Original

Meningococcal carriage in the Japan Disaster Relief team candidates: a series of cross-sectional studies

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Abstract: [Background] Young individuals living in dormitories are at a high risk of meningococcal disease. This study aimed to investigate the risk of meningococcal carriage of the Japan Disaster Relief (JDR) team of Self-defense Forces (SDF) in relation to their behaviors. [Methods] We surveyed JDR personnel(2020-2022) to detect bacteria in pharyngeal swab fluid by culture, amplification of the flagella gene (*ctrA*) using the Loop-mediated isothermal amplification method, and questionnaires. [Results] Five consecutive surveys were conducted every six months in response to the replacement of JDR candidates. Among the registered 731 individuals, 5/147 (3.4%) in group 1, June 2020 were culture-positive, and the others were all culture-negative. The five isolates were identified as serogroups B(N＝2), 29E(N＝1), and ungroupable(N＝2); B/29E were *ctrA*(+). The genotypes were consistent between the two serogroup B and two non-groupable strains, respectively. Living in multiple-bed rooms in dormitories exhibited relatively high-risk ratios with no statistically significant differences (Odds Ratio; 2.9, 95%CI; 0.2-154.6). [Discussion] This is the first study on meningococcal carriage in SDF. The carriage rate in group 1 exceeded previous reports for the general Japanese population, highlighting increased risk among the personnel. The isolation of MenB strains emphasizes the need for MenB-containing vaccines, besides the available MenACWY vaccine.

Key words: meningococcal carriage ／ JDR

Introduction

Neisseria meningitidis causes meningococcal infections. Humans are the only carriers of such bacteria, and their transmission from patients or carriers to the pharynx of healthy close contacts is required for disease onset. Although most carriers are subclinical, some develop the disease if they spread systemically from the mucous membranes of the respiratory tract, causing headaches, fever, nausea, and vomiting. If the disease progresses rapidly from bacteremia and meningitis to shock, the fatality rate can reach 10%[1)]. Sporadic cases and outbreaks have been reported among adolescents living in dormitories and enlisted in the military, in which high carriage rates have been observed[2-5)]. In

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2017, a fatal case of an invasive meningococcal infection was reported in a student at the National Defense Academy. Notably, meningococcal meningitis is an important disease for the Japan Self-defense Forces (SDF).

Meningococcal carriage, which is prerequisite of the disease, is known to be more common in the age group of approximately 20 years[6]. A domestic survey of meningococcal carriage showed 0.4% in oral swabs of students, adults, the elderly, and foreigners; 0.8% in university students commuting from home; and 0.4–2.1% in college dormitory students[7-9]. Besides the above fatal case reports, the carriage rates among SDF are unknown.

In the SDF, a preparatory unit of the Japan Disaster Relief (JDR) team is established by changing its members every six months in preparation for possible requests for international emergency assistance. A higher level of carriage rate other than previous studies among domestic non-military people is expected and JDR members likely have a higher risk of exposure to meningococci compared to others in the SDF during domestic living and training in concentrated groups and overseas deployment. We believe that a series of cross-sectional studies would be useful for maximal risk assessments.

Materials and Methods

Cross-sectional studies were conducted in five consecutive groups from 2020-2022 to survey meningococcal carriage rates and evaluate associated risk factors. To determine the status of live bacteria, pharyngeal swabs were collected onsite by medical doctors among authors with Opti-swab® and Dry transport system® swabs (Puritan, Inc., ME USA) and were transferred and cultured at a commercial laboratory (BML, Inc., Tokyo, Japan) on modified Thayer-martin medium and chocolate agar medium at 5% CO_2 at 35℃ for 18-24 h. The culture was followed by colony identification using the oxidase test, Gram staining, mass spectrometry, and VITEK-MS®[9]. Meningococcal isolates were sent to the National Institute of Infectious Diseases for serotyping and genotyping. To detect encapsulated meningococci in swabs with high sensitivity, the capsular *ctrA* gene was tested using loop-mediated isothermal amplification (LAMP) method at the National Defense Medical College[10]. For each survey, we conducted a self-administered questionnaire in which demographic and behavioral histories for the month before the test were recorded. For instance, sex, age, living style, behaviors as travel abroad, smoking, alcohol drinking, social parties, kissing, sharing food and drinks, as well as medical history of upper respiratory tract infection and antibiotics administration. Odds ratio (OR) values with their 95% confidence intervals were calculated using Stata 16.0 (Stata, College Station, TX USA).

The study was approved by the Ethics Committee of the National Defense Medical College (No.4134) and written informed consent was obtained from all participants.

