Neurology Asia 2019; 24(3) : 235 – 242

Neurologic outcome of Filipino children diagnosed with central nervous system infection

[1]Aida M. Salonga *MD*, [1]Peter Francis Raguindin *MD MSc*, [2]Mishelle H. Imperial *MD*, [2]Marilyn H. Ortiz *MD*, [3]Martha L. Bolaños *MD*, [4]Maria Lourdes M. Trajano *MD*, [5]Madeleine Grace M. Sosa *MD*, [6]Bernadette Chua-Macrohon, [7]Jo Janette R. de la Calzada *MD*, [8]Maria Lourdes E. Amarillo *MPH*

[1]Institute of Child Health and Human Development, National Institutes of Health-University of the Philippines Manila; [2]Child Neurosciences Center, Philippine Children's Medical Center; [3]Department of Neurosciences, Philippine General Hospital, University of the Philippines Manila; [4]Baguio General Hospital and Medical Center; [5]De La Salle University Medical Center, De La Salle Health Sciences Institute; [6]Zamboanga City Medical Center; [7]Cebu Doctors University Hospital; [8]Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila, Philippines

Abstract

Background: Neurologic infections are related to chronic and life-long neurologic impairment. We aim to describe the outcomes of Filipino children with neurologic infections upon, and within one year from discharge. This data will be useful in developing programs for the prevention and improvement of outcomes in children with neurologic infections. *Methods:* This is a multicenter, cross-sectional, retrospective cohort study at six tertiary hospitals across the Philippines within four years (2007-2010). A standardized report form was used to collect clinical profile and outcome using inpatient and outpatient records. Neurologic outcome was classified and staged at 3-, 6-, 9- and 12-months post-discharge. *Results:* A total of 480 patients were included in the analysis (mean age 4.7 ± 5.3 y), most were bacterial in etiology (275 cases, or 57.3%). Severity of illness on admission (Stage 3, $p < 0.001$) and etiologic agent (viral, $p < 0.001$) were correlated with poor neurologic outcome on discharge. Of the 154 patients that had follow-up, 91 cases were observed to have neurologic deficits (severe, 50; moderate, 29; and mild 12). Twenty patients had improvement of neurologic impairment on subsequent follow-up. Motor deficits (64 cases), cognitive disorders (26 cases) and seizures (17 cases) are the most common neurologic sequela.
Conclusion: Outcomes of neurologic infections in children are dynamic. Close monitoring of the neurodevelopmental status after treatment is recommended to institute early intervention and rehabilitation programs that can modify the long-term outcome for children.

Keywords: Meningitis, neurologic outcome, developmental delay

INTRODUCTION

Central Nervous System Infections (CNSI) are among the most serious and potentially fatal infections affecting infants and children.[1,2] These are associated with high rates of acute complications and long-term neurological sequelae. A multitude of pathogens can invade the CNS, depending on various factors such as the prevalence of the pathogens in the environment, their virulence and neurotropism, and the patient's age and immune status.[3] The extent of involvement can range from focal lesions, such as abscess, granuloma or infarct, or to a more diffuse involvement of the meninges, brain, or spinal cord. Presence of etiologic agent or inflammatory reactions within the area causes neuronal injury that explains the impairment from the infection. In contrast with adult neurologic infections, pediatric patients are unique as they have a higher capability for neurogenesis leading to better structural repair. They are also able to entrain other neurons to take over functions of lost neurons.[3,4]

The understanding of the epidemiology and pathophysiology of CNSI has tremendously increased over several decades, leading to

Address correspondence to: Aida M. Salonga, MD, Institute of Child Health and Human Development, National Institutes of Health – University of the Philippines Manila, 112 G/F National Institutes of Health Bldg., 623 Pedro Gil Street, Ermita 1000 Manila, Philippines. Tel: (632) 254-5205, Email: aida.salonga@yahoo.com

improved treatment regimens, more accurate diagnostic tests, and prophylactic vaccines that led to changes in the epidemiology of the disease.[1-3,5] However, there are limited data on the neurological sequelae among Filipino children. Increased understanding of the acute and long-term complications of CNS infections will help shape the approach to the management of CNSI and consequently, improve the neurologic outcome.

