The Indian Journal of Pediatrics (January 2019) 86(1):49–51
https://doi.org/10.1007/s12098-018-2745-6

EDITORIAL

Central Nervous System Infections in Children: An Ongoing Challenge!

Pratibha Singhi[1]

Received: 29 June 2018 / Accepted: 2 July 2018 / Published online: 22 August 2018
© Dr. K C Chaudhuri Foundation 2018

Central nervous system (CNS) infections are an important cause of morbidity and mortality in children. Estimated incidence of acute encephalitis syndrome in children is 10.5–13.8/100000 [1]. The case fatality rate is 30% and neurological disabilities occur in one–third of survivors [2]. Global burden of disease network (WHO) estimated that in 2010 meningitis caused approximately 422,900 deaths and encephalitis, 143,500 deaths [3].

Almost all organisms can infect the CNS; however there are distinct etiological differences in various geographical regions and in different seasons. Some pathogens are endemic, others sporadic and yet others cause epidemics. Hence the precise epidemiology of CNS infections is difficult to determine; also in many cases there are difficulties in determining an exact microbiological diagnosis particularly in resource limited countries. A recent multinational study of community acquired CNS infections found that 8.8% people died, and 18.5% were left with sequelae [4]. The most frequent infecting pathogens in this study were *Streptococcus pneumoniae* (8%) and *Mycobacterium tuberculosis* (5.9%). The study cannot be generalized globally.

The common organisms that cause childhood meningitis are *N. meningitidis*. *H. influenzae B* (Hib) and *S. pneumoniae*. Worldwide, the incidence of meningitis due to *N. meningitidis* is highest in the "meningitis belt" of sub-Saharan Africa. Around 30,000 cases are still reported each year from that area [5]. If untreated, meningococcal meningitis is fatal in 50% of cases and may result in brain damage, hearing loss or disability in 10 to 20% of survivors. The estimated incidence rate of meningitis due to Hib is 31 cases per 100,000 [6] and that due to *S. pneumoniae* is 17 cases per 100,000 population in children less than 5y of age [7]. These proportions are however changing after the widespread use of vaccinations in many parts of the world.

✉ Pratibha Singhi
doctorpratibhasinghi@gmail.com

[1] Director Pediatric Neurology and Neurodevelopment, Medanta, The Medicity, Gurgaon, Haryana, India

Several viruses can cause CNS infections in sporadic, endemic, epidemic, or pandemic patterns. The pattern can change over time, such as epidemic to endemic. Japanese encephalitis virus (JEV) is the most important cause of viral encephalitis in Asia; it primarily affects children. Nearly 68,000 clinical cases of JE occur globally each year, with approximately 13,600 to 20,400 deaths. Most JEV infections are mild (fever and headache) or without apparent symptoms, but approximately 1 in 250 infections results in severe clinical illnesses. The case-fatality rate among those with encephalitis can be as high as 30%. Permanent neurologic or behavioral sequelae can occur in 30%–50% of those with encephalitis [8]. Herpes simplex virus (HSV) is the commonest cause of sporadic encephalitis, and a common cause of fatal encephalitis and meningoencephalitis worldwide. In 2012, an estimated 3.7 billion people under the age of 50, or 67% of the population, had HSV-1 infection [9]. In tropical countries, scrub typhus, dengue and salmonella are also important causes of meningo-encephalitis [10].

Neurocysticercosis (NCC) and malaria are the most common parasitic infections of the CNS. NCC caused by larval cysts of *T. solium*, is the commonest cause of acquired epilepsy in India [11]. In 2015, the WHO Foodborne Disease Burden Epidemiology Reference Group identified *T. solium* as a leading cause of deaths from food-borne diseases, resulting in a considerable total of 2.8 million disability-adjusted life-years (DALYs).

The total number of people suffering from neurocysticercosis, including symptomatic and asymptomatic cases, is estimated to be between 2.56–8.30 million [12]. NCC is endemic in areas of Latin America, Asia, and sub-Saharan Africa; however it is seen throughout the world because of global travel. The article by Singhi and Saini [13] provides a comprehensive review on NCC including the mode of transmission, the various clinical manifestations and the current evidence based management of childhood NCC. Cerebral malaria is common in sub Saharan Africa and in some parts of Asia. In 2016, there were 216 million cases of malaria with 445,000 deaths [14]. In endemic areas, cerebral malaria commonly affects children between 6 mo and 5 y of age.

Fungal infections of the CNS, their diagnosis and treatment have been discussed by Singhi and Saini [15]. Fungal infections occur usually in immunocompromised children (Candida, Aspergillus, Zygomycetes, Trichosporon spp) but at times in immunocompetent children as well (Cryptococcus, Coccidioides, Histoplasma, Blastomyces, Sporothrix sp). The main etiologies include Aspergillus, Cryptococcus, Candida, Mucorales, dematiaceous molds, and dimorphic endemic fungi.

