IJABR

International Journal of Advanced Biotechnology and Research (IJABR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-10, Issue-2, 2019, pp87-93
http://www.bipublication.com

Research Article

Frequency of Haemophilus Influenzae CNS Invasive Disease (Meningitis) In Vaccinated Children below 5 Years Age and Its Outcome

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[Received: 21/02/2019; Accepted: 07/04/2019; Published: 09/04/2019]

ABSTRACT

Objective: To determine the frequency of H. Influenzae causing meningitis in the children below five years of age vaccinated with Hib (three primary doses) its outcome.

Material and methods: This case series study was conducted at Department of Pediatrics Lahore General Hospital, Lahore from July 2018 to December 2018 over the period of 6 months. Total 183 patients of bacterial meningitis having age <5 years either male or female vaccinated with three doses of Hib vaccine as recorded on the vaccination card were selected for this study. H. influenza and mortality rate was analyzed.

Results: A total of 183 patients were included in the study. The mean age of presentation was 16.28 months. The growth of H.influenzae was found in 35 patients (19.1%).

Out of the total of 183 patients, male patients were 115 (62.8%) and females were 68 (37.2%).

H. Influenzae growth was found in 21 male patients and no growth in 94 male patients. H. Influenzae growth was found in 14 female patients and no growth in 54 female patients.

Mortality in male patients was 12 and in female patients it was 7. A total of 19 patients died giving a mortality rate of 10.38%.

Conclusion: H. Influenzae CNS invasive disease is still an important cause of meningitis even in vaccinated children below 5 years of age.

Key words: H. Influenzae, Central nervous system, Cerebrospinal fluid, Meningitis.

INTRODUCTION

Haemophilus influenzae (H influenzae) is a small Gram-negative coccobacillus with capsulated and uncapsulated strains.[1] Encapsulated strains express 1 of 6 antigenically distinct capsular polysaccharides (a through f); non-encapsulated strains lack capsule genes and are designated non-typable.[2] H.influenzae remains a significant pathogen in spite of availability of vaccination against serotype b.[3] In the prevaccine era, approximately 20,000 cases of invasive Haemophilus influenzae type b (Hib) disease were reported annually in the United States, affecting approximately 1 child in every 200 younger than 5 years.[4]

The invasive disease is defined as the isolation of H. influenzae from an otherwise sterile site such

as the blood stream or cerebrospinal fluid. The invasive diseases caused by H influenzae include meningitis, epiglottitis, bacteremia without localized disease, septic arthritis, cellulitis, and pneumonia.[5] H influenzae serotype b (Hib) is responsible for approximately 95% of all invasive diseases caused by H influenzae though the other serotypes can also cause invasive disease in the normal host.[6] There is a striking age distribution of cases, with >90% cases in children <5 yr of age. The commonest invasive H. influenzae disease is meningitis.[7]About 5% of children with H influenzae meningitis die, in spite of appropriate clinical management.[8]

After the advent of an effective type b conjugate vaccine in 1988 the incidence of invasive H influenzae disease declined but the effectiveness of immunization is not equal in the different populations and the certain groups of children show a reduced or no vaccine response. In several countries, i.e. UK, Ireland, and the Netherlands, a rise in the incidence of invasive disease was reported several years after the introduction of vaccination.[9]

Since no study was conducted in this area on H influenzae causing meningitis and limited available Pakistani data showed the conflicting results, so this study is planned to know the current local frequency of H influenza invasive disease after the administration of vaccine in children less than 5 years.

MATERIAL AND METHODS

This case series study was conducted at Department of Pediatrics Lahore General Hospital, Lahore from July 2018 to December 2018 over the period of 6 months. Total 183 patients of bacterial meningitis having age <5 years either male or female vaccinated with three doses of Hib vaccine as recorded on the vaccination card were selected for this study. Children with history of parenteral antibiotics that can cross blood brain barrier e.g. third generation cephalosporin, penicillin group etc before subjecting for lumbar puncture, Children not fulfilling the criteria of probable bacterial meningitis.The children in whom lumbar puncture is not possible were excluded from the study.

After taking history and doing physical examination including fundoscopy to rule out any contraindication of lumbar puncture, these children were subjected to lumbar puncture.

Lumbar puncture was done after observing aseptic conditions and 1 ml of CSF was taken into each of the 3 tubes; first into tube labeled '1' for chemical analysis (glucose and proteins), then tube '2' for microbiological analysis and then tube '3' for total and differential leukocyte count. Trans-Isolate (T-I) media was used if CSF cannot be transported and processed by the laboratory within 1 hour. T-I media was stored at 4°C. It was removed from refrigerator, making sure broth is clear and it must be at room temperature (25˚C) before CSF is being added.

If using T-I media, 1.0 ml of CSF from tube #2 by sterile needle and syringe was transferred into the T-I medium. The CSF specimens was transported to the Pathology department of the hospital where appropriate biochemical analysis, total and differential leukocyte counts and microbiological analysis were done. CSF specimen was cultured on Chocolate Agar Plate (CAP) using sheep or horse blood supplemented by supplemented with X and V factors and incubated at 37 8C in 5–10% carbon dioxide and was processed further to confirm the presence of H influenzae in CSF specimen. Children were diagnosed to have H influenzae meningitis on the basis of a positive CSF culture.

