Original Article

MRI Spectrum of *Haemophilus influenzae* Meningoencephalitis in Children

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Abstract

Background and Purpose: *Haemophilus influenzae* type b (Hib) infection occurs mostly in children and is transmitted from person to person through the respiratory pathway. Hib strain is associated with meningitis or encephalitis. It is not an uncommon infection, particularly, in the developing world. This prospective cohort study was done with the aim of describing imaging findings in patients with Hib meningoencephalitis. **Materials and Methods:** In a prospective cohort study, consecutive children admitted in the pediatric emergency unit with acute febrile encephalopathy were enrolled. The clinical details, CSF analysis, and microbiological and serological investigations were recorded on a case record proforma. Children with confirmed Hib meningoencephalitis were included in this study. Clinicoradiological features were assessed. **Results:** A total of 16 patients with acute febrile encephalopathy, in whom CSF latex agglutination, CSF culture, or CSF multiplex PCR were positive for *H. influenzae* were included in this study. All these children were investigated with magnetic resonance imaging (MRI) brain. Important imaging findings were meningitis, predominantly around frontoparietal lobes (43%), cerebritis (28%), ventriculitis (14%), and subdural collections (21.5%). One patient had features consistent with acute disseminated encephalomyelitis (ADEM) while four patients had normal MRI scan. **Conclusions:** *H. influenzae* is still a common cause of meningitis in infants and children in the developing world. We have tried to study the most common MRI features associated with Hib infection to help radiologists alert the treating clinicians to further investigate these patients for appropriate prognostication.

Keywords: Children, *Haemophilus influenzae*, meningoencephalitis

Introduction

Haemophilus influenzae type b (Hib) is a gram-negative anaerobic bacteria, considered to be an opportunistic pathogen.[1,2] It is responsible for localized diseases like upper respiratory tract infection or more severe invasive diseases such as bacteremia, sepsis, arthritis, pneumonia, or meningoencephalitis mostly in the pediatric population (usually less than 5–8 years of age) and very rarely in adults.[3] Transmission is mostly through droplet spread from the upper respiratory tract during the infectious period.[4] In recent sentinel surveillance multicentric study from India reported in children <5 years, the etiology was *S. pneumoniae* in 82.9%, *H. influenzae* type b in 14.4%, and *N. meningitidis* in 2.7% cases.[5] Since it is difficult to elicit signs such as neck stiffness in infants, nonspecific symptoms such as fever, vomiting, and altered sensorium in this age group, the clinical possibility of Hib infection increases.[6-8] Hib conjugate vaccines provide immunization against capsulated pathogens and not from unencapsulated strains.[9] Although vaccination and early use of antibiotics have greatly reduced the mortality associated with Hib infection, the affected children usually have a risk of permanent neurological deficits such as mental retardation, seizures, deafness, and so on.[10]

With the advancement of imaging modalities and availability of high field scanners, knowledge about the imaging findings of Hib infection may help radiologists alert the referring physicians for timely initiation of focused treatment for better prognosis. However, to our knowledge, there is very limited literature available describing early imaging features of Hib infection. Few case reports are available describing MRI features in Hib infection such as probable ADEM,[11] subdural hygroma,[12] and cervical myelopathy.[13] We have tried to summarize major findings seen in the majority of patients with Hib infection.

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Materials and Methods

This was a prospective cohort study conducted in the pediatric emergency and intensive care unit of the department of pediatrics in a tertiary care research institute. The study was conducted the from the year 2013 and 2015. Consecutive children <12 years of age admitted with acute febrile encephalopathy, signs and symptoms of meningitis, or febrile seizures were enrolled in the study. These children were evaluated clinically and CSF was analyzed for bacterial cultures. CSF was subjected to multiplex PCR for bacterial and viral agents. Children with *H. influenzae* meningitis confirmed with CSF latex agglutination, CSF culture, and CSF multiplex PCR were included in this study [Table 1]. Out of 16 patients, who were serologically proven to have Hib infection, 14 underwent MR Imaging. These MRI cases were retrieved from our database system and were re-evaluated for imaging features. MR imaging was performed on 1.5T (Aera; Siemens, Erlangen, Germany) or 3T ((Verio; Siemens, Erlangen, Germany) scanners. All the MRI scans were re-evaluated by a neuroradiologist. All the patients were clinically followed up at 3, 6, and 12 months. Neurological outcome was assessed with pediatric cerebral performance scale (PCPC) and pediatric overall performance scale (POPC) during follow up, and screening of hearing impairment was done with BERA at discharge.