METHODS

This is a retrospective cross-sectional study conducted in six major tertiary hospitals across different regions in the country with attending pediatric neurologists. This study was approved by the UP Manila Review Ethics Board (UPMREB). We aim to describe the neurological outcome of pediatric patients, aged 0 to <18 years old, diagnosed with CNSI. We identified patients for inclusion using outpatient consult and hospital admission logbooks, medical records, and hospital registries from January 1, 2007, to December 31, 2010. Patients were identified using ICD-10 codes for CNSI (G00-G09) or a primary discharge diagnosis of bacterial, viral or tuberculous CNS infections. The following data were collected from inpatient and outpatient records: age, sex, duration of hospital stay, presenting signs and symptoms, duration of symptoms, clinical diagnosis, laboratory findings, onset of treatment, clinical stage of the disease, fatality during hospital stay and severity of sequelae on follow-up. A uniform data collection form was used by the participating centers and was accomplished by respective pediatric neurologists and neurology fellows-in-training. Patients' records were subsequently reviewed for re-classification of functional status on outpatient visits at 3-, 6-, 9-, and 12-month follow-up period. Patients with no follow-up were excluded from the analysis of neurologic outcomes.

Cases were determined based on clinical features, laboratory examinations, and neuroimaging studies. The severity of illness was assessed using the British Medical Research Council (BMRC)[6] staging as evaluated by the respective center's pediatric neurologist (Table 1). A separate scale was used to determine the severity of neurologic sequelae upon discharge based on functional status.[7] (Table 1)

The pediatric neurologists and neurology fellows-in-training documented the neurologic sequelae, and classified as mild, moderate, and severe. Findings under mild neurologic sequelae include mild hemiparesis, mild cranial nerve palsies, mild speech difficulties, and hyperactivity. Findings associated with moderate neurologic sequelae were hemiplegia, moderate cranial nerve palsies, epilepsy, spasticity, gait abnormality, coordination problems, and dysphagia, but with borderline mental function. Having an intellectual disability, severe cranial nerve palsies, quadriplegia and/or severe motor handicap, decorticate posturing, hearing loss, visual impairment, motor and language delay were the findings in severe neurologic sequelae.

Neurologic deficits were also classified according to the functional domain of the deficits, namely, motor, hearing, visual, cognitive, behavioral deficits, and seizure disorder.

STATA® (StataCorp, Texas)[8] was used for all statistical analysis. Percentage and confidence intervals per etiology were computed. Multiple logistic regression analysis was used to correlate categorical variables such as clinical profile, imaging results, etiology, demographic data and severity scale on admission in relation to neurologic outcome on discharge. A p-value of ≤ 0.05 was considered to be statistically significant. The burden of unfavorable neurologic outcome infection among pediatric CNSI was also described by computing for case fatality rate.

Table 1: Severity grading used in the classification of cases for the retrospective review

A. British Medical Research Council staging (for severity of illness on admission)
   a. Stage 1 – nonspecific symptoms, fully conscious, does not have any neurologic signs,
   b. Stage 2 – confused, signs of meningitis, cranial nerve palsies, and
   c. Stage 3 – stupor or comatose, systemic toxicity, with more severe neurologic signs.

B. Classification of neurologic outcome on discharge
   a. Category I – completely recovered
   b. Category II – mild neurologic deficit
   c. Category III – moderate and severe neurologic deficit
   d. Category IV – died

RESULTS

A total of 480 patients were included in the analysis (Table 2). Mean age at diagnosis was at 4.7 years old (std. dev. ± 5.3 y). Most of the cases were bacterial in etiology (57.3% or 275 cases). Upon discharge, most cases had a mild impairment (50.0% or 240 cases). There were 62 cases (12.9%) of mortality, and the remaining cases (37.1% or 178 cases) had moderate-severe neurologic sequela.

Upon hospital admission, the factors that were observed to be correlated with an adverse outcome upon discharge were clinical stage on admission (Stage 3, p <0.001) and causative agent (viral etiology, p <0.001). The stage and etiology of the disease of the patients were found to be significantly associated with the outcome at discharge using multivariate regression analysis (Table 3). The odds of having category III (moderate) or IV (severe) outcomes among patients who had stage 2 disease were 2.7 times more than those who had stage 1 disease.

