ORIGINAL ARTICLE

MENINGOCOCCAL DISEASES: POST MEN C VACCINATION ERA

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Abstract

Introduction: Meningococcal infections are caused by Neisseria Meningitidis and they are manifested in a spectrum of disease in particular meningitis. There are different strains of this bacteria which are A, C, B, W and Y. Mortality rates are from 5-15% with 10-15% suffering permanent disability. After the introduction of Men C vaccination in the year 2000, the incidences of meningitis caused by both Neisseria Meningitidis Serotype C and Serotype B have significantly reduced. **Methods:** A retrospective study of children whom lumbar puncture was performed with the preliminary diagnosis of meningococcal disease/ meningitis. Total numbers of children were 30 after excluding neonates, those with non-infectious diagnosis and failed lumbar puncture. Symptoms, signs and investigations results were collected in a data collection sheet using the documented data from the patients' chart. **Results:** Five children had positive results in either the cultures or the PCR samples sent. None of these children had Serotype C. Three children had Serotype B and 2 others were Serotype W135. **Conclusions:** There were presence of Nisseria Meningitidis Serotype B and Serotype W135 when blood and cerebrospinal fluid samples were sent. It shows how significant is the value of lumbar puncture to be done to secure a definite diagnosis of meningitis. The preventive strategy to include Men B vaccination in the national vaccination schedule is definite so that death and morbidity can be reduced.

Keywords: Meningococcal, Meningitis, Vaccination, Lumbar Puncture
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Introduction

Meningococcal infections are caused by Neisseria Meningitidis and they are manifested in a spectrum of disease in particular meningitis. There are different strains of this bacteria which are A, C, B, W and Y. The infection is endemic in Northern Europe with a background incidence of 2-3 cultures proven cases per 100,000 per annum in pre vaccination era [1]. In Ireland, most meningococcal infection is sporadic and occurs mostly during the winter and early spring. Meningococcal disease may

occur at any age but sporadic infection is most common in infancy and early childhood, with a second smaller peak of incidence in adolescents and young adults. The meningococci are transmitted by respiratory aerosols, droplets or by direct contact with the respiratory secretions of someone carrying the bacteria. The incubation period is from 2 to 7 days and the presentation of disease ranges from severe acute and overwhelming features, to insidious with mild prodromal symptoms. Ireland has one of the highest notification rates of invasive meningococcal disease in Europe based on confirmed cases in the EU/EEA, 2008-2012. Mortality rates are from 5-15% with 10-15% suffering permanent disability [1].

Presentation of Meningococcal disease caused by Neisseria Meningitidis

The children can present with an abrupt onset of fever with or without a rapidly progressing purpuric rash (especially non-blanching rash), seizures, shock and death. However the presentation can be insidious with a mild upper respiratory for 2 or 3 days. In infants or young children, the symptoms are non-specific (reluctance to feed, fever and irritability). It is sometimes difficult to recognise meningococcal disease in the initial phase. The skin may appear blotchy or pale. A typical non-blanching petechial or purpuric rash may be present with meningococcal septicaemia although the rash may be very scanty and only erythematous. During the first 4-6 hours, the children whom are admitted would have non –specific symptoms. Early symptoms of sepsis (leg pains, cold hands and feet, abnormal skin colour) are usually present at a median time of 8 hours. Haemorrhagic rash, meningism and impaired consciousness develop later with the median onset 8-10 hours in the younger children, but later in older children). The signs and symptoms of meningococcal meningitis are difficult to distinguish from those of bacterial meningitis caused by other pathogens, with the exception of the rash, which is present in some 40% of patients. Mortality rates are from 5 to 15%, with 10-15% suffering permanent disability and mortality is higher in those presented with septicaemia [1]. Complications in survivors include seizures, skin scarring, digit or limb amputation, chronic renal failure, hearing loss and intellectual deficits.

Implementation of Men C vaccination in the Republic of Ireland

After the introduction of Men C vaccination in the year 2000, the incidence of meningococcal disease caused by Neisseria Meningitidis Serotype C has significantly reduced, from crude incidence rate of 4/ 100 000 population in the year 1999 to almost none in 2015. Interesting enough the incidence of those caused by Serotype B has also reduced which is most probably due to cross protection given by Men C vaccination from crude incidence of 14.5/100 000 population in year 1999 to approximately 4/100 000 population in 2015 [1].

With the significant mortality and morbidity before the introduction of the vaccination, it is important to evaluate the value of lumbar puncture in preliminary diagnosis of meningococcal disease/ meningitis especially after the introduction of Men C vaccination in 2000.

