We have envisioned this section with the purpose of taking the present day reader back in time. Each month, we plan to select an article that was published in *Indian Pediatrics* exactly 50 years ago, and would still be of interest to pediatricians of today. After summarizing the salient features reported by the authors, the current perspective shall be discussed. It should be interesting to see how scientific knowledge has evolved over these years, and humbling to realize how our colleagues managed with the limited diagnostic and therapeutic options available in that era. I hope that our readers will find the series interesting. We would welcome any comments; these may be directly communicated to the author, or to the journal office at *jiap@nic.in.*

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Cryptococcal Meningoencephalitis – A Tale of 50 Years

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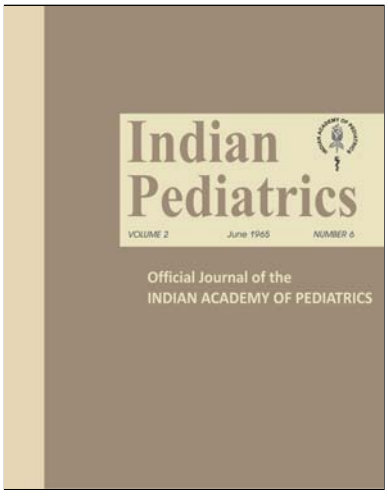
In 1965, the second year of its existence, the June issue of *Indian Pediatrics* comprised of 43 pages, and had only six articles. These were: a clinical study cum review of cerebral palsy, a brief review of pyuria in children, and case reports (named as 'case records') on cryptococcal meningoencephalitis, acute intermittent porphyria and diastematomyelia. A report of the 2nd Afro-Asian Congress of Pediatrics and current literature (consisting of interesting abstracts) was also included.



THE PAST

We shall review the case of cryptococcal meningoencephalitis reported by Krupanidhi and Rao [1] from Mysore Medical College, India.

Case report: A 3-year-old boy presented with inability to walk and frontal headache for a week. He had a history of a short febrile illness with rashes three weeks previously, which was presumed to be chicken pox. At presentation, he was febrile with scabs on his face and limbs. Sensorium, cranial nerves and fundus were normal. The lower limbs were flaccid with depressed deep tendon reflexes and negative Babinski's sign. Moderate neck stiffness was present. There were no other salient clinical findings. A presumptive clinical diagnosis of Varicella lymphocytic chorio-meningitis with myelitis was kept, and he was started on tetracycline and prednisolone. Further investigations revealed a total leukocyte count of 22,000/mm^3 with a differential of 72 polymorphonuclear cells, 20 lymphocytes and 8 monocytes. Right lower zone patchy opacities were found on the chest *X*-ray. The cerebrospinal fluid (CSF) was under increased pressure and appeared turbid. There were 380 lymphocytes/mm^3; the glucose and protein levels were 25 mg/dL and 80 mg/dL, respectively. A wet mount revealed yeast like cells staining positive on India ink preparation. Sabarouds dextrose agar culture media grew budding cryptococci. Bone marrow aspiration was normal. Hematological malignancy, tuberculosis and syphilis were ruled out by absence of abnormal cells in bone marrow and negative Tuberculin and Wassermann's tests, respectively. Once cryptococcal meningoencephalitis was established, steroids were withheld, and crystalline penicillin and sulphadiazine were given for an unspecified period. There was gradual improvement with the child becoming ambulatory with support by 5 weeks. Subsequently, he was lost to follow-up. The authors recommended that a CSF wet mount examination with India ink should be routinely performed in any suspected chronic meningitis as cryptococcal meningoencephalitis was not as rare as generally believed.

Historical background and past knowledge: The first few patients with cryptococcal disease (retrospectively recognized) started being reported around 1891. The organism was isolated by San Felice in 1894, and named Saccharomyces. After the absence of ascospores was pointed out by Vuillemir in 1901, it was renamed Cryptococcus. Cryptococcal meningo-encephalitis was independently described by von Hansemann from Germany and Stoddard and Cutler in America around 1914. The organism was called *Torula histolytica* and the disease 'Torulosis' in USA while in Europe it was referred

to as European blastomycoses. Finally in 1935, a comprehensive study by Benham lead to identification of *Cryptococcus hominis* based on morphology, fermentation and serological studies, and it was concluded that all the organisms mentioned above were the same. Cryptococcus was introduced into microbiology textbooks in 1956.

The clinical manifestations of cryptococcal infection recognized in the 1960s were: dermatological (rashes), neurological (meningoencephalitis and myelitis) and bony. The association of cryptococcal meningoencephalitis with lymphoblastomas, leukemias and sarcoidosis was known. At that time, the modalities of identification were isolation of the typical mucoid colonies in agar culture and demonstration of the organism on wet mounts of emulsified pus, sputum, CSF sediment or colony growths prepared with India ink [2]. Treatment was with Sulfapyrine and Sulfadiazine [3]. Amphotericin B had just successfully completed 'clinical trials', and was reserved as a second-line drug. In India, penicillin, sulphonamides, streptothricin (an antibiotic derived from actinomyces) and Actidione (an antibiotic derived from streptomyces) was being used, although outcomes were uncertain. The prognosis was bad with 80% mortality within the first year, and a waxing and waning course in the survivors.

THE PRESENT

Over the last six decades, the awareness of this disease has been progressively increasing due to increasing numbers of immunodeficient patients resulting from chemotherapy, organ transplants and Acquired Immune Deficiency Syndrome (AIDS). Simultaneously, there have been major advances in the understanding of the organism, its pathogenesis, disease manifestations, detection and management. It is now known that Cryptococcus spreads via inhalation of airborne spores originating from the soil and pigeon excreta. There are three human pathogens, including the recently discovered *C. laurentii* that affects premature babies [4]. Its virulence arises from its ability to grow at 37 °C, the protective polysaccharide capsule and the ability to synthesize melanin which is protective against host oxidative reactions.

The clinical manifestations and pathogenesis in immunocompetent and immunocompromised patients is now well described. Its neurotropism is hypothesized to result from its abilities to cross the blood brain barrier in infected host cells and utilize catecholamines (neurotransmitters) to synthesize melanin. The most common central nervous system presentation is sub-acute or chronic meningoencephalitis. Spinal cord involvement is extremely rare. Apart from this child, only a few case reports of adults presenting with acute flaccid paralysis in cryptococcal infection were found on a literature search [5,6]. The diagnosis of cryptococcal meningoencephalitis is still essentially by lumbar puncture. Demonstration of the organisms by India ink preparation in CSF has low (40-80%) diagnostic yield. Detection of the polysaccharide antigen in CSF has high (>90%) sensitivity and specificity, and it can be detected in the early asymptomatic stages before CSF abnormalities become apparent. This method is also used in serum for screening AIDS patients for potential meningoencephalitis. The organism can be identified in histopathological specimens with mucicarmine and alcian blue stains.

Treatment strategies vary according to immune status and site. The current strategy is to use a sequential combination of anti-fungal drugs [7]. In CNS disease, rapid CSF sterilization in achieved in the induction phase with amphotericin B and flucytosine for 2-10 weeks, followed by consolidation with oral flucanozole for 6-12 months, which is effective once the fungal load is reduced. In non-HIV patients, maintenance therapy is considered only if immunosuppression persists, whereas in children with AIDS, maintenance is continued lifelong to prevent relapses. The prognosis has definitely improved significantly since 1965. The current mortality rate is 15-30%, with higher rates in HIV infection.

To conclude, we reiterate the authors' opinion that cryptococcal meningoencephalitis should be considered in any child with subacute or chronic meningoencephalitis of indeterminate origin, irrespective of immune status.

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