Commentary

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Inquiry into some gap among oseltamivir use and severe abnormal behavior in Japanese children and adolescents with influenza

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Summary **The Fukushima research has examined data form a cohort study of 10,000 Japanese children under 18 years old with influenza during three months to demonstrate that the relative risk of A-type abnormal behavior of patients with oseltamivir was 30 times greater than without oseltamivir. By contrast, our research group found that patients who had been administered no neuraminidase inhibitors (NI) or those administered peramivir had higher risk of abnormal behavior than those administered oseltamivir, zanamivir, or laninamivir. A plausible explanation for this gap is that the two studies specifically examined different criteria to report abnormal behavior. In actually, some A-type abnormal behavior might not be life-threatening. Our definition of severe abnormal behavior is better matched to public health concerns and comparison among incidents according to the administered drug is more appropriate as an analytical procedure.**

Keywords: Influenza, abnormal behavior, oseltamivir, neuraminidase inhibitors

Since two influenza-infected Japanese junior high school students jumped from a great height and died in February 2007, abnormal behavior in influenza patients, especially teenagers, has been the subject of international public health concern. On March 22, 2007, the Ministry of Health, Labour (MHLW) issued emergent safety information to prohibit the administration of oseltamivir to 10-19 years-old influenza patients (*1*). Given those circumstances, epidemiological research efforts of two types were activated.

One research effort was a cohort study of 10,000 patients under 18 years old during three months in 2007 (*2*). This was unparalleled huge and amazing survey. Moreover, this research group continued the analyses for ten years. "Oseltamivir use and severe abnormal behavior in Japanese children and adolescents with influenza: Is a self-controlled case series study applicable?" (Hereinafter, the Fukushima research) was the latest result reported by this group (*3*). We are strongly impressed by their inquisitive approach that is focused on finding truth. The research found that the relative risk of A-type abnormal behavior, the most severe abnormal behavior in the data, of patients with oseltamivir was 30 times greater than without oseltamivir, although they did not emphasize that point in their conclusion because they were unable to isolate the effect of oseltamivir use from the effect of high fever.

Our research group started studying abnormal behavior of influenza patients in 2007. That study is continuing today under a granted by MHLW and Agency for Medical Research and Development in Japan (*4-6*). This group did not set up a cohort because abnormal behavior leading to death is apparently very rare. Instead of the cohort, it asked all physicians to report abnormal behavior of influenza patients with details of abnormal behavior and administered drugs

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such as several neuraminidase inhibitors (NI) or acetaminophen. In other words, it set a nationwide cohort to capture very rare events. Results of that study demonstrated that patients who have taken all types of NI showed severe abnormal behavior. Moreover, patients without the antivirals showed severe abnormal behavior. Therefore, it was concluded that influenza itself causes the severe abnormal behavior, even if drugs of some kinds might exacerbate it. The study also found that the rate of incidences of abnormal behavior were not different among types of NI such as oseltamvir, zanamivir and laninamivir, with the exception of peramivir. Therefore, zanamivir and laninamivir carry almost equivalent risk to that of oseltamivir. The incidence with peramivir or no antivirals administered were significantly higher than those associated with oseltamivir, zanamivir or laninamivir. However, the numbers of the un-administered patients or those taking peramivir were smaller than for the other NI. This evidence also reinforces the view that influenza itself causes the severe abnormal behavior. Hereinafter, we designate this effort as our research.

How should we interpret these different results related to the putative association between oseltamivir and abnormal behavior? The key point for understanding might be the frequency and definition of abnormal behavior.

The survey used for the Fukushima study found 28 cases of A-type abnormal behavior. The incidence was therefore 0.28% (28/10,000). By contrast, our research found 106 severe cases and 120 moderate cases in the same period.

Unfortunately, the precise number of influenza patients nationwide was not available in 2007. In fact, it is not notifiable disease in Japan, but it is monitored by sentinel in the National Official Sentinel Surveillance of Infectious Diseases (NOSSID) based on Japanese Infectious Disease Control Law. In an almost equivalent period (1st to 13th epidemiological week) NOSSID reported 896,136 influenza patients. NOSSID received the number of influenza patients from 5,000 sentinels, which accounts for almost one-tenth of all hospital and clinics. Therefore we can estimate the total number of influenza patients nationwide during the same period as 8.96 million. Nevertheless, NOSSID does not publish the age distribution of influenza patients for that period. Recently, almost all medical claims have become available for research since 2010. We designate such a huge database as the National Database of Medical Claims (NDBEMC). Our research group applied to MHLW to use it as the denominator of the incidence rate of abnormal behavior. That use was approved. Actually, NDBEMC shows the average proportion of patients younger than 20 years old in the 2010/2011-2013/2014 seasons as 52.5%. Consequently, the number of influenza patients younger than 20 years old was estimated as 4.71 million (8.96 million × 52.5%) during that period. The incidence of severe abnormal behavior in our research group was estimated as 0.0023% (106/4.71 million).