Study design

A retrospective study of children whom lumbar puncture was performed with the preliminary diagnosis of meningococcal disease/ meningitis during admissions under Paediatric team. Total numbers of children were 30 after excluding neonates, those with

non infectious diagnosis and failed lumbar puncture.

Methods

Thus the total number of patients data was extracted from was 30 patients. Data was extracted from case records using a structured data collection sheet (as shown in Appendix A). Information extracted included the age, vaccination status, symptoms at presentation, signs shown during the examination, source of infection, investigation results, initial diagnosis and final diagnosis. Investigations results that were taken into account for this study were Cerebrospinal fluid (CSF) culture, CSF Polymerase chain Reaction (PCR) analysis for meningococcal, Blood PCR analysis for meningococcal, Peripheral blood culture (Blood C&S), C-Reactive Protein (CRP) of more than 10 and Total white cell count (WCC) of >15 or <4. The study has excluded the biochemistry results of glucose as most of the patients did not have serum blood glucose done at the time of lumbar puncture thus making it impossible to make a comparison. Protein count is also excluded in view of different levels are used biochemically for different age groups in order to state whether the results are significant or not. White cell count in the CSF is also excluded as a number of the lumbar puncture done resulted in traumatic tap making it difficult to justify the significance of the presence of white cell in the CSF. We have also included the imaging done for these children.

Results

Descriptive data of the studied patients

During the study, there is variation of ages collected. The gender distribution is almost similar as out of the 30 patients, 52.6% were males and 47.3% were females. Most of the lumbar punctures performed were for the children in the range of 1-6 months of age. As out of the 30 patients 53% of them were within this age group. The numbers of lumbar puncture done were lesser in the older age group. The younger they were, the threshold of performing lumbar puncture was lower.

In regards with the vaccination status from these 30 patients, 21(70%) children received the Men C vaccination and 9 (30%) did not. We did not include the reason why these children did not receive the vaccination in this study.

Descriptive by the presenting symptoms and signs

We have included the symptoms which most of these patients would be presented with when they were given the preliminary diagnosis of meningococcal disease. These include; fever, rash, seizures, non specific abnormal movements, confusion and irritability, vomiting and headache (Table 1). The signs we have included in this study are; tachycardia of more than 140, temperature of >38 degrees or <36 degrees, bulging fontanels, non blanching rash, capillary refill of more than 2 seconds and neck stiffness (Table 2).

Table 1. Distribution according to symptoms

Symptoms	Number of patients (n=30)	Percentage
Fever	27	90%
Rash	6	20%
Seizures	5	16%
Non specific abnormal movements	2	6%
Confusion and irritability	15	50%
Vomiting	10	33%
Headache	2	6%

Most of these children presented with fever (90%) and confusion and irritability (50%). Only 2 of them had headache and both of these patients were at the age range of 11-14 years old which was expected as they were able to report so to the clinicians. The younger children were not able to specify if there was any headache thus they would present with irritability instead.

Table 2. Distribution according to signs

Signs	Number of patients (n=30)	Percentage
Tachycardia >140	13	43%
Temperature >38/ <36	26	87%
Bulging fontanel	1	3%
Non blanching rash	4	13%
CRT >2seconds	6	20%
Neck stiffness	3	10%

Twenty-six of these children had a documented temperature of more than 38 degrees instead of less than 36 degrees. Twenty-seven children had a complaint of fever as we have mentioned earlier. The numbers are almost matched thus we are able to conclude that the complaints given by parents are almost always true and history taking is very important. Four children (13%) had non blanching rash detected by the clinicians and 6 children had CRT of more than 2 seconds secondary to shock. Three children who had neck stiffness were also at the range of age 11-14 years old.

Investigation results obtained

The investigations included were; CSF culture, CSF PCR analysis, Blood PCR analysis for meningococcal, Peripheral blood culture, C-Reactive Protein of more than 10 and Total white cell count of >15 or <4 (Table 3 and 4).

