Case Series

Case series of meningococcal sepsis: are we seeing the real picture?

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Abstract

Invasive meningococcal sepsis caused by *Neisseria meningitidis* is of global health concern with high morbidity and mortality. *N. meningitidis* can cause sporadic cases, focal outbreaks (institutional based) and large epidemics. Here we report eleven cases of invasive meningococcal sepsis in Sri Lanka during a period of eight months which is a significant occurrence. In our case series, age of presentation ranged from 1.5 to 67 years. There were 7 (63.6%) males. Four patients were associated with inmates of two prisons. The majority of patients were from urban, crowded areas in Colombo and the adult working population. All were promptly treated with antibiotics on suspicion and aetiology confirmed by blood cultures. Contact tracing, notification and prescription of chemoprophylaxis to contacts of these sporadic cases were carried out. Four (36.3%) patients died, and the others recovered without any complication. It is important to maintain a strong surveillance programme to identify epidemics early and to initiate timely preventive measures in the population.

Key words: Neisseria meningitidis, meningococcemia, meningitis, invasive meningococcal disease, epidemics Sri Lanka

Introduction

Meningococcal sepsis is not commonly reported in Sri Lanka. Only a few cases have been reported[1,2], and this is the largest case series managed in Sri Lanka. Invasive disease due to *Neisseria meningitidis* is a medical emergency. The prognosis is good in meningococcal meningitis if treated adequately and promptly, whereas meningococcemia is often lethal despite treatment and can result in death rapidly.[3] Serogroups A, B, C, W135, X and Y account for the majority of invasive disease and are capable of initiating epidemics.

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Therefore, understanding of disease burden in our community is essential to decide and implement preventive strategies and to maximize utilization of healthcare resources.

We report a case series of invasive meningococcal disease in Sri Lanka within a short period of time which is alarming. Vaccines are available globally but are not a part of the Expanded Programme of Immunization (EPI) in Sri Lanka.

Case series

Several cases of confirmed meningococcal sepsis were encountered in major tertiary care hospitals in Sri Lanka from July 2019 to February 2020, which is a significant occurrence in our local setting. A possible source of exposure was not identified in any of these patients.

Table 1: Clinical presentation of cases

Case	Month	Place of case reported	Age /yrs	Sex	Occupation	Presentation	Diagnosis	Outcome
1	July 2019	Maradana	39	M	street vendor	fever, purpuric skin rash, septic shock	Meningococcemia	death
2	July 2019	Mattakkuliya	12	F	school child	fever, altered level of consciousness, purpuric skin rash	Meningococcemia & meningitis	death
3	August 2019	Colombo 10	33	F	housewife	fever, headache, photophobia	Meningococcemia & meningitis	complete recovery
4	September 2019	Welikada Prison	56	M	prison inmate	fever, septic shock	Meningococcemia	death
5	October 2019	Mattakkuliya	6	M	school child	fever, purpuric skin rash, septic shock	Meningococcemia	death
6	December 2019	Colombo 13	45	M	businessman	fever	Meningococcemia	complete recovery
7	December 2019	Pannipitiya	38	M	factory worker	fever, purpuric skin rash, septic shock	Meningococcemia & meningitis	complete recovery
8	January 2020	Mannar	1.5	M		fever, purpuric skin rash, septicaemia	Meningococcemia	complete recovery
9	January 2020	Batticaloa Prison	27	M	prison inmate	fever, headache, vomiting, purpuric skin rash	Meningococcemia & meningitis	complete recovery
10	January 2020	Batticaloa	25	F	housewife	fever, generalized body aches, purpuric skin rash	Meningococcemia	complete recovery
11	February 2020	Modara, Colombo 15	67	F	labourer	fever, loss of consciousness	Meningococcemia & meningitis	complete recovery

There were eleven culture confirmed patients with invasive meningococcal disease reported from July 2019 to February 2020. Their demographic features, clinical presentation and clinical outcome are highlighted in Table 1.