Conversely, our research group requested all physicians at the influenza sentinel to report moderate abnormal behavior cases. Influenza patients younger than 20 years old were 0.471 million (0.896 million × 52.5%) if we presume that the age distributions nationwide and of the sentinel are the same. Therefore, the incidence rate of moderate abnormal behavior in our research group was 0.025% (120/0.471million).

In other words, the incidence of A-type abnormal behavior in the Fukushima research was 100 times higher than severe abnormal behavior and ten times higher than moderate abnormal behavior, as judged by the our research group. The reason is that the two research efforts specifically examined different definitions or criteria to report abnormal behavior.

For instance, in the Fukushima research, A-type abnormal behavior was defined as "Abnormal behavior potentially leading to an accident or harm to another person." By contrast, our research group considered severe abnormal behavior as active motion behavior that can be life-threatening given no intervention, including behaviors such as sudden running away, jumping from a high place, or rampaging involving self-injury. Moreover, it defined the moderate abnormal behavior as unusual behavior that might not be life-threatening.

Therefore, some behaviors considered as A-type abnormal in the Fukushima study might not meet the definition of life-threatening severe abnormal behavior in our study, but might be included as a moderate abnormal behavior. These differences of case definition might affect the study outcome.

However, the severe abnormal behavior examined in our research also might result from underreporting. We cannot evaluate the degree of underreporting, but reports of only a few fatality cases with abnormal behavior of influenza patients have been published by mass media since 2007. Moreover, we have sent request letters from government to almost all hospital and clinics, more than 60 thousands, every year. Therefore, we consider that the bias of underreporting might not be so serious for severe abnormal behavior.

Both studies emphasize different aspects of abnormal behavior. If we were to construct a cohort study like the Fukushima research to examine life-threatening behavior specifically, we need 0.1 million cohort for 2.8 cases with life-threatening abnormal behavior based on our research group's result. Comparison of incidence according to the administered drug seems to be more appropriate as an analytical procedure. Moreover, we consider that our definition of severe abnormal behavior better matches for public health concerns.

Be that as it may, the final conclusion in Fukushima research "we could not deny the possibility that

abnormal behavior was induced by influenza itself" is fully acceptable from the view point of our research group. Our discussion presented in this paper might be useful for new anti-influenza virus drug including endonuclease inhibitor, baroxabil malboxyl.

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References

1. Chugai Pharmaceutical Co., Ltd. The Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter) about abnormal behavior after administrated Tamiflu. *http://www.pmda.go.jp/files/000147877.pdf* (in Japanese). (accessed 24 November, 2017)
2. Fujita T, Fujii Y, Watanabe Y, Osaka H, Wada T, Mori M, Yokota S. A pharmacoepidemiologic study on the relationship between neuropsychiatric symptoms and therapeutic drugs after influenza infection, Jpn J Pharmacoepidemiol. 2010; 15:73-92. (in Japanese)
3. Fukushima W, Ozasa K, Okumura A, Mori M, Hosoya M, Nakano T, Tanabe T, Yamaguchi N, Suzuki H, Mori M, Hatayama H, Ochiai H, Kondo K, Ito K, Ohfuji S. Oseltamivir use and severe abnormal behavior in Japanese children and adolescents with influenza: Is a self-controlled case series study applicable? Vaccine. 2017; 35:4817-4824.
4. Nakamura Y, Sugawara T, Ohkusa Y, Miyazaki C, Momoi M Y, Okabe N. Abnormal behavior during influenza in Japan during the last seven seasons: 2006-2007 to 2012-2013. J Infect Chemother. 2014; 20:789-793.
5. Nakamura Y, Sugawara T, Ohkusa Y, Miyazaki C, Momoi M Y, Okabe N. Life-threatening abnormal behavior incidence in 10-19 year old patients administered neuraminidase inhibitors. PLoS One. 2015; 10:e0129712.
6. Nakamura Y, Sugawara T, Ohkusa Y, Miyazaki C, Momoi MY, Okabe N. Severe abnormal behavior incidence after administration of neuraminidase inhibitors using the national database of medical claims. J Infect Chemother. 2018; 24:177-181.

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