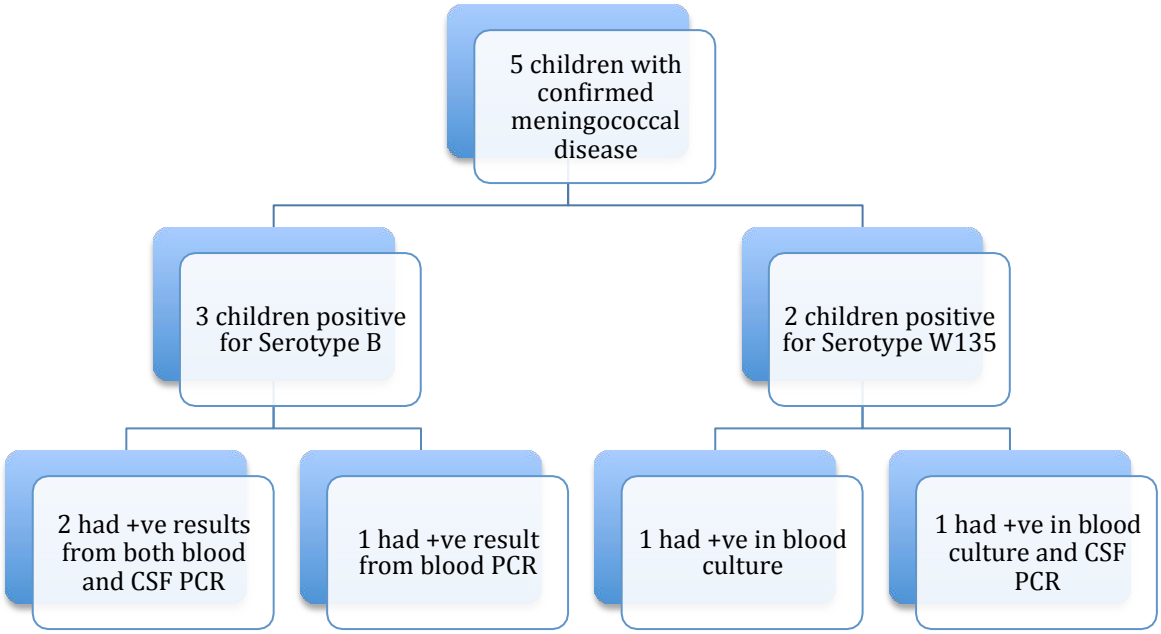
The diagnoses

Thirty patients had undergone lumbar puncture with the preliminary diagnosis of meningococcal disease with query meningitis. None of these children had

undergone imaging once the preliminary diagnosis of meningitis and possible meningococcal disease were given. Out of these, Three patients had confirmed case of meningitis, five were treated as possible meningitis due to the clinical presentations although no biochemical results positive.

Nineteen patients were labelled as having viral illness with no specific source of infection and Three patients with specific source of infection that lead to other concrete final diagnosis which were vulval abscess, E. coli urinary tract infection and Kawasaki disease.

Figure 1. Children with positive result in CSF or blood samples sent



From these 5 children, 3 of them had positive result for Meningococcal Serotype B and these children received Men C vaccination (Figure 1). The other 2 children who were also positive for meningococcal disease but did not receive any Men C vaccination had Serotype W135 in the culture/PCR. None of these children had N. Menigitidis Serotype C even though 2 of these children did not receive any Men C vaccine. Thus it proves how effective the vaccination has been and herd immunity has been achieved. It is also a new discovery of W135 detection in Republic of Ireland since year 2000 when Men C vaccination was implemented.

We have decided to show in details what were the symptoms, signs and other investigation results for these children who were diagnosed as meningoccoccal disease/ meningitis.

Table 3. Patients with positive N. Meningitidis Serotype B:

No	Age	Symptoms	Signs	Investigations
1	14yo	Fever, rash	Temp >38, non blanching rash, neck stiffness, CRT >2secs	Negative in blood and CSF cultures. Positive in blood and CSF PCR. CRP>10, WCC >15
2	2yo	Fever, rash, irritability, vomiting	HR >140. Temp >38, non blanching rash, CRT>2secs	Negative in blood and CSF cultures. Positive in blood and CSF PCR. CRP>10, WCC >15
3	5mo	Fever, rash, irritability, vomiting	Temp >38, non blanching rash, neck stiffness, CRT >2secs	Negative in blood culture, CSF culture and blood PCR. Positive in blood PCR. CRP>10, WCC >15

Table 4. Patients with positive N. Meningitidis Serotype W135:

No	Age	Symptoms	Signs	Investigations
1	10mo	Fever	Temp >38	Negative in CSF culture, CSF PCR and blood PCR. Positive in blood culture. CRP<10, WCC >15
2	15mo	Fever, irritability,	Temp >38	Negative in CSF culture and blood PCR. Positive in blood culture and CSF PCR. CRP<10, WCC >15

The presence of rash and non blanching rash in the documented symptoms and signs with high CRP of more than 10 was 100% in the children with positive N. Meningitidis Serotype B in the culture/PCR. Both children with Serotype W135 did not present with any rash and surprisingly enough the CRP is less than 10. But all of them had documented fever and in addition to that they all had WCC >15. The 2-year-old with positive N. Meningitidis Serotype B was severely ill, needing intubation, ventilation and transferred to a tertiary hospital in Republic of Ireland. Subsequently after the treatment he recovered well with no neurological deficit so far.