The clinical presentation of CNS infections, especially in younger children is often nonspecific and requires a high index of suspicion and a syndromic approach. Most cases present with an acute meningoencephalitic syndrome secondary to acute bacterial or viral meningitis or encephalitis. As compared to bacterial meningitis, patients with viral encephalitis are more likely to present with rapid alteration in consciousness or new onset seizures. A practical approach to the diagnosis and management of acute encephalitis is provided in the article by Aneja and Sharma [16]. Some children present with a subacute or chronic meningitic syndrome wherein tubercular, fungal and parasitic meningitis need to be considered. There are no pathognomonic symptoms and signs of fungal CNS infections; most children present with chronic meningitis or meningoencephalitis.

Singhi and Angurana have discussed in detail the various modalities available to the clinician for the diagnosis of CNS infections [17]. Examination of the cerebrospinal fluid (CSF) provides important diagnostic information. While there are several CSF parameters that may help distinguish bacterial from viral infections, most of these are not diagnostic per se. CSF cultures have a poor yield especially in resource limited countries where children have often received antibiotics before meningitis is suspected. The increasing availability of point of care diagnostic modalities and multiplex PCRs comprising of panels that include both bacteria and viruses is extremely helpful in such cases. If done properly, most of these tests are reasonably sensitive and specific and provide a diagnosis within a few hours. Neuroimaging, especially MRI can provide important etiological clues in suspected encephalitis as certain viruses have specific patterns of involvement of the brain. In cases of bacterial infections, neuroimaging is helpful in early detection of the complications of bacterial meningitis and for the diagnosis of focal suppurative infections; these aspects have been discussed in the article by Suthar and Sankhyan [18]. Availability of magnetic resonance spectrometry (MRS) and advanced neuroimaging sequences have helped in further etiological differentiation of CNS infections such as pyogenic *vs*. tubercular or fungal. Autoimmune encephalitis is being increasingly recognised as an important differential diagnosis of infectious encephalitis and should be investigated for if there are clinical clues, particularly if the MRI brain is normal and the multiplex polymerase chain reaction (PCR) for organisms causing meningoencephalitis is negative.

Rapid diagnosis, early initiation of antimicrobial therapy, urgent control of life-threatening issues such as raised intracranial pressure and status epilepticus and appropriate supportive and adjunctive therapy are crucial for improving the outcome of CNS infections [19]. These aspects have been detailed in the article by Singhi and Angurana [17]. Empiric antibiotic therapy should be started in children with acute bacterial meningitis pending a definitive etiologic diagnosis. In cases with an encephalitic picture, acyclovir is started until a definite etiological organism is identified. It should be remembered that PCR for herpes simplex may be false negative in the first 72 h and should be repeated if Herpes simplex virus (HSV) is strongly suspected. As emphasized in the article by Singhi and Saini, in endemic areas, any child presenting with fever and altered sensorium should be investigated and treated for cerebral malaria [15].

Better understanding of fluid therapy has changed the practice of the traditionally recommended fluid restriction in all cases of acute meningoencephalitis. It is now recognized that optimization of cerebral perfusion pressure by maintaining normovolemia and keeping the blood pressure around the 90th centile is associated with a better outcome [20]. Hypertonic saline is preferred to mannitol for the control of raised ICP in traumatic brain injury [21]. Our data have shown similar results in children with CNS infections (unpublished data).

CNS infections are the commonest cause of refractory status epilepticus in most resource-limited countries and control of seizures can be challenging. Valproate infusion has been shown to successfully control seizures without causing respiratory depression or hypotension [22]. IV Levetiracetam is increasingly being used for acute control of status epilepticus [23] particularly in cases where valproate cannot be used.

Almost all CNS infections are preventable. Vaccines are the cornerstone of prevention and control of bacterial meningitis and their widespread use has markedly decreased the incidence of Hib and pneumococcal meningitis in countries where they are part of universal immunization program. Since 2010, the use of a meningococcal A conjugate vaccine through mass preventive immunization campaigns in the meningitis belt, the proportion of the meningococcus A serogroup has declined dramatically. In May 2018 the WHO introduced "Defeating meningitis by 2030" for WHO immunization activities on the African continent [24].

The prevention of NCC requires large scale water and sanitation measures and improved animal husbandry. A new vaccine (Cysvax®) for the prevention of cysticercosis in pigs has been recently (2016) licensed in India [25]. Oxfendazole administration to pigs can control the cystic stage of the parasite in pigs, and thus break the life-cycle of the tapeworm that is transmitted to humans. The WHO is collaborating with other international agencies to find the most effective strategies for controlling taeniasis and NCC on a global scale [25].

With active efforts directed at prevention, and also at improvements in the accessibility and efficiency of point of care diagnostic services, particularly in resource-limited settings [26] it is hoped that at least some reduction in the burden of CNS infections, as well as improvements in health outcomes can be anticipated in the coming years.

