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Effect of Pre-antibiotics Use before the First incident Stroke on Recurrence and Mortality: A Longitudinal Study with the Korean National Health Insurance Service Database

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Objective

Dysbiosis, an imbalance in gut microbiota, is associated with various diseases, including stroke. Although stroke-related dysbiosis is well-established, the effect of pre-stroke dysbiosis on stroke outcomes remains unknown. This study aims to investigate the effects of pre-antibiotic use on secondary stroke, mortality after stroke occurrence, and the effect of dysbiosis before stroke on long-term outcomes.

Materials and Methods

The National Health Insurance Service (NHIS) database was used to investigate the effect of pre-antibiotics use on long-term outcomes, including secondary stroke and mortality, in patients with acute ischemic stroke (AIS) and acute hemorrhagic stroke (AHS), who were hospitalized between 2007 and 2015. Antibiotic usage before acute stroke was identified through claim data and classified into seven classes based on target mechanisms. Pre-antibiotics use was identified seven days to one year before acute stroke occurrence, excluding topical antibiotics. Duration of antibiotic use was not considered.

Results

159,181 patients with AIS (AIS group) and 49,077 patients with AHS (AHS group) were included (Table 1.). Pre-antibiotics use significantly increased the risk of secondary AIS in the AIS group (p=0.009), and secondary AHS in the AHS group, respectively (p<0.001) (Table 2.). Pre-antibiotics use in the AIS group was associated with a lower risk of mortality (p<0.001) (Figure. 1). However, no significant association was found between pre-antibiotics use and mortality risk in the AHS groups. Class 4 antibiotics were significantly associated with secondary stroke, but the outcomes according to the types of antibiotics were discordant among studies.

Table 1. Baseline characteristics of patients with primary AIS and AHS.

Variables	AIS group (n = 159,181)	AHS group (n = 49,077)	p-value
Age, years	68.5 ± 11.5	67.6 ± 11.2	<0.001
Female, n (%)	78,134 (49.1)	26,013 (53.0)	<0.001
Socioeconomic status, n (%)			<0.001
Level 1	53,184 (33.4)	15,442 (31.5)	
Level 2	47,244 (29.7)	15,665 (31.9)	
Level 3	58,753 (36.9)	17,970 (36.6)	
Hypertension, n (%)	149,622 (94.0)	41,557 (84.7)	<0.001
Diabetes, n (%)	46,152 (29.0)	7547 (15.4)	<0.001
Dyslipidemia, n (%)	76,647 (48.2)	13,177 (26.8)	<0.001
Prior antibiotics use, n (%)	75,605 (47.5)	21,125 (43.0)	<0.001
Antibiotics classes, n (%)			
Class 1	41,705 (26.2)	11,788 (24.0)	<0.001
Class 2	20,569 (12.9)	5633 (11.5)	<0.001
Class 3	5819 (3.7)	1670 (3.4)	0.008
Class 4	43,044 (27.0)	11,522 (23.5)	<0.001
Class 5[a]	none	none	
Class 6	650 (0.4)	182 (0.4)	0.27
Class 7	2829 (1.8)	724 (1.5)	<0.001

Table 2. Cox-proportional hazards models for secondary AIS, AHS, and death according to pre-antibiotics use.

Variable	aHR[a]	95% CI	p-value	Secondary events
AIS group with pre-antibiotics use	1.03	1.01–1.05	0.009	AIS
AHS group with pre-antibiotics use	0.98	0.92–1.04	0.49	
AIS group with pre-antibiotics use	0.95	0.89–1.01	0.09	AHS
AHS group with pre-antibiotics use	1.08	1.03–1.12	<0.001	
AIS group with pre-antibiotics use	0.95	0.94–0.96	<0.001	Death
AHS group with pre-antibiotics use	0.96	0.96–1.01	0.18	

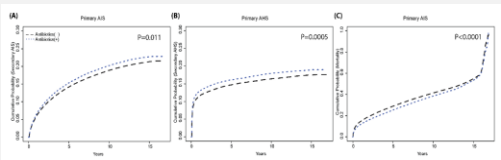

Fig. 1 Kaplan-Meier curves for the cumulative probability according to pre-antibiotic use. (A) Pre-antibiotics use significantly increases the cumulative probability of secondary AIS in the AIS group and secondary AHS in the AHS group. On the other hand, (C) pre-antibiotics use in the AIS group significantly decreases the cumulative probability of death.

Conclusion

This study is the first to analyze the effects of dysbiosis caused by pre-antibiotics use before an acute stroke event on recurrence and mortality at the population level. The use of antibiotics prior to stroke was identified as an independent risk factor for secondary stroke and discordant outcomes depending on the types of antibiotics.