Of the 154 patients' records with clinic follow-ups, 91 patients were observed to have neurologic deficits (severe 50 patients; moderate 29 patients; and mild 12 patients). Within 3-month follow-up period, three patients were observed to have a progression of neurologic sequela. One of which is a six-month-old baby with bacterial meningitis who was discharged without neurologic deficits, but developed a motor impairment on follow-up. Additional cases were a two-, and a seven-year-old children with mild deficits on discharge, who progressed to severe impairment with motor

Table 2: Demographic and clinical profile of patients (n=480)

Age, mean ± sd, years	4.7 ± 5.3
Sex, n (%), male	260 (54.2)
Place of origin	
Urban, n (%)	392 (81.7)
Rural, n (%)	88 (18.3)
Immunization status*	
Complete, n (%)	18 (3.8)
Incomplete, n (%)	410 (85.4)
None, n (%)	29 (6.0)
Unrecalled, n (%)	23 (4.8)
Duration of symptoms	
1 week	258 (53.8)
2 weeks	88 (18.3)
3 weeks	39 (8.1)
≥ 4 weeks	78 (16.2)
No information	17 (3.5)
Severity Scale on Admission	
Mild, n (%)	134 (27.9)
Moderate, n (%)	271 (56.5)
Severe, n (%)	75 (15.6)
Etiologic Agent	
Bacterial, n (%)	275 (57.3)
Viral, n (%)	108 (22.5)
Tuberculous, n (%)	91 (18.9)
Undetermined, n (%)	6 (1.3)
Severity Scale on Discharge	
Mild, n (%)	240 (50.0)
Moderate n (%)	75 (15.6)
Severe, n (%)	103 (21.5)
Death, n (%)	62 (12.9)

*EPI, Expanded Program for Immunization in the Philippines consists of BCG1, HepB3, DTwP3, OPV3, MCV1, ascertained by records or by history (caregiver/parent recall)

Table 3: Multivariate logistic regression analysis showing association of admission features with discharge outcomes of patients

Variables	Odds ratio	Z	*p*-value
Age of onset			
>1 mo – 3 yrs	0.75	-0.56	0.579
>3 yrs – 6 yrs	0.82	-0.28	0.778
>6 yrs	0.47	-1.28	0.201
Causative agent			
Viral	4.35	3.64	<0.001
TB	2.79	2.65	0.008
Stage on admission			
Stage 2	2.74	2.68	0.007
Stage 3	14.675	5.58	<0.001
Neuroimaging results			
Abscess	2.82	2.11	0.035
Infarct	3.01	2.08	0.037
Meningeal enhancement	2.11	2.01	0.044

and language delay on follow-up. On the other hand, half of the patients discharged with severe neurologic sequela had improvement in their neurologic status.

At one year follow-up, nine patients were observed to have a progression of impairment; seven of which were discharged with full recovery but were re-assessed to have severe impairment on follow-up. Two patients–with mild deficits on discharge, and were observed to have severe deficits on follow-up (i.e., motor delay, language delay, and epilepsy). The changes in the severity grading on 6-, and 9-month follow-up were minimal, with the majority of patients retaining the initial severity grade. A significant number of patients with changes in severity grading was observed during 3- and 12-month follow-up periods. We observed twenty patients with improvement in impairment across different observation periods.

Motor deficits are the most prevalent type of neurologic sequela across different etiologies (Table 4). It is commonly manifested as spasticity or paresis. Language or speech delays are also observed frequently among the population and is the predominant form of cognitive disability. Visual disorders are observed more commonly in tuberculous infection compared to other etiologies. Finally, Attention Deficit-Hyperactivity Disorder is the only behavioral abnormality documented in our study.

The case fatality rate among the study population was 12.9%, with bacteria as the most common etiology (53%). Septic shock was reported as the most common cause of death. Neurologic causes of death were cerebral herniation (8 cases), intracranial bleeding (1 case) and status epilepticus (1 case). Majority of the mortalities belonged to the younger age group (40.3%).

DISCUSSION

To our knowledge, this is the most comprehensive study on the neurologic outcome of children across different neurologic infections in the Philippines. Past publications and unpublished data in our country has focused on a specific type of CNS infection[7,9-12], has used single-center data[13-15], or has focused on a special group of patients.[16-18] Our approach of using data from sentinel sites across different regions aims to obtain a sample that is representative of our population. We included different forms on central nervous system infection, which are analyzed in parts and in whole, to determine the impact of acute inflammation on a developing brain.