MR imaging

The MRI of the patients included the following sequences; 2D axial T2 and FLAIR sequences for the brain, pre- and post-contrast 3D T1 spoiled gradient recalled sequence, diffusion-weighted images, and susceptibility-weighted images. The diffusion-weighted images were acquired using a single-shot fast spin-echo echo-planar sequence with sensitizing gradients applied in all three orthogonal planes with b-values of 50 s/mm^2 and 1000 s/mm^2. The 2D sequences were acquired using a slice thickness of 4 mm while the 3D sequences were acquired using a slice thickness of 0.9 mm. Intravenous gadolinium (Gd-DTPA) was injected at a dose of 0.1 mmol/kg of body weight for postcontrast sequences unless the use of gadolinium-based contrast agents were contraindicated in the patient. All the MR images were evaluated by an experienced neuroradiologist having 5 years of experience in evaluating brain MRI.

All discrepancies were solved by discussion and re-evaluation until a conclusion was reached. Following imaging parameters were assessed: presence of leptomeningeal thickening and enhancement, ependymal enhancement (smooth, nodular), ventricular debris/enlargement, extra-axial collections (subdural, extradural, along convexities, fall or tentorium), gray matter involvement (cortical or deep nuclei), supratentorial and infratentorial white matter changes, findings on diffusion-weighted (DWI), and susceptibility-weighted sequences (SWI) and other features if present.

Statistical analysis

All the cases were analyzed, and the findings were tabulated. Major MRI findings associated with Hib infection were further analyzed. All the analyses were performed on the Statistical Package for Social Sciences software, Version 23.0 (IBM, Armonk, New York). Statistical significance was set at 0.05.

Results

Clinical features

The median age of children with Hib meningitis was 54 months (10–90 months IQR), and 9 (56%) were boys. Immunization according to national immunisation schedule was received by 13 (81%) children. The most common clinical features were fever in 16 (100%), encephalopathy in 13 (81%), and seizures in 10 (62%) children. The median duration of fever was 4 (2–5) days and duration of encephalopathy was 1 to 3 days. Examination findings were meningeal signs in 12 (75%), coma in 4 (25%), pupillary inequality in 2 (12.5%), and cranial nerve palsies in 2 (12.5%). CSF analysis showed the presence of 450 cells (median. IQR 20–1900 cells), and median CSF protein was 122 mg/dL (median, IQR 54–222 mg/dL) and median CSF glucose was 40 mg/dL (IQR 30–67 mg/dL). CSF gram stain was positive in 4 (25%), CSF culture was positive in one (6.3%), and latex agglutination was positive in 5 (31.3%) cases. CSF multiplex PCR for Hib was positive in all these 16 patients. All children were treated with supportive care in the pediatric emergency and intensive care unit. Ceftriaxone was used as an empirical antibiotic in all these patients, and doxycycline and acyclovir were also used in children with clinical suspicion of meningoencephalitis. Antimicrobials were narrowed based on the cultures and serological investigations reports. Hib meningoencephalitis was managed with ceftriaxone for 10–14 days duration. Antibiotics were prolonged to 4–6 weeks duration in cases with subdural empyema and ventriculitis. In one patient, the subdural collection was drained through burr hole aspiration.

At discharge, 10 (62.5%) patients had a neurological disability, mild-to-moderate disability according to PCPC score in 6 (36.6%), and 3 (18.8%) had a severe disability. Hearing evaluation with BERA at discharge and follow-up showed severe hearing impairment in one (6.3%) patient.