Case 1: The first patient in our case series was a 39 year old male from Maradana (Figure 1) with meningococcemia who presented with a one day history of fever, rash and being generally unwell. He died despite treatment with intravenous (IV) meropenem for 2 days following admission in July 2019.
Case 2: A few days later, a 12 year old girl from Mattakkuliya (Figure 1) presented with fever, rash and altered level of consciousness. IV meropenem was commenced after taking blood for culture which became positive in 24 hours. She was diagnosed as having meningococcaemia and meningitis. She died despite treatment in intensive care after 4 days. Her father was an inmate of the Welikada Prison who was released 1 week prior to her admission.
Case 3: In August 2019, a 33 year old housewife from Colombo 10 (Figure 1) was investigated for fever and headache of two days duration and diagnosed with meningococcemia and meningitis. She was treated with IV ceftriaxone and discharged after 14 days.
Case 4: A 56 year old prison inmate from Welikada Prison (Figure 1) died due to meningococcemia in September 2019. He received IV meropenem but succumbed to his illness by the time blood culture became positive for meningococcus.
Case 5: In October 2019, a 6 year old boy from Mattakkuliya (Figure 1) was admitted to a tertiary care centre with fever which appeared since early morning of the day of admission and rash which appeared 6 hours later. Two days prior to the onset of his symptoms he had attended a children's' day activity programme. IV crystalline penicillin and ceftriaxone were started after taking blood for culture. He deteriorated over 6 hours into septic shock. He died of meningococcemia leading to multi organ failure 48 hours after admission.
Case 6/7: In December 2019 two cases of invasive meningococcal disease were reported from Colombo 13 and Pannipitiya (Figure 1). Both were males treated with IV ceftriaxone and recovered fully without any sequelae.

Thereafter 3 cases were reported outside the Colombo district.

Case 8: A one year and 5 month old baby presented with a history of fever for 1 day which was diagnosed as meningococcemia in January 2020 in Mannar (Figure 1). He received combined treatment of IV meropenem and ciprofloxacin and had an uneventful recovery.
Case 9/10: Another 2 cases of meningococcemia connected to the Batticaloa Prison (Figure 1) were reported in January 2020. One patient was an inmate who was admitted complaining of fever, headache, vomiting, rash and giddiness for 2 days. He was treated with IV ceftriaxone for meningococcemia and meningitis. He was discharged after 25 days of hospital stay. The other patient reported from Batticaloa was a spouse of an inmate who presented 1 week after the release of her husband from the Batticaloa Prison. She was admitted to the hospital complaining of fever, rash and generalized body aches for 2 days and diagnosed with meningococcal sepsis. She was managed with IV ceftriaxone and discharged after 12 days from the hospital. A one week prior to the notification of above cases in Batticaloa, there was a transfer of prison inmates from Welikada prison to Batticaloa prison. One week prior to the notification of these cases in Batticaloa, there was a transfer of prison inmates from Welikada Prison to Batticaloa Prison.
Case 11: In February 2020, a manual labourer from Modara, Colombo 15 (Figure 1) complained of fever for two days and became unresponsive on the day of admission. She was

treated for meningococcemia and meningitis for 7 days with IV ceftriaxone and discharged without complications.