The data was entered on a predesigned Performa.Death or discharge of the patient within 10 days of hospitalization was noted as outcome of the disease in performa.

Data was analyzed in SPSS version 17. Mean and standard deviation was calculated for age and duration of illness.

Frequency and percentages were calculated for gender and outcome variables i.e. H.influenzae infection and mortality (yes/no). Effect modifiers were controlled through stratification of age,

gender and duration of illness to see the effect of these on outcome variables followed by Chi-square test taken $P \leq 0.05$ as significant.

RESULTS

A total of 183 patients were included in the study. Mean age was 16.28 ± 15.57 months and mean duration of illness was 2.06 ± 0.990 days. H. influenza was detected in 35 (19%) patients. (Fig. 1) Out of 183 patients, total 19 (10%) patients were expired. (Fig. 2)Patients were divided into 4 age groups i.e. age group ≤1 month, age group 1-6 months, age group 6-12 months and age group >12 months.

Total 41 (22.40%) patients belonged to age group ≤1 month followed by 33 (18.03%) to 1-6 months, 25 (13.66) to 6-12 months and 84 (45.90%) to >12 months. H. influenza was detected in 11 (26.82%), 8 (24.24%), 6 (24%) and 10 (11.90%) patients respectively.

There were insignificant association between H. influenza infection and age groups was noted with p value 0.148. Total 4 (10.81%) patients, 2 (6.06%) patients, 5 (20%) patients and 8 (9.52%) patients were expired respectively in all age groups. But no significant association of mortality with age groups was detected with p value 0.35. (Table 1) Total 115 (62.84%) patients were male and 68 (37.16%) patients were female. H. influenza was detected in 21 (18.26%) male patients and in 14 (20.59%) female patients. But statistically insignificant association between H. influenza detection and gender was noted with p value 0.69. Total 12 (10.43%) male patients and 7 (10.29%) female patients were expired but no association of mortality with gender was detected with p value 0.97.

(Table 2) Selected patients were detected in 4 groups according to duration of illness i.e. <1day group, 1 t0 2 days group, 2 to 3 days group and ≥3 days group. Total 65 (35.52%) patients belonged to <1day group, 61 (33.33%) patients to 1 t0 2 days group, 38 (20.77%) patients to 2 to 3 days group and 19 (10.38%) patients belonged to ≥3 days group.

H. influenza was detected in 12 (18.46%) patients, 15 (24.59%) patients, 7 (18.42%) patients and in 1 (5.26%) patients respectively. Statistically insignificant association between detection of H. influenza and duration of illness was noted with p value 0.31. Total 5 (7.69%), 8 (13.11%), 6 (15.79%) and 0 patient were expired respectively in all groups but no significant association was detected with p value 0.12. (Table 3)