MR imaging findings

Out of fourteen MRI scans reviewed, 7 patients, were below 3 years of age (youngest being 4 months), 2 patients were more than 6 years of age (eldest being 18 years) and 5 patients were in 3–6 years age group. Four patients did not have any imaging abnormality, and these patients presented with fever, three had seizures and one had altered sensorium. MRI findings were divided into five patterns.

1. Leptomeningeal thickening and enhancement [Figure 1a to 1c]: Out of 14 cases, 6 patients presented with leptomeningeal thickening and postcontrast enhancement favoring features of meningitis. Five patients had smooth meningeal enhancement while one patient had some nodularity. Mostly the leptomeninges in the sulcal spaces over frontoparietal lobes was involved, except for one

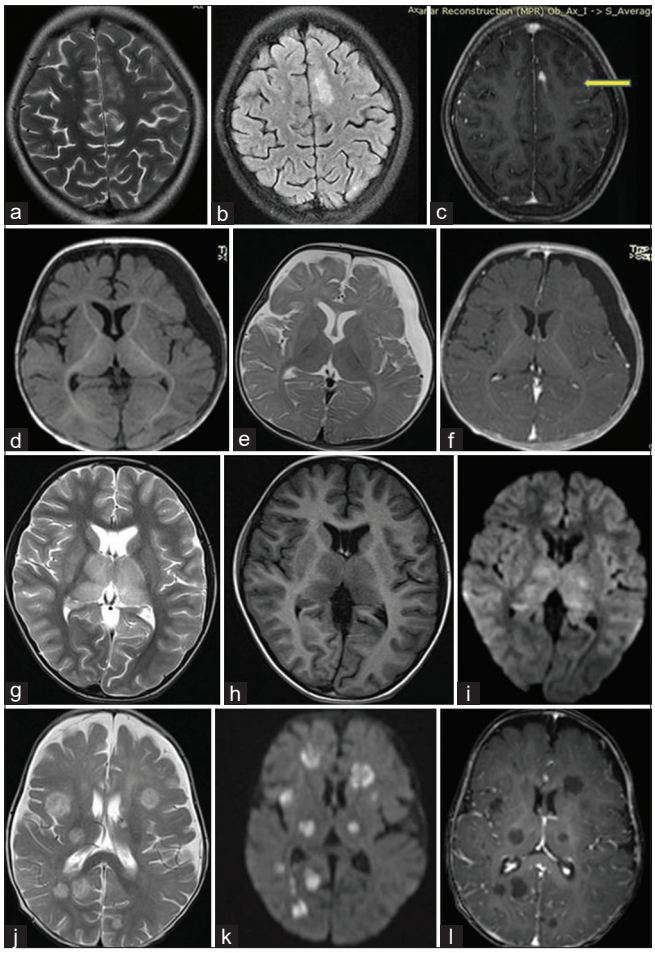

Figure 1: Axial T2 (a) and FLAIR (b) images showing hyperintensity in the left frontal lobe (paracentral lobule) with axial postcontrast T1 image (c) showing smooth leptomeningeal thickening in the left pericallosal cistern (yellow arrow). Left frontotemporal subdural collection following CSF signal intensity on axial T1 (d) and T2 (e) without any meningeal enhancement on postcontrast image (f). Bilaterally symmetrical thalamic T2 hyperintensity (g) and T1 hypointensity (h) with mild diffusion restriction (i). Axial T2 (j) image showing multiple well-defined round to oval hyperintense lesions in subcortical and deep white matter of bilateral cerebral hemispheres and bilateral thalami with intense diffusion restriction (k). Subtle predominantly peripheral postcontrast enhancement was noted in some of the lesions (l)

patient where extension up to temporo-occipital region was also noted. Associated pachymeningeal enhancement was seen in two cases.