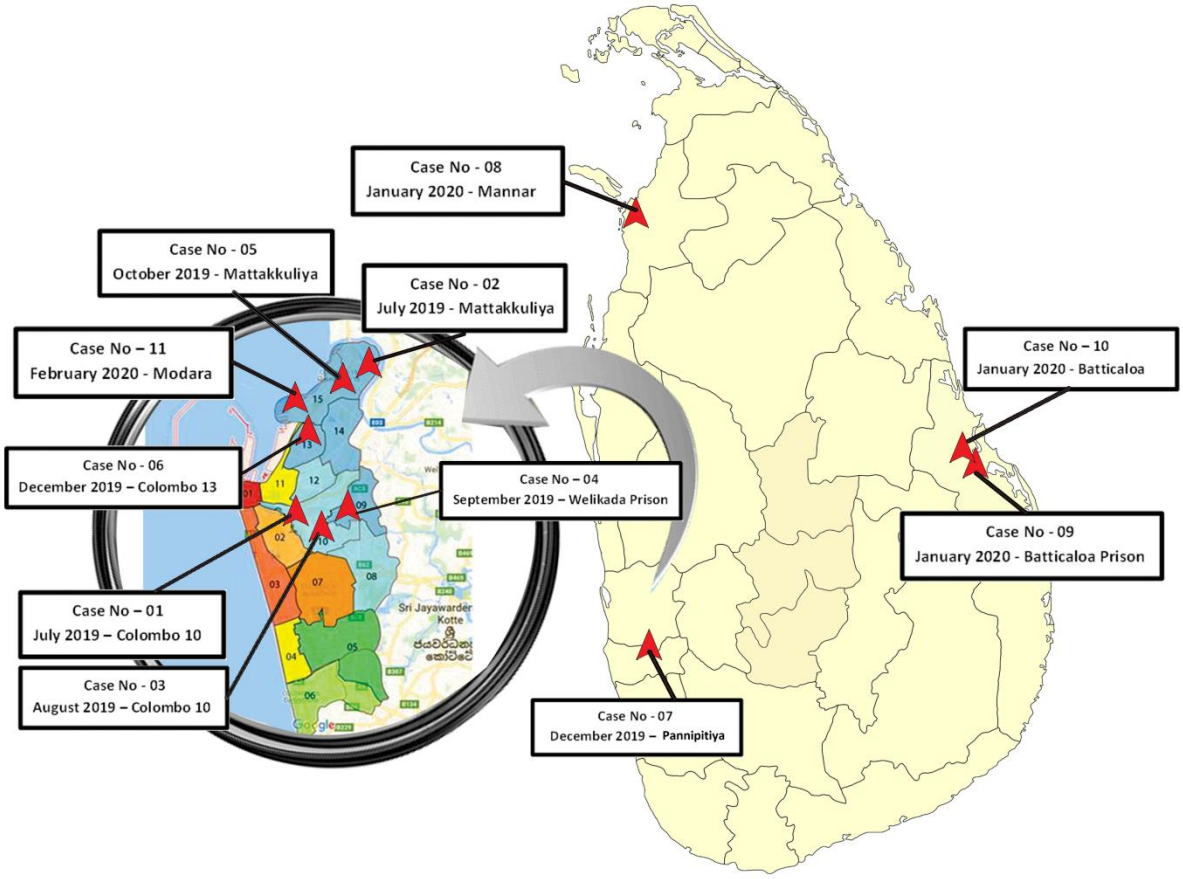

Fig 1: Distribution of confirmed cases of meningococcal sepsis in Sri Lanka

None were known to have any comorbidities or immunodeficiency. Residing in high population dense areas of Colombo district and association with the prisons were the main risk factors identified in three patients in this cohort.

Table 2: CSF full report and culture results of patients with meningitis

Index Case No	CSF full report						CSF Gram stain	CSF Culture
	Protein (mg/dL)	Glucose (mg/dL)	RBS (mg/dL)	Neu (/mm3)	Lym (/mm3)	RBC (/mm3)		
2	No LP done, clinically diagnosed meningitis							
3	163	15	163	4823	9	782	NOS	NG
7	49.4	64	118	360	36	-	NOS	NG
9	77	66.6	172.8	205	80	-	NOS	NG
11	172	82	200	1440	20	-	NOS	NG

NOS: No organism seen NG: No growth

All patients had positive blood cultures for *N. meningitidis*, 8 of which were confirmed by PCR at the Medical Research Institute, Colombo and biochemically (3 isolates) at the Central Laboratory at National STD/AIDS Control Programme. Five (45.5%) patients had meningococcal meningitis. Except for index case 2, the other 4 patients underwent lumbar puncture, which was suggestive of bacterial meningitis (Table 2).

Contact tracing for the 11 cases followed by chemoprophylaxis of healthcare workers/close contacts and relevant authority notification were carried out. Close contacts were prescribed either ciprofloxacin or ceftriaxone as chemoprophylaxis. Four patients died and the others recovered without any complication. A significant contributory factor or delayed presentation was not found in the 4 patients who died and all 11 were promptly directed to appropriate clinical management. Three of the deceased patients received intensive care treatment.