Several pathogenic agents, deemed causes for neurologic infections, can invade the protection conferred by the blood-brain barrier. Mechanisms

Table 4: Neurologic outcomes of patients with neurologic infections (n=154)*

Domains	Bacterial	Viral	Tuberculous	TOTAL
Motor deficits#	29	14	21	64
Cognitive disabilities§	13	8	5	26
Seizure disorders	10	4	3	17
Vision deficits	3	2	10	15
Hearing deficits	6	1	0	7
Behavioral disorders¶	0	3	2	5

* Reported as number of events. One or more events may be associated with a patient
# Motor deficits include motor weakness, vestibular dysfunction, balance deficits, spasticity, spastic quadriplegia, choreoathetosis, tremors
§ Cognitive disabilities include mental retardation, specific learning disabilities, speech/language delay
¶ Behavioral disorders include Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant (OD)

that were hypothesized for microbiologic invasions include paracellular, intracellular, or use of infected phagocytes.[3,5] Recent studies have proven that molecular interaction between host receptors and pathogenic agents are the key for the invasion of host barriers.[3] Presence of etiologic agents within the host induce inflammation, and the inflammatory reaction is crucial to the pathogenesis of the impairments during infections in the central nervous system.[19-22]

Inflammatory reaction in the brain affects the development of the neuronal network.[21,22] Since infants and children have immature neurons, their lack of full functional specificity enables shifting of specialization. But this same property carries vulnerability issues via derailment of genetically determined developmental processes leading to failure of recovery.[23] Another unique characteristic that immature neurons have is the high success for neurologic recovery.[3,4,23,24] Thus, full impact of the injury may not be apparent at the onset, and clinical manifestation is dependent on age-appropriate developmental milestones. According to Anderson in 2011, acute impairments from injurious stimuli to immature brain represent transient impairment that can undergo recovery.[23]

In our study, the stage of illness was directly related with the outcome on discharge. Among patients admitted in stage 1 and 2 of illness, the majority had been assessed to have fully recovered on discharge, 71.7%, and 40.2% respectively. Recovery declined to 5.3% once in stage 3 of illness. Mortality is highest in children with Stage 3 disease on admission. However, significant changes in outcome grading were noted for various patient groups on the different periods on follow-up.

Majority of acute or in-hospital sequela was gross motor or sensory neurologic deficits that are related to neuroimaging findings of hydrocephalus, empyema, and infarcts.[25,26] We found a significant number of motor deficits that include spasticity, dystonia, and weakness that are graded moderate to severe. Subsequently, this translates to a large number of children being chronically dependent or would require some degree of assistance for daily living. Speech delay and mental retardation were seen as another common sequela for neurologic infections. Foreign literature had seen different forms of cognitive abnormalities with wide spectrum of severity. Severe forms of intellectual disability and speech delays were seen as acute sequela, while mild disabilities and specific learning disorders were more frequently observed upon surveillance in prospective cohort and retrospective studies. We found less behavioral disabilities probably due to the short observation period and limitations inherent on a retrospective records review. Although literature had varying time-frames in the observation of neurologic outcomes, data has been consistent with differences in sequela observed at different time-frames.[26-30] Behavioral disabilities and some specific learning disabilities were observed in studies within a 5-10 year period with a prevalence of 78.3%, compared to gross motor and special sensory deficits found immediately on discharge or within a five-year period with the prevalence of 14.3%. In the same study by Anderson in 2011, they noted an improvement of speech delay noted

upon discharge to high-level language deficits after a 12-year follow-up.[23]

Hearing deficits were seen less in our study. This goes against the trend of some studies reporting it as a major morbidity for survivors of meningitis.[31-33] Several factors were seen as a cause for the disparity. Institutional case management protocols in our country do not include a routine hearing screen for survivors of meningitis. They were picked up at outpatient clinics either as language delay or poor regard and would be diagnosed on subsequent follow-up after a series of examination for a hearing disorder.

There are varying case fatality rates (CFR) from literature depending on the region. A meta-analysis of outcomes on neurologic infections in North America, Europe, and Australia showed an aggregated CFR of 3%.[27] In developing countries, African countries have a CFR at 27%[26], Mexico has 16%[29], and for neighboring countries Thailand 17.3%[25], and Malaysia 15%.[34] Our data showed CFR of 12.9% closely related to data from developing countries. This is mainly due to differences in vaccination coverage among countries.[35] Majority of children in our cohort has low vaccine compliance (Table 1). Vaccines which has an impact on neurologic infections, BCG and measles, only reached 70% coverage despite the expanded immunization program of the government. Varicella, pneumococcal and Hib vaccines have dismal figures with only 0.9%, 0.7% and 1.8% respectively. This may be attributed from the recent inclusion of these vaccines starting year 2010, which has poor coverage as reflected in our data. Our data also demonstrated that a large majority of Filipino children are still at high risk for neurologic infections, and subsequently its neurologic complications.