Fig. 1: Frequency of H. influenza

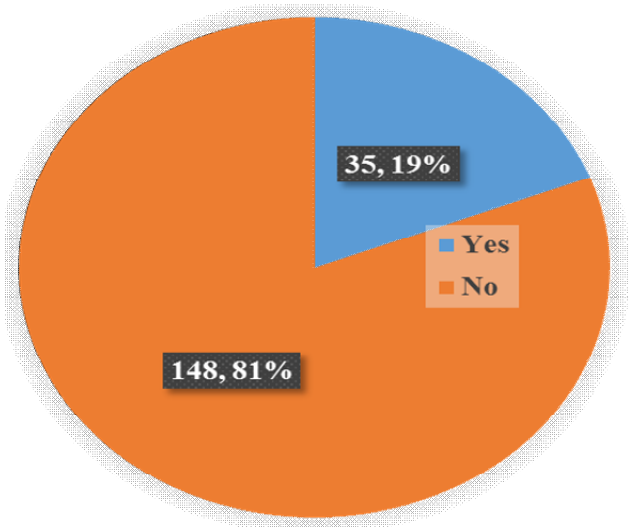

Fig. 2: Mortality rate

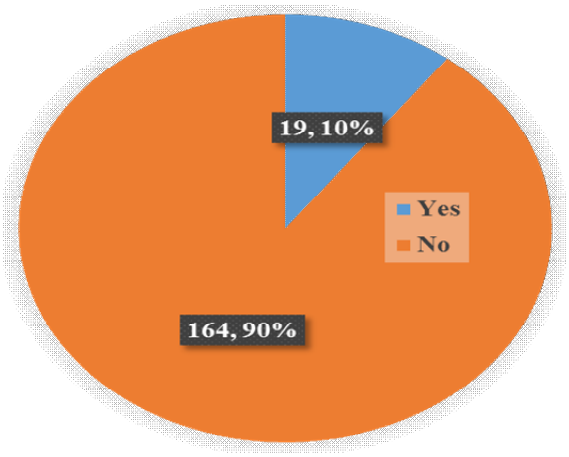

Table 1: Association of H. influenza and mortality with Age

Age Group	Yes	No	Total	P value
H. influenzae				0.148
≤1 month	11 (26.82)	30 (73.17)	41 (22.40)	
1-6 months	8 (24.24)	25 (75.76)	33 (18.03)	
6-12 months	6 (24)	19 (76)	25 (13.66)	
>12 months	10 (11.90)	74 (88.09)	84 (45.90)	
Total	**35 (19.13)**	**148 (80.87)**	**183**	
Mortality				0.35
≤1 month	**4 (10.81)**	**37 (90.24)**	41 (22.40)	
>1-6 months	**2 (6.06)**	**31 (93.94)**	33 (18.03)	
6-12 months	**5 (20)**	**20 (80)**	25 (13.66)	
>12 months	**8 (9.52)**	**76 (90.48)**	84 (45.90)	
Total	**19 (22.89)**	**164 (89.62)**	**183**	

Table 2: Association of H. influenza and mortality with gender

Gender	Yes	No	Total	P value
H. influenzae				0.69
Male	21 (18.26)	94 (81.74)	115 (62.84)	
Female	14 (20.59)	54 (79.41)	68 (37.16)	
Total	**35 (19.13)**	**148 (80.87)**	**183**	
Mortality				0.97
Male	**12 (10.43)**	**103 (89.57)**	115 (62.84)	
Female	**7 (10.29)**	**61 (89.71)**	68 (37.16)	
Total	**19 (22.89)**	**164 (89.62)**	**183**	

Table 3: Association of H. influenza and mortality with duration of illness

Duration of illness	Yes	No	Total	P value
H. influenzae				
<1day	12 (18.46)	53 (81.54)	65 (35.52)	0.31
1 t0 2 days	15 (24.59)	46 (75.41)	61 (33.33)	
2 to 3 days	7 (18.42)	31 (81.58)	38 (20.77)	
≥3 days	1 (5.26)	18 (94.74)	19 (10.38)	
Total	**35 (19.13)**	**148 (80.87)**	**183**	
Mortality				
<1day	**5 (7.69)**	**60 (95.38)**	65 (35.52)	0.12
≥1 t0 <2 days	**8 (13.11)**	**53 (86.89)**	61 (33.33)	
≥2 to <3 days	**6 (15.79)**	**32 (64.21)**	38 (20.77)	
≥3 days	**0**	**19 (100)**	19 (10.38)	
Total	**19 (22.89)**	**164 (89.62)**	**183**	

DISCUSSION

Haemophilus influenzae type b (Hib) was the leading cause of bacterial meningitis in children worldwide until the introduction of the Hib conjugate vaccine in the early 1990s [1]. Since then, the incidence of Hib disease has declined dramatically in high-income countries and virtually eliminated in parts of the United States and Europe.[10] In 1994, the Hib-conjugated vaccine was introduced into the Israeli National Immunization Program. In 1997, a four-dose vaccine schedule was adopted, given at 2, 4, 6, and 12 months of age. Prospective surveillance estimated that vaccine effectiveness was 95% (95% CI 92–96%) against any invasive disease and 97% (95% CI 93–98%) against bacterial meningitis.[11]

A total of 183 patients were included in the study according to sample size. The mean age of presentation was 16.28 months. The growth of H.influenzae was found in 35 patients (19.1%) and total 19 (10%) patients were expired.

Estimates of the burden of H influenzaein children in Pakistan are limited. The adjusted incidence of Hib meningitis was 16 per 100 000 population of less than 5 years of age in the Punjab Province of Pakistan in 2002.[12] The H influenzae type b vaccine was included in the national immunization program of Pakistan in 2008. The study conducted at Karachi and Hyderabad during March 2004-February 2005 in children less than 5 years of age with bacterial meningitis showed that CSF was positive for H influenzae in 19% cases with no mortality in H influenza meningitis[13] while a similar study conducted in the same cities during July 2008-December 2011 showed that CSF was positive for H influenzae in 13.8% cases with mortality of 26.9%.[14] These studies showed that, though, there is decline in frequency but increase in mortality due to H influenzae meningitis. The study conducted in Northern Uganda during April 2003-August 2006 in children less than 5 years of age with possible bacterial meningitis showed that CSF was positive for H influenza in 8.5% cases where the Hib conjugate vaccine was introduced in June 2002.[15] The study conducted at KEM Hospital, Pune, India April 1997-March 1999 showed the mortality of 21.4% in H influenzae meningitis.[16]

CONCLUSION

From the results obtained in our study and the comparison with international studies as well as other studies conducted all over Pakistan, it can safely be deducted that the frequency of H. Influenzae CNS invasive disease is decreased in vaccinated children below 5yrs age. In case of diseased children, who received the vaccine, the outcome was improved. With the introduction of Hib vaccine, Hib CNS invasive disease is reduced in Pakistan and, in case of disease, its outcome is improved. The introduction of Hib vaccine as part of the routine childhood immunization program is an effective step towards reducing morbidity and mortality due to Hib CNS invasive disease in children.

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