Results

In response to the replacement of all JDR members, a survey was conducted every six months. There were five targeted groups in three years, namely groups 1-5. We enrolled 731 participants (69-196 per group) (Table 1). Because JDRs were not dispatched during the study period, this study focused on their pre-deployment status. Among the 147 participants in group 1, five (3.4%) were culture-positive, and

Table 1. Meningococcal carriage survey in five groups of JDR during 2020-2022

Group	Data collected	Number of Participants	Positive (%)
1	Jun 2020	147	5 (3.4%)
2	Nov 2020	196	0 (0%)
3	Dec 2021	132	0 (0%)
4	Jul 2022	187	0 (0%)
5	Dec 2022	69	0 (0%)

Table 2. Characteristics of the isolated meningococcal strains in group 1

No.	serogroup	genotype	ctrA
1	B	ST-6878 (cc41/44)	+
2	B	ST-6878 (cc41/44)	+
3	29E	ST-15569 (cc178)	+
4	NT	ST-11026 (cc32)	–
5	NT	ST-11026 (cc32)	–

those in groups 2-5 (n = 584) were all negative.

The five strains isolated from group 1 were identified as serogroups B (N = 2), 29E (N = 1), and non-typable (non-producing capsular polysaccharide) (N = 2) (Table 2). The LAMP method revealed that strains B (N = 2) and 29E (N = 1) were positive for *ctrA* in the capsular polysaccharide locus, which is consistent with the identification of encapsulated serogroups.

Serogroup B isolates (N = 2) were genotyped as ST-687 (cc41/44), and the non-typable (NT)

Table 3. Characteristics of the participants in group 1

			Meningococci positive (n = 5)	Meningococci negative (n = 142)	Odds Ratio	95%CI
Demographics						
Sex	Men		5 (100.0%)	121 (85.2%)	–	–
	Women		0 (0.0%)	21 (14.8%)	reference	reference
Age (y)	Median (IQR)		29 (22.5-34)	35 (28-42)		
Living style	Dormitory – multiple-bed room		3 (60.0%)	55 (38.7%)	2.9	0.2-154.6
	Dormitory – single-bed room		1 (20.0%)	32 (22.5%)	1.7	0.02-132.4
	Outside the station		1 (20.0%)	53 (37.3%)	reference	reference
	Unknown		0 (0.0%)	2 (1.4%)	–	–
Behaviors during the past month						
Travel abroard		Yes	1 (20.0%)	53 (37.3%)	0.4	0.01-4.4
		No	4 (80.0%)	89 (63.0%)	reference	reference
Smoking		Yes	2 (40.0%)	41 (28.9%)	1.6	0.1-14.8
		No	3 (60.0%)	101 (71.1%)	reference	reference
Alcohol drinking		≥ 1/week	1 (20.0%)	68 (47.9%)	0.2	0.003-2.1
		≥ 1/month	1 (20.0%)	41 (28.9%)	0.3	0.005-3.6
		No drinking	3 (60.0%)	33 (23.2%)	reference	reference
Social parties		≥ 1 / week	0 (0.0%)	2 (1.4%)	0.0	–
		≥ 1 / month	0 (0.0%)	10 (7.0%)	0.0	–
		No drinking	5 (100.0%)	130 (91.5%)	reference	reference
Kissing		Yes	1 (20.0%)	28 (19.7%)	1.0	0.02-11.3
		No	4 (80.0%)	113 (79.6%)	reference	reference
		Unknown	0 (0.0%)	1 (0.7%)	–	–
Sharing food and drinks		Yes	1 (20.0%)	27 (19.0%)	1.1	0.02-11.3
		No	4 (80.0%)	115 (81.0%)	reference	reference
Upper respiratory tract infection		Yes	0 (0.0%)	8 (19.0%)	0.0	–
		No	5 (100.0%)	134 (81.0%)	reference	reference
Antibiotics		No	5 (100.0%)	140 (94.4%)	–	–
		Yes	0 (0.0%)	1 (0.7%)	reference	reference
		Unknown	0 (0.0%)	1 (0.7%)		

strains (N = 2) were matched with ST-11026 (cc 32). The first two individuals in serogroup B belonged to distinct companies at the same station. The latter two, with NT, belong to distinct companies at the same station. However, there was no further epidemiological link between them in the questionnaire. The 29E strain (N = 1) was genotyped using ST-15569 (cc178). This carrier traveled to the United States before the survey.

For group 1, living in multiple-bed rooms in the dormitory exhibited higher odds ratio compared to other factors, but there was no statistically significant difference (OR; 2.9, 95% CI; 0.2-154.6, Table 3).