Signs of hydrocephalus and increased intracranial pressure, namely vomiting, seizure and lethargy, are correlated with poor outcome and death using univariate analysis. De Jonge *et al*. did a meta-analysis to determine clinical features related to mortality.[36] Signs of shock, namely hypoperfusion, coma, seizure, and severe respiratory failure, were related to mortality. Age was determined as an important prognostic factor, of which the younger age group was observed to have a poorer prognosis because of their immunologic immaturity.[36] Such finding was observed similarly in our study, and so with other literature.

An inherent weakness in any retrospective study is the limitation on available data based on medical charts. Our study had a fair success rate on data retrieval, with only 35% of the 1,371 probable cases included for analysis. Various factors had been identified including poor manual record-keeping, decentralized or autonomous management of participating hospitals, and differences in case management protocols. Secondly, we saw a high drop-out rate due to poor patient follow-up, highlighting the poor health-seeking behaviors among Filipinos, and a similar problem in other developing countries. Finally, there could be a bias of follow-up favoring those with neurologic deficits, more so those with poorer and deteriorating functional status. A neurologic deficit is a cause of concern and thus a reason for caregivers to continue seeking medical care.

In conclusion, neurologic infections carry high mortality and the majority of its sequela are chronic and related to life-long impairments. However, because of the immaturity of neuronal networks, inflammatory reactions that lead to permanent damage to the central nervous system are different in pediatric in comparison with adult patients. An intricate balance of vulnerability and plasticity is present in an immature brain that leads to either progression or improvement of impairment. We emphasize the importance of continuous close follow-up for all survivors of neurologic infections in children to establish an early rehabilitation program and to monitor the development of neurologic impairment. Such practice may not only be of help in the recovery for neuronal injury but also in the anticipatory care and support for chronically-ill children. Likewise, prevention of infection through immunization should equally be emphasized.

We recommend that further studies on neurologic outcomes venture into developing a standardized disability evaluation tool for Filipino children to be utilized on discharge and subsequent follow-up assessments. This tool can be used for early detection of neurodevelopmental sequelae, monitoring of impairment progression, and guidance in the institution of prompt intervention. Second, we also recommend the establishment of a routine hearing screen for survivors of neurologic infections to determine the extent of hearing impairment at an early stage, and to initiate early management. Third, we suggest the establishment of early, routine, cost-effective rehabilitation for neurologic infection survivors in primary care setting. This strategy could prevent chronic impairments and long-term disabilities from neurologic infections in children. Finally, vaccines that have an impact on neurologic infections should be considered, and immunization