2. *Ventriculitis:* Two patients had dependent debris in occipital horns of lateral ventricles showing diffusion restriction with subtle smooth periventricular ependymal enhancement suggestive of ventriculitis. Subtle periventricular diffusion restriction was seen in one case. Both the patients had predominant polymorphs with reduced sugar and mildly raised protein on CSF analysis.
3. *Subdural Collections* [Figure 1d to 1f]*:* Three patients had extra-axial subdural collections along frontotemporal convexity. Two patients had simple subdural hygromas that followed CSF signal intensity on all sequences. The third patient had a thin subdural collection that showed diffusion restriction suggestive of empyema. One of the patients had large subdural hygromas with mass effect over underlying brain parenchyma.
4. *Encephalitis* [Figure 1g to 1i]*:* Four patients had patchy areas of T2 hyperintensity involving the cortex and subcortical or deep white matter. One patient had bilaterally symmetrical thalamic hyperintensity, more commonly seen in Japanese encephalitis. Another patient had altered signal intensity with diffusion restriction in the left cerebral hemisphere with the involvement of basal ganglia and thalami. One patient who presented with repeated episodes of seizures with febrile encephalopathy had symmetrical periventricular white matter involvement in parieto-occipital regions that showed diffusion restriction. No evidence of micro or macro hemorrhage was seen in any case.
5. *ADEM-like appearance* [Figure 1j to 1l]*:* One patient had multiple asymmetrical wells defined round to oval lesions in the subcortical white matter of bilateral cerebral hemispheres, basal ganglia, thalami, and cerebellar hemispheres. These lesions were hyperintense on T2WI and showed intense diffusion restriction. Few of the lesions showed susceptibility changes, consistent with hemorrhages. These lesions gave appearance resembling acute disseminated encephalomyelitis. However, the differential diagnosis of vasculitis with infarcts was also considered.

Table 1: Showing brief clinical history and MRI findings

Sex	Age (months)	Clinical history	MRI findings
M	36	Fever, Vo, AS	LMT, SDC
M	24	Fever, Vo, AS	LMT, SDC
M	18	Fever, Sz, AS, NR	ADEM-like
F	24	Fever, Vo, Sz, HA	Ventriculitis, LMT
F	36	Fever, Vo, AS, Sz	SDC (Empyema)
F	30	Fever, Sz, AS, NR	LMT, B/L PVWM HI
F	10	Fever, Vo, HA, AS	C/Sc T2 HI
M	48	Fever, Vo, AS, Sz	B/L Thalamic HI
M	54	Fever, Vo, AS, Sz	Ventriculitis
M	90	Fever, HA, LOC	LMT, C/Sc T2 HI
F	60	Fever, Vo, AS, Sz	C/Sc T2 HI
F	36	Fever, Vo, AS, Sz	C/Sc T2 HI
M	72	Fever, HA, LOC	LMT
M	60	Fever, AS, LS, Sz	B/L Thalamic, C/Sc HI
F	72	Fever, HA, LOC	Not done
M	48	Fever, Sz, AS, NR	Not done

Abbreviations: ADEM: Acute Disseminated Encephalomyelitis; AS: Altered Sensorium; B/L: Bilateral; C/Sc: Cortical/Subcortical; HA: Headache; HI: Hyperintensity; LMT: Leptomeningeal Thickening; LOC: Loss Of Consciousness; LS: Loose Stools; NR: Neck Rigidity; PVWM: Periventricular white matter hyperintensity; SDC: Subdural Collection; Sz: Seizures; Vo: Vomiting

Discussion

Haemophilus influenzae type b (Hib) is a gram-negative anaerobic bacteria responsible for localized upper respiratory

tract infection or systemic bacteremia presenting as pneumonia or meningoencephalitis mostly affecting the pediatric population (usually less than 5–8 years of age) and very rarely adults.[3,14] Most of the Hib isolates in adults are nontypable.[14] Following droplet inhalation, the organism invades the respiratory mucosa and local lymph nodes. Patients may present with fever, altered sensorium, nausea or vomiting, headache, irritability, or seizures. Depending upon the immune status of the infected individual, there is bacteremia with the invasion of the meninges by the bacteria.