Discussion

Meningococcal disease is an acute, potentially fatal illness caused by *N. meningitidis*. It is a major cause of bacterial meningitis globally and of significant public health concern due to high mortality, morbidity and ability to create outbreaks.[1,2,3] The fatality rate is about 13% even with treatment whereas without treatment it rises up to 50%-90% and 3%-4% of survivors suffer from complications.[3]

This case series of invasive meningococcal disease is the first and largest reported in Sri Lanka which highlights an impending serious health problem for our community.

Data for meningococcal disease in Sri Lanka is limited to a few case reports with 2 cases from Colombo published in 2012 and 2020.[4,5] From July 2019 to February 2020, we report 11 cases in Sri Lanka with a fatality rate of 36.3%. Survivors didn't develop any complications. Eight patients in our cohort were from the Colombo district.

In 2012 Dissanayake et al. reported a 2.5 year old boy who presented with meningococcal septic shock and died soon after admission to a tertiary care hospital in Colombo. He gave a one day history of fever and vomiting followed by rapid deterioration of his conscious level with a progressive generalized purpuric skin rash. His postmortem revealed haemorrhages in adrenals, brain and lungs. Cardiac blood obtained during postmortem yielded *N. meningitidis*.[4] In our cohort the youngest patient was 1.5 years old who had an uneventful recovery. However, the other 2 paediatric patients in our case series died with multi organ failure. None of our cases underwent postmortem since antemortem blood cultures were available.

Another case was reported by Puthra et al. in 2020 that describes meningococcemia in an adult male patient who presented to a tertiary care hospital in Colombo. He presented with fever and constitutional symptoms for 3 days, subsequent development of shock and reduced consciousness. Later he developed a purpuric skin rash. He made a full recovery following successful treatment with intravenous ceftriaxone for meningococcemia and meningitis. His close contacts were prescribed ciprofloxacin as chemoprophylaxis.[5]

Both case reports occurred in previously healthy patients. Similarly, in our case series there were no underlying host defects such as asplenia, autoimmune diseases or immunosuppressive treatment that predisposed to meningococcal sepsis.[3,5]. Association with overcrowding and prison are well known risk factors for meningococcal disease as *N. meningitides* is highly contagious and transmitted by inhalation of respiratory droplets or direct contact with respiratory secretions of colonized persons.[1, 6] Also disease transmission is significantly increased in closed populations such as military stations, prisons, slums, schools and nurseries.[3,5]

In the previously reported two cases, one patient who had meningococcemia without meningitis died. In our case series, three of the four deceased patients had meningococcemia only. Meningococcemia is more severe than meningitis as there is endovascular inflammatory response and thrombosis whereas in meningitis the inflammatory response is localized to an extravascular compartment.[7]

Both patients reported previously had the classical purpuric skin rash accompanying shock. In our patients, the majority developed a purpuric skin rash and those who succumbed to death had rapid onset of multi organ failure and shock.

The gold standard of diagnosis remains the culture. The detection of antigen or DNA of *N. meningitidis* from sterile site also confirms the disease.[2,6,7] Gram staining of blood, CSF and skin aspirates facilitates early identification of patients for targeted therapy. All our patients had meningococcemia and their meningococcal isolates were subsequently confirmed by biochemical tests and PCR. Facilities for serogrouping of *N. meningitidis* which is essential for the establishment of epidemiological links were not available in Sri Lanka.

In 2004, there were 8 paediatric patients with meningitis reported in the Colombo district identified by latex agglutination test for *N. meningitidis* in cerebrospinal fluid. However, they were culture negative, although automated blood cultures were done in these patients.[8] Our case series reported 5 patients with meningococcal meningitis. The 12 year old girl in our case series passed away even with aggressive treatment and was unable to undergo LP due to clinical instability. Four other patients underwent lumbar puncture and CSF samples were suggestive of bacterial meningitis based on cell count and biochemical profile. Direct Gram stain and culture of CSF was negative. Latex agglutination test was not performed due to the limited CSF volume.