Discussions

Knowingly, this is the first study of meningococcal carriage in SDF. The percentage of isolates in group 1 was 3.4%, which is higher than the results of previous studies on non-military citizens in Japan[7-9]. The two isolates belonged to ST-687 (cc41/44), which has been commonly detected in Japan since the 1980s[4, 11]. The other two were non-capsulated (non-typable), indicating low pathogenicity. These results suggest the possibility of human-to-human transmission of meningococci due to collective living and training. Furthermore, the 29E carrier returned from the United States immediately before the survey. The genotype ST-15569(cc178) of this strain has not been previously reported in Japan, suggesting travel-related carriage.

The survey for group 1 was conducted in June 2020, but no carriage was identified in subsequent surveys for groups 2-5 until 2022. These results are consistent with the national meningococcal disease surveillance, which showed a declining trend from 20-40 cases to nearly zero annually[12]. The decrease in the number of notifications may be related to restrictions on human behavior because of the COVID-19 pandemic, as shown in the literature[13], and the widespread use of masks. This unexpected incident might have led us not to find obvious risk factors for carriage during pre-deployment phase. In the SDF, wearing masks was assumed to have an inhibitory effect on the spread of meningococcal meningitis. Additionally, overseas travel to Japan was greatly restricted during this period and the frequency of international travel by SDF personnel was reduced, which may have greatly reduced the opportunity for exposure to overseas meningococci. Therefore, it is reasonable to evaluate the carriage rates for each survey rather than the cumulative carriage rate for the five surveys.

In the United States, a meningococcal vaccination program in the military was initiated in the 1970s in response to a series of reported cases involving military personnel. Starting with a monovalent vaccine, the incidence in the army declined significantly from 1990-2009 with vaccine development and was no longer significantly different from the incidence in the general population (0.5 vs. 0.7 per 100,000)[2, 3]. Currently, vaccination with the Meningococcal group A, C, W-135 and Y conjugate vaccine (MenACWY) is mandatory upon enlistment in the SDF, with additional vaccination depending on the risk if deployed in overseas endemic areas. Similar programs are in place in the French and British Armed Forces. The Canadian Armed Forces provides an additional group B vaccine to high-risk personnel, besides the quadrivalent vaccine. In South Korea, vaccination of new recruits became mandatory following an outbreak of meningococcal disease at an army recruitment training center in 2011[14].

In Japan, there is no routine meningococcal vaccination program for the public, and only voluntary vaccination is offered to travelers. In 2017, a student at the National Defense Academy developed a fatal invasive meningococcal infection. Therefore, the MenACWY was made routine to new recruits aged < 20 years, but younger members who had been enlisted before

the program started remained unvaccinated. Furthermore, group B vaccination remains unplanned.

Given frequent transfer to their stations nationwide and personnel exchanges between troops through joint trainings, and rising expectations for dispatches to epidemic areas overseas and international exchange, further studies on meningococcal carriage among high-risk groups will be needed to consider group B monovalent and/or pentavalent vaccine as approved in the USA[15].

Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

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国際緊急援助隊候補者における髄膜炎菌保菌調査―横断的研究―

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要旨：［背景］寮生活を送る若年者は髄膜炎菌感染症に罹患するリスクが高い。本研究の目的は，自衛隊国際緊急援助隊（JDR）隊員の行動に関連した髄膜炎菌保菌リスクを調査することである。［方法］JDR準備隊員（2020～2022年）を対象に，咽頭ぬぐい液の細菌培養，鞭毛遺伝子（*ctrA*）のLAMP法による増幅，質問票により調査した。［結果］JDR隊員の半年の交代ごとに５回の調査を連続的に実施した。登録された731人のうち，2020年６月のグループ１の５/147（3.4％）が培養陽性で，その他はすべて培養陰性であった。５つの分離株は，血清群B（N＝2），29E（N＝1），および群別不能（N＝2）と判明した。B/29Eは*ctrA*（+）であった。２つの血清群B株と２つの非分類株の遺伝子型はそれぞれ一致していた。相部屋での生活は比較的高いオッズ比を示したが有意差はなかった（OR; 2.9，95％ CI; 0.2-154.6）。［考察］これは，自衛隊員における髄膜炎菌保菌に関する初めての研究である。グループ１の保菌率が一般日本人のこれまでの報告を上回ったことは，隊員のリスクの高さを示唆している。血清群Bが分離されたことにより，利用可能なMenACWYワクチンに加えて，MenBを含むワクチンの必要性が考えられた。

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