According to the literature, there are encapsulated and unencapsulated strains of *Haemophilus influenzae* identified based on the presence of capsular antigens. Type b is associated with most of the invasive diseases in children.[9,15] The encapsulated strains are resistant to phagocytosis with lack of antibodies in children between 6 months to 3 years of age. The passively acquired antibodies from the mother through the placental circulation of breast milk last for 6–8 months only.[16] The unencapsulated (nontypable) strains lack invasiveness and are responsible for respiratory disease in adults, frequently as superadded infections in patients of COPD.[2,16] Hib is still considered a major cause of meningitis in children between the ages of 6 months to 3 years.[17] Asymptomatic Hib colonization in the nasopharynx is usually found in approximately 2–5% of children[18] and rates are usually much higher for household contacts of the index case. Invasive diseases require Hib to enter the bloodstream resulting in bacteremia, usually after interference with the host immunity.[18] CNS spread usually occurs at sites of the absent blood-brain barrier (e.g. choroid plexus) or through nasopharyngeal venous pathways. Risk factors associated with the invasive disease include low socioeconomic status, crowded living, twin sibling, and lack of immunization.[7] Immunization for Hib was not part of the national immunization schedule during the study period, it is introduced in a phased manner in the national immunization program as a pentavalent vaccine.

Brain imaging is mostly done in these patients to look for focal encephalitis, abscess, empyema, and hydrocephalus to exclude possible risks of planned lumbar puncture. According to our study, the most common finding was leptomeningeal thickening seen mostly over frontoparietal convexity seen in nearly 43% cases. Mostly the meningeal thickening was smooth (5 out of 6 cases). This was well correlated with clinical symptoms of fever, headache, and meningismus. Two patients had imaging features suggestive of ventriculitis. CSF findings in both these patients' revealed features of bacterial meningitis (raised proteins, reduced sugar and predominant neutrophils). Subdural collections were present in three patients with subdural empyema in one patient. The definite cause of subdural hygroma is unknown but is believed to be secondary to arachnoid membrane rupture with CSF trapping in the subdural space.[19] One patient presented with imaging and clinical features of probable acute disseminated encephalomyelitis (ADEM) secondary to Hib infection. This patient presented with fever and vomiting for 3 days and one episode of generalized tonic-clonic seizures followed by altered sensorium. CSF favored bacterial meningitis. Imaging showed multiple bilateral lesions in subcortical white matter, thalami, and basal ganglia. Follow up MRI done after 3 months for this patient showed resolution of the white matter and deep grey matter lesions. Many studies have concluded that ADEM secondary to infection can be considered in patients of meningitis with worsening encephalopathy and persistent fever.[20] Addition of steroids can help in the management of such cases.[21] Though clinical features were suspicious of encephalitis, MRI scans were normal in four patients. One patient had nonspecific involvement of bilateral thalami and basal ganglia as is seen in cases of Japanese encephalitis or West Nile virus encephalitis.

Hence, we conclude that imaging differential diagnosis of Hib meningoencephalitis can be considered especially in pediatric patients presenting with clinical symptoms of fever, headache, vomiting or meningismus with supportive CSF serology. Imaging also helps in looking for complications such as hydrocephalus (before lumbar puncture), abscesses, subdural hygromas/empyema, and so on.

Limitations

Although a small sample size of this study might not be suitable to generalize the findings, it might help our radiology colleagues to raise the suspicion of Hib infection in proper clinical settings.

Conclusions

Imaging differential diagnosis of Hib meningoencephalitis can be considered especially in pediatric patients presented with clinical symptoms of fever, headache, vomiting, or meningismus with supportive CSF serology. Common findings include subdural collections, leptomeningeal thickening over frontoparietal lobes with or without ventriculitis. Rarely ADEM like appearance may be seen. Timely diagnosis and early initiation of appropriate treatment might help to reduce morbidity and mortality.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