Compliance with Ethical Standards

Conflict of Interest None.

References

1. Jmor F, Emsley HC, Fischer M, Solomon T, Lewthwaite P. The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. Virol J. 2008;5:134.
2. Centers for Disease Control and Prevention (CDC). Expanding poliomyelitis and measles surveillance networks to establish surveillance for acute meningitis and encephalitis syndromes–Bangladesh, China, and India, 2006-2008. MMWR Morb Mortal Wkly Rep. 2012;61:1008–11.
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380:2095–128.
4. Erdem H, Inan A, Guven E, et al. The burden and epidemiology of community-acquired central nervous system infections: a multinational study. Eur J Clin Microbiol Infect Dis. 2017;36:1595–611.
5. WHO Meningococcal meningitis. Factsheet 19 February 2018. Available at: http://www.who.int/news-room/fact-sheets/detail/meningococcal-meningitis. Accessed on 17th June 2018.
6. Watt JP, Wolfson LJ, O'Brien KL, et al. Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. Lancet. 2009;374:903–11.
7. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet. 2009;374:893–902.
8. WHO Japanese-encephalitis. Fact Sheet 31 December 2015. Available at: http://www.who.int/news-room/fact-sheets/detail/japanese-encephalitis. Accessed on 17th June 2018.
9. WHO. Herpes simplex virus 31 January 2017. Available at: http://www.who.int/news-room/fact-sheets/detail/herpes-simplex-virus. Accessed on 17th June 2018.
10. Singhi S, Chaudhary D, Varghese GM, et al; the Indian Society of Critical Care Medicine Tropical Fever Group. Tropical fevers: management guidelines. Indian J Crit Care Med. 2014;18:62–9.
11. Singhi S, Singhi PD. Clinical profile and etiology of partial seizures in north Indian infants and children. J Epilepsy. 1997;10:32–6.
12. WHO. Taeniasis/cysticercosis. 15 February 2018. Available at: http://www.who.int/en/news-room/fact-sheets/detail/taeniasis-cysticercosis. Accessed on 17th June 2018.
13. Singhi P, Saini AG. Pediatric neurocysticercosis. Indian J Pediatr. 2018; https://doi.org/10.1007/s12098-017-2460-8.
14. WHO. Malaria fact sheet. 20 April 2018. Available at: http://www.who.int/news-room/fact-sheets/detail/malaria. Accessed on 17th June 2018.
15. Singhi P, Saini AG. Fungal and parasitic CNS infections. Indian J Pediatr. 2018; https://doi.org/10.1007/s12098-017-2487-x.
16. Aneja S, Sharma S. Diagnosis and management of acute encephalitis in children. Indian J Pediatr. 2018; https://doi.org/10.1007/s12098-018-2775-0.
17. Singhi S, Angurana SK. Principles of management of central nervous system infections. Indian J Pediatr. 2018; https://doi.org/10.1007/s12098-017-2583-y.
18. Suthar R, Sankhyan N. Bacterial infections of the central nervous system. Indian J Pediatr. 2018; https://doi.org/10.1007/s12098-017-2477-z.
19. Singhi S. Principles of management of CNS infections. In: Singhi P, Griffin DE, Newton C, editors. Central nervous system infections in childhood. London: Mac Keith Press; 2014. p. 20–39.
20. Kumar R, Singhi S, Singhi P, et al. Randomized controlled trial comparing cerebral perfusion pressure-targeted therapy versus intracranial pressure-targeted therapy for raised intracranial pressure due to acute CNS infections in children. Crit Care Med. 2014;42:1775–87.
21. Li M, Chen T, Chen SD, Cai J, Hu YH. Comparison of equimolar doses of mannitol and hypertonic saline for the treatment of elevated intracranial pressure after traumatic brain injury: a systematic review and meta-analysis. Medicine (Baltimore). 2015;e736:94.
22. Mehta V, Singhi P, Singhi S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children - a randomized controlled trial. J Child Neurol. 2007;22:1191–7.
23. Zaccara G, Giorgi FS, Amantini A, et al. Why we prefer levetiracetam over phenytoin for treatment of status epilepticus. Acta Neurol Scand. 2018;137:618–22.
24. WHO Emergencies. Meningococcal meningitis. Available at: http://www.who.int/emergencies/diseases/meningitis/en/. Accessed on 17th June 2018.
25. WHO. Neglected tropical diseases. First ever licensed vaccine and antihelmintic against the major cause of epilepsy in the developing world. Available at: http://www.who.int/neglected_diseases/news/First-licensed-vaccine-and-anthelmintic-against-epilepsy/en/. Accessed on 17th June 2018.
26. Kuupiel D, Bawontuo V, Mashamba-Thompson TP. Improving the accessibility and efficiency of point-of-care diagnostics services in low- and middle-income countries: lean and agile supply chain management. Diagnostics. 2017;7:1–14.