herbs and reduced intake of hepatotrophic factors was reviewed. Issues related to inadequate breast feeding and/or ‘humanized cow’s milk’, achieved by unacceptable dilution of cow’s milk, and other adverse domestic practices were critically examined. Accordingly, a series of experiments were conducted on relatively young laboratory rats and mice. They were maintained for a few weeks or months on 3-5 per cent low protein diets, combined with potentially toxic drugs. Initial trials were conducted with the following herbs: ginger, kalajeera, Asafoetida (Hing) and garlic rich in polysulphides and/or selenium, katha with polyphenols, and alkaloids of Vayuvidanga (Embelia ribes) and Chitramoolum (Plumbago zeylanica) and Tankanam (Borax). Several of them produced interesting “unit lesions”, usually seen in Vayuvidanga (available at http://www.icmr.nic.in/) inclusive of its local variants (Abies webbiana, as well as Taxus wellichiana). All of them were employed in indigenous paediatric practice in regions where ICC was prevalent. Also recent evidence about drug induced liver disease (DILD) suggests that several of these have potential antimicrotubular effects. Later on it may be worthwhile to complement the results with in vivo studies on hepatic cell lines.

Initially the adverse effects of single drugs would be established, followed by appropriate combinations, analogous to “Kayam and Sowbhagyasonthi”, popular indigenous herbal formulations of the past.

It is hoped that such concerted efforts would enable not only the development of a proper experimental model of ICC, but open new vistas of indigenous drugs, with wider applications.

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References


19. Satyanarayana Sarma E. a) Diseases of Childhood, Srikakulam (India), 1929 b) Advice to the pregnant woman, Srikakulam (India), 1952.