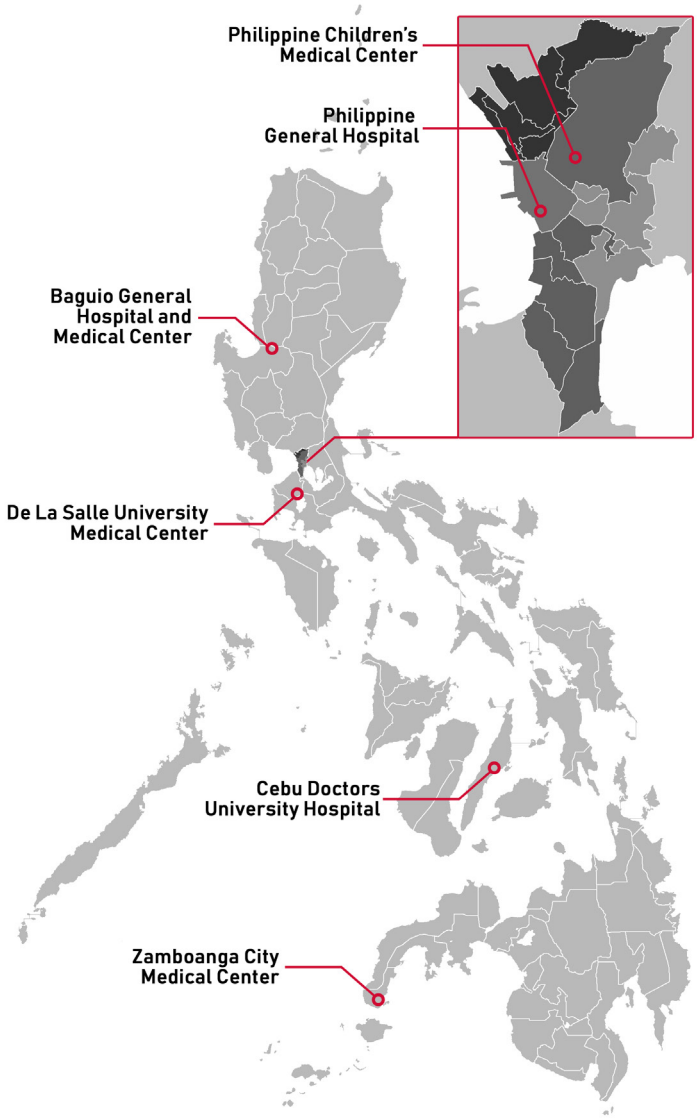

Figure 1. Study sites

service delivery should be strengthened as part of the primary preventive strategies.

ACKNOWLEDGEMENTS

We acknowledge the help of Mr. Von Luigi Valerio of the UPM-NIH for helping us with map used in the manuscript. We thank the participating hospitals, the Philippine Neurological Association for supporting the study.

DISCLOSURE

Financial support: This study was funded by the National Institutes of Health - University of the Philippines Manila (UPM-NIH) and Philippine Neurological Association (PNA).

Conflicts of interests: None

REFERENCES

1. Smith AL. Bacterial meningitis. *Pediatr Rev* 1993;14(1):11-8.
2. Wubbel L, McCracken GH. Management of bacterial meningitis: 1998. *Pediatr Rev* 1998;19(3):78-84.
3. Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis* 2010;10(1):32-42.
4. de Jonge R, van Furth AM, Wassenaar M, Gemke R, Terwee C. Predicting sequelae and death after bacterial meningitis in childhood: A systematic review of prognostic studies. *BMC Infect Dis* 2010;10(1):232.