None of the CSF cultures are positive in comparison with the blood cultures. The CSF and blood PCR were the most sensitive tests as most of the positive results were shown in the PCR tests.

Discussion

The presenting symptoms and signs

History taking is vital in order to guide a clinician to decide whether or not to proceed with the lumbar puncture. It was shown that the threshold to do lumbar puncture was lower in the younger patients, especially those below 6 months. The reasons for this are most probably due to the fact they have not received the total doses of the vaccinations and they presented with non-specific symptoms when they attended the clinic/hospital. The age of greatest risk of meningococcal disease/meningitis is still under 1 year of age [2].

Most of these children presented with fever with documented temperature of more than 38 degrees. The presence of meningitis with a non blanching rash is likely to be meningococcal. Only those with Serotype B presented with non blanching rash in this study. Those with positive W135 did not present with any rash. Thus, the suspicion of meningococcal disease/meningitis should not just be based on the rash seen but also the other clinical factors as well.

Sensitivity and specificity of the investigations and results obtained

From this study, none of the CSF culture showed any positive results. Due to the concern of meningococcal septicaemia evolving, antibiotics were already given in the General Practitioner's clinic (GPs). If lumbar puncture is not thought to be safe, empirical antibiotics therapy should be given without delay. However, as the antibiotics were given before hand- the cultures from the CSF would be negative. The CSF cultures are negative 2 hours after parenteral antibiotics are given in meningococcal meningitis [3].

New molecular technique for simultaneous detection of N.Meningitidis by CSF PCR may be helpful. The most sensitive and specific investigations are the PCR (either the blood or CSF PCR). Four out of 5 children with positive diagnosis of meningococcal disease/ meningitis had positive meningococcal PCR in this study. Meningococcal PCR of CSF obtained at a delayed lumbar puncture has a sensitivity of 81 % [5]. On the other hand, in a prospective study, sensitivity of blood PCR is only 47% but recently there have been suggestions that it has increased to 88% [6].

Two children with meningococcal meningitis Serotype W135 had positive blood cultures and they didn't present with rash. We were able to yield positive blood culture from those positive with W135 as children did not present with any rash and not sick thus they did not receive any intramuscular antibiotics when they attended the GP practise. Blood culture helps to identify the causative organisms. Blood cultures are positive in 23% of cases of meningococcal septicaemia but less than 10% if antibiotics are given [7] for suspected childhood meningitis without a non blanching rash [8]. The yield from blood culture was better than the CSF in our study could be explained from our practice of taking blood cultures earlier during the intravenous cannulation which was vital for initial resuscitation/ fluids/ investigations.

Imaging in children with meningitis

None of the children with the preliminary diagnosis of meningitis had any imaging done as they did not have any evidence of raised intracranial pressure. Computed tomography (CT) scanning done in children with clinical presentations of meningitis mostly are normal scans except those showing evidence of clinical raised intracranial pressure [9].

Herd Immunity

Herd immunity is the prevalence of immune individuals in a population. The term is used commonly in a broader sense to relate to the concept that the presence of immune individuals in a population can indirectly protect those who are not immune against infection [10]. Two of our patients who did not receive vaccination for Men C were not infected with Serotype C.

Meningitis with Meningococcal bacteria Serotype B

Three of the children with positive Serotype B recovered well when they were treated correctly. Despite the incidence of Serotype B has decreased, it is still a major cause of severe meningococcal septicaemia. An Irish study involving 2 tertiary paediatric hospitals conducted from 2001-2011, showed out of 382 cases studied, 94% were serotype B and another 3% were Serotype C [11]. Fifteen (3.6%) patients died [11].

Emergence of W135 in Ireland

Serotype W135 made a big headline in 2000 after the Hajj when there was a major outbreak, subsequently after that few countries had recorded positive results in both groups of "pilgrims-contact" and "non pilgrims-contact" especially in Great Britain and France [12]. With the migration and mixtures of population, W135 Serotype carriers may possibly present in Republic of Ireland.

Conclusion

The success of Men C vaccination can be seen as the incidence has decreased substantially and there is none in our cohort. However, there are still positive yield of Serotype B and also the emerging W135. Confirming the diagnosis of meningococcal disease is important now that serotype C conjugate meningococcal vaccine is given in United Kingdom/Ireland, to confirm the vaccine's efficacy and also to help us to detect children who do not respond to the vaccination. This study has shown the important value of lumbar puncture to diagnose meningitis. The value of PCR in securing definite diagnosis is undeniable as diagnosis of meningococcal disease/meningitis are assisted by PCR results. As the Irish study had shown, Serotype B infections remain dominant. The preventive strategy to include Men B vaccination in the national vaccination schedule is definite so that death and morbidity can be reduced.

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