In our cohort of patients, none received antibiotics prior to their hospital admission. Patients in our case series received IV antibiotics and some were treated in the intensive care unit. Intensive care treatment and significant stay in hospital cause additional health expenditure. The majority of our cases were male adults who lost their income during the period of illness. All were previously healthy, and the mortality rate is alarming. Their illness was a serious loss to their families.

Puthra et al. reported prescribing ciprofloxacin as the chemoprophylactic agent.[5] Chemoprophylaxis prevents invasive disease by eliminating meningococcus carriage where close contacts are 1000 times more susceptible to develop.[6,7,9] It has been shown that chemoprophylaxis is highly cost effective in the short term as well as long term by reducing the morbidity, mortality and healthcare cost.[9,10] Ciprofloxacin and ceftriaxone were prescribed as chemoprophylaxis for close contacts in our cohort of patients.

In Sri Lanka, meningitis is a notifiable disease, but meningococcal disease is not included in the national notifiable diseases and not considered as endemic. However, all our cases were reported to the Epidemiology Unit due to the seriousness and potential ability to cause an outbreak.

Though laboratory facilities are established to isolate and identify *N. meningitidis* from body fluids, serogrouping which is important in establishing preventive measures is not available in Sri Lanka. Spread of meningococcal infection can easily occur due to increased global travel. As a preventive measure, a tetravalent vaccine (A, C, W135, Y) is mandatory for

people who travel to endemic areas and pilgrims to Hajj, Ramadan Omra, Saudi Arabia.[11] Being an obligate human pathogen, meningococcus does not survive in the environment or animals. A single case signifies the presence of hundreds of persons with upper respiratory tract colonization. In an outbreak there is continuous transmission and acquisition of invasive *N. meningitidis* via asymptomatic carriers throughout the population. Therefore, meningococcal cases might not be directly related to close contacts.[9] WHO defines an outbreak outside the meningitis belt as a considerable escalation of invasive meningococcal disease than expected by place and time in a defined population. This could be even two cases of meningococcal disease by the same serogroup in a population over a short period of time.[12]

This case series signifies clear evidence of a surge of meningococcal infection in our community and the density of the infection signifies possible patterns of spread in Sri Lanka, which raises many questions regarding meningococcus:

- What is the serogroup that is circulating in our population?
- None of the cases gave a contact history with travellers to endemic region. Therefore, does this signify the possibility of this deadly disease becoming endemic in our community?
- Do we have to consider mass antibiotic chemoprophylaxis or vaccination of risk populations in the future?
- Do we have to start surveillance studies to determine whether meningococci are prevalent in upper respiratory flora in risk populations such as prisons?

The greatest limitation in Sri Lanka is the unavailability of serogrouping of *N. meningitidis*. As a result, the connection between the cases and establishment of an outbreak is not possible.

This case series emphasizes the need to establish laboratory facilities for serogrouping of *N. meningitidis* for surveillance as well as early identification of outbreaks. In addition, measures to improve recognition of *N. meningitidis* infection would be helpful to both clinical and laboratory staff. As previously mentioned, improved notification of both meningitis and sepsis with improved diagnostic capability of culture negative samples would also help in identifying the scale of this infection. At the same time publishing a protocol for treatment, contact tracing and prophylaxis would also assist in improving outcomes where possible.

The necessity of meningococcal vaccination in our population needs to be re-evaluated which largely depends on the knowledge of meningococcal disease burden. Apart from that, it is essential to ensure the sustainability of vaccination of travellers to endemic region.

Conclusion

Invasive meningococcal infection is reported as sporadic cases in Sri Lanka. However, this case series suggests the possibility of endemicity. The disease burden is not known at the moment. Sri Lanka needs to enhance diagnostic facilities and establish laboratory facilities for serogrouping of *N. meningitidis* for surveillance as well as early identification of outbreaks.

Declarations

Conflict of interest: There are no conflicts of interest.
Ethics statement: No ethical approval was obtained as no patient identification details were divulged.
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Author contributions
JG, NSC and CGUAP drafted the article.
All authors contributed to the manuscript intellectually.
JG, NSC, CGUAP, MD, VRF and CTH were involved in the patient management.
LK was involved in the molecular diagnosis of *N. meningitidis.*
CGUAP supervised the study.

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