References

1. Kilian M. Haemophilus. In: Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA, editors. Manual of Clinical Microbiology. Vol. 18. Washington: American Society of Microbiology; 2007. p. 636-48.
2. Middleton AM, Dowling RB, Mitchell JL, Watanabe S, Rutman A, Pritchard K, *et al*. Haemophilus parainfluenzae infection of respiratory mucosa. Respir Med 2003;97:375-81.
3. Bosch AATM, Biesbroek G, Trzcinski K, Sanders EAM, Bogaert D. Viral and bacterial interactions in the upper respiratory tract. PLoS Pathog 2013;9:e1003057.
4. Nørskov-Lauritsen N. Classification, identification, and clinical significance of Haemophilus and Aggregatibacter species with host specificity for humans. Clin Microbiol Rev 2014;27:214-40.
5. Jayaraman Y, Veeraraghavan B, Chethrapilly Purushothaman GK, Sukumar B, Kangusamy B, Nair Kapoor A, Gupta N, *et al*. Burden of bacterial meningitis in India: Preliminary data from a hospital based sentinel surveillance network. PLoS One 2018;13:e0197198.
6. Uduman SA, Adeyemi E, El-Khadir A, Jose K, Benedict S, Bener A. *Haemophilus influenzae* type b still remains a leading cause of meningitis among unvaccinated children—A prospective CSF analysis study. J Trop Pediatr 2000;46:331-410.
7. Limcangco MR, Salole EG, Armour CL. Epidemiology of *Haemophilus influenzae* type b meningitis in Manila, Philippines, 1994 to 1996. Pediatr Infect Dis J 2000;19:7-11.
8. Lehmann D, Yeka W, Rongap T, Javati A, Saleu G, Clegg A, *et al*. Aetiology and clinical signs of bacterial meningitis in children admitted to Goroka Base Hospital, Papua New Guinea, 1989-1992. Ann Trop Paediatr 1999;19:21-32.
9. Slack MP, Azzopardi HJ, Hargreaves RM, Ramsay ME. Enhanced surveillance of invasive Hemophilus influenzae diasease in England, 1990 to 1996: Impact of conjugate vaccines. Pediatr Infect Dis J 17:204-7.
10. Peltola H. Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: Global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev 2000;13:302-17.
11. Beleza P, Ribeiro M, Pereira J, Ferreira C. Probable acute disseminated encephalomyelitis due to Haemophilus influenzae meningitis. Dev Med Child Neurol 2008;50:388-91.
12. Suryavanshi KT. Haemophilus influenzae type B meningitis with subdural hygroma. J Acad Clin Microbiol 2014;16:106-8.
13. Miller V. Craniocervical myelopathy associated with Haemophilus influenzae meningitis MRI findings. Neurology 1992;42:1121-2.
14. Brouwer MC, van de Beek D, Heckenberg SG, Spanjaard L, de Gans J. Community-acquired Haemophilus influenzae meningitis in adults. Clin Microbiol Infect 2008;13:439-42.
15. Ryan, KJ, Ray CG. Sherris Medical Microbiology. McGraw Hill; 2004. p. 396-401.
16. Hill SL, Mitchell JL, Stockley RA, Wilson R. The Role of Haemophilus parainfluenzae in COPD. Chest 2000;117:293.
17. Naik DG, Seyoum M. Hemophilus influenzae type b meningitis in children, Eritrea. Emerg Infect Dis 2004;10:155-6.
18. Lupisan SP, Herva E, Nohynek H, Lucero MG, Sombrero LT, Quiambao BP. Incidence of invasive Haemophilus influenzae type b infections in Filipino children. Pediatr Infect Dis J 2000;19:1020-2.
19. Sharma P, Mishra A, Arora G, Tripathi M, Bal C, Kumar R. Post meningitis subdural hygroma: Anatomical and functional evaluation with ^{99m}Tc-ehylene cysteine dimer single photon emission tomography/computed tomography. Indian J Nucl Med 2013;28:23-5.
20. Proulx NL, Freedman MS, Chan JW, Toye B, Code CC. Acute disseminated encephalomyelitis associated with Pasteurella multocida meningitis. Can J Neurol Sci 2003;30:155-8.
21. Shahar E, Andraus J, Savitzki D, Pilar G, Zelnik N. Outcome of severe encephalomyelitis in children: Effect of high-dose methylprednisolone and immunoglobulins. J Child Neurol 2002;17:810-4.