5. Mann K, Jackson MA. Meningitis. *Pediatr Rev* 2008;29(12):417-29; quiz 30.
6. Streptomycin in Tuberculosis Trials Committee - Medical Research C. Streptomycin in treatment of tuberculous meningitis. *Lancet* 1948;1:582-96.
7. Lee LV. Neurotuberculosis among Filipino children: an 11 years experience at the Philippine Children's Medical Center. *Phil J Microbiol Infect Dis* 2000;29(3):141-8.
8. Stata Corp. Stata Statistical Software. Texas: StataCorp LP; 2013.
9. Luis AS, Hayes CG, Rourke TO, Manaloto CR. The Neurologic features of Japanese encephalitis in the Philippines. *Phil J Microbiol Infect Dis* 1990;19(2):39-48.
10. Santana-Arciaga RT, Capeding MR, Tirador A, Sombrero LT, Velmonte M. The epidemiology of invasive Hemophilus influenzae disease among Filipinos. *Phil J Microbiol Infect Dis* 1994;23(2):52-9.
11. Ablaza-Medalla CM, Oh D, Chua AC, Salonga AM, Gatchalian SR. Brain abcess in children at Philippine General Hospital: A prospective epidemiologic study. *Pediatr Infect Dis Soc Phil J* 2000;4(1):15-21.
12. Limcangco MR. Economic evaluation of a Haemophilus influenza type B meningitis prevention program in Manila, Philippines: Department of Pharmacy, Faculty of Science, University of Sydney; 1998.
13. Lupisan SP, Herva E, Sombrero LT, *et al*. Invasive bacterial infections of children in a rural province in the central Philippines. *Am J Trop Med Hyg* 2000;62(3):341-6.
14. Abucejo-Ladesma E, Simoes EAF, Lupisan SP, *et al*. Serious community-acquired paediatric infections in rural Asia (Bohol Island, Philippines): bacterial meningitis in children less than 5 years of age. *Scand J Infect Dis* 2007;39(11-12):983-9.
15. Abucejo-Ladesma E, Lupisan SP, Quiambao BP, *et al*. Bacterial meningitis in children less than five years of age at a provinvcial hospital in the Philippines. *Pediatr Infect Dis Soc Phil J* 2000;4(1):31-7.
16. Morelos AM, Gatchalian S. Clinical profile of meningitis among Filipino neonates: A twelve-year collaborative review. *Pediatr Infect Dis Soc Phil J* 1995;14:24-7.
17. Landangan M, Lukban M. Prospective evaluation of sensorineural hearing loss as a complication of meningitis among pediatric patients admitted in a tertiary hospital. *Pediatr Infect Dis Soc Phil J* 2005;9(1):16-20.
18. Gatchalian S, Quiambao BP, Morelos AM, *et al*. Bacterial and viral etiology of serious infections in very young Filipino infants. *Pediatr Infect Dis J* 1999;18:50-5.
19. Bechmann I, Woodroofe N. Immune privelege of the brain. In: Woodroofe N, Amor S, eds: Neuroinflammation and CNS disorders. Sussex: John Wiley & Sons, Ltd, 2014:1-8.
20. Cosby SL, Galbraith S, Healy D. CNS infections. In: Woodroofe N, Amor S, eds: Neuroinflammation and CNS disorders. Sussex: John Wiley & Sons, Ltd, 2014:151-84.
21. Male D. Adaptive immune response in the CNS. In: Woodroofe N, Amor S, eds: Neuroinflammation and CNS disorders. Sussex: John Wiley & Sons, Ltd, 2014:35-57.
22. Moore CS, Durafort BA, Antel JP. Innate immunity in the CNS - A focus on the myeloid cell. In: Woodroofe N, Amor S, eds: Neuroinflammation and CNS disorders. Sussex: John Wiley & Sons, Ltd, 2014:9-35.
23. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioral plasticity after early brain insult. *Brain* 2011;134:2197-221.
24. Anderson V, Anderson P, Grimwood K, Nolan T. Cognitive and executive function 12 years after childhood bacterial meningitis: effect of acute neurologic complicationss and age of onset. *J Pediatr Psychol* 2004;29:67-81.
25. Chotpitayasunondh T. Bacterial meningitis in children: etiology and clinical features, an 11-year review of 618 cases. *Southeast Asian J Trop Med Public Health* 1994;25(1):107-15.
26. Ramakrishnan M, Ulland AJ, Steinhardt LC, Moïsi JC, Were F, Levine OS. Sequelae due to bacterial meningitis among African children: a systematic literature review. *BMC Med* 2009;7(1):47.
27. Chandran A, Herbert H, Misurski D, Santosham M. Long-term sequelae of childhood bacterial meningitis: an underappreciated problem. *Pediatr Infect Dis J* 2011;30(1):3-6.
28. Ansari I, Pokhrel Y. Culture proven bacterial meningitis in children: agents, clinical profile and outcome. *Kathmandu Univ Med J* 2011;9(33):36-40.
29. Franco-Paredes C, Lammoglia L, Hernández I, Santos-Preciado JI. Epidemiology and outcomes of bacterial meningitis in Mexican children: 10-year experience (1993-2003). *Int J Infect Dis* 2008;12(4):380-6.
30. Jit M. The risk of sequelae due to pneumococcal meningitis in high-income countries: a systematic review and meta-analysis. *J Infect* 2010;61(2):114-24.
31. Legood R, Coen PG, Knox K, *et al*. Health related quality of life in survivors of pneumococcal meningitis. *Acta Paediatr* 2009;98(3):543-7.
32. Edmond K, Dieye Y, Griffiths UK, *et al*. Prospective cohort study of disabling sequelae and quality of life in children with bacterial meningitis in urban Senegal. *Pediatr Infect Dis J* 2010;29(11):1023-9.
33. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10(5):317-28.
34. Erleena Nur H, Jamaiah I, Rohela M, Nissapatorn V. Bacterial meningitis: A five year (2001-2005) retrospective study at University Malaya Medical Center, Kuala Lumpur, Malaysia. *Southeast Asian J Trop Med Public Health* 2008;39:73-7.
35. World Health O. Report: State of the world`s vaccines and immunization. 3rd ed. Geneva: World Health Organization, 2010:157-63.
36. de Jonge RCJ, van Furth AM, Wassenaar M, Gemke RJBJ, Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. *BMC infect Dis* 2010;10(1):232.