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NEUROLOGICAL ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) ON HEALTH WORKFORCE OF A SECONDARY REFERRAL HOSPITAL IN SOUTH SULAWESI WHO RECEIVED THE COVID-19 VACCINATION

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ABSTRACT

Background: The COVID-19 vaccination can relate to the occurrence of neurological adverse events following immunization (AEFI) that could impact work and daily activities. This problem is particularly important in the health workforce. However, little is known about neurological AEFI among the health workforce working in peripheral facilities.
Objective: To study the neurological AEFIs and their impact among the health workforce who received the COVID-19 vaccination in a secondary referral hospital in South Sulawesi, the Andi Makassau Hospital (Rumah Sakit Umum Daerah Andi Makassau/RSAM).
Methods: The COVID-19 pandemic, we created a questionnaire about neurological AEFIs and their effects which were distributed online using the Google Form application to the health workforce at the RSAM who had received at least one dose of COVID-19 vaccination.
Results: We obtained 97 subjects. There were 78.5% neurological AEFIs with the most reported type being muscle pain (16%). Most neurological AEFIs were experienced by women (84.9%), age group 21-35 years (53.8%), and non-doctors/nurses (60.8%). The significant influencing factors in multivariate analysis were age group 36-45 years ($p = 0.04$), nursing proffesion ($p = 0.005$), and non-viral-based baccine type ($p = < 0.0001$).
Conclusion: Neurological AEFI is commonly found among the health workforce who received the COVID-19 vaccination. However, it only has a little impact on their work and attitudes towards vaccination. This may be because all subjects experienced mild neurological AEFI.

Keywords: Neurological AEFI, health workforce, COVID-19 vaccine, South Sulawesi

Introduction

Efforts to prevent and control COVID-19 in Indonesia are not only carried out with health protocols but also with COVID-19 vaccination. One of the goals of vaccination is to achieve herd immunity, in which the majority of people who have been protected will indirectly protect vulnerable groups of people, including groups who are not the target of vaccination. This condition can be achieved if vaccination coverage is high and evenly distributed in all regions with a minimum vaccination target of 70%, according to the recommendations of WHO and the Indonesian Technical Advisory Group on Immunization (ITAGI).[1,2]

Vaccination can be associated with the incidence of Adverse Events Following Immunization (AEFI). AEFI is a term used to describe adverse medical events that occur after vaccination. These events do not always have a cause-and-effect relationship with the use of vaccines. AEFIs can be in the form of vaccine reactions, procedural errors, coincidences, anxiety reactions, to an undetermined causal relationship.[3]

One important and frequently reported form of AEFI is neurological AEFI. Neurological AEFI describes sign(s) or symptom(s) associated with central and/or peripheral nervous system dysfunction that occurs after vaccine administration. Neurological AEFI symptoms include headache, motor symptoms, sensory symptoms, focal signs, and altered mental status (including syncope). A 2021 descriptive study conducted by Grimshaw et al in Mexico identified the presence of a neurological AEFI (65.1%) with the most symptom being headache (62.2%) among the first recipients of the COVID-19 vaccine.[4]

As the frontliners in the COVID-19 pandemic, the health workforce played an important role in the treatment and prevention of the COVID-19 pandemic. This duty is putting

them at a higher risk of contracting the disease. Hence, they become a priority for vaccination.

The presence of a neurological AEFI can have an impact on work and activities of daily living, even if it is mild. For the health workforce, neurological AEFI can disrupt health services that they provide, including a negative perception towards vaccination.

Health workforce who are more aware of adverse events potential but more prone to self-medicate and probably underreport them. Little is known about the neurological AEFI among the health workforce working in peripheral facilities in Indonesia. They may have different characteristics and may perceive the vaccination differently.

Methods

This study is a cross-sectional study that is divided into two stages, descriptive and analytic. We designed and self-validated an online questionnaire to study the neurological AEFI. This questionnaire was then distributed online via Google Form software to the health workforce in a secondary referral hospital in South Sulawesi, the Andi Makassau Hospital (Rumah Sakit Umum Daerah Andi Makassau/RSAM). This hospital serves COVID-19 patients in Parepare Regency, South Sulawesi and its surrounding regions. This hospital was designated as a Type B Non-Educational Hospital and there are 529 medical health workforce at the RSAM as of November 2021.

The questionnaire data collection was carried out for one week, starting from November 15 to November 22, 2021. Sample selection using the simple random sampling method. Subjects must meet the eligibility criteria set by the researchers. They must be at least 21 years old, health workers, working in RSAM, and have received at least 1 dose of COVID-19 vaccination. Those who refused to participate were not included in the study.

For statistical analysis, a normality test was performed using the Kolmogorov-Smirnov test. The results were considered statistically significant if the p-value was < 0.05. Bivariate analysis was performed using the Student T or Mann-Whitney test for numerical variables, the Kolmogorov-Smirnov test for ordinal variables, and the Chi-square test for dichotomic variables. Independent variables with a p-value < 0.25 were further analyzed in multivariate analysis.

This study has been approved by the Health Research Ethics Committee of R.D. Kandou Hospital (Ethical Approval number 196/EC/KEPK-KANDOU/XI/2021).

Results

The We found 97 eligible subjects. The mean age of the subjects was 37 years (SD±9.1). The characteristics of the subjects are shown in Table 1.

It should be understand that for the vaccine name and the occurrence of AEFI variables, the number (n) is obtained from the cumulative number of vaccine doses given. In the neurological AEFI variable, the number given is the total number of cases experiencing AEFI events. Finally, the number on the type of neurological AEFI type, the severity of neurological AEFI, and the interval to the onset of neurological AEFI variables represent all cases with neurological AEFI.

Table 1. The Characteristics of the Subjects

Variable	Total	Percentage (%)
Age group		
21 – 35 years	50	51.5
36 – 45 years	32	33.0
≥ 46 years	15	15.5
Gender		
Male	17	17.5
Female	80	82.5
Occupation		
Doctors	7	7.2
Nurses	39	40.2
Other Health Workers	51	52.6
History of allergy		
Yes	32	33.0
No/do not know	65	67.0
History of neurological disease		
Yes	26	26.8
No/do not know	71	73.2
History of metabolic disease		
Yes	10	10.3
No/do not know	87	89.7
History of COVID-19 infection		
Yes	29	29.9
No/do not know	68	70.1
Number of COVID-19 vaccine dose		
1	2	2.1
2	4	4.1
3	91	93.8
Vaccine name (n = 283)		
Sinovac-CoronaVac	191	67.5
AstraZeneca	2	0.7
Moderna	90	31.8
Occurrence of AEFI (n = 283)		
Yes	237	83.7
No	46	16.3
Occurrence of neurological AEFI (n = 237)		
Yes	186	78.5
No	51	21.5
Type of neurological AEFI (n = 186)		
Central Nervous System	67	36.0
Peripheral Nervous System	27	14.5
Mixed (CNS & PNS)	89	47.9
Unspecified	3	1.6
Severity of neurological AEFI (n = 186)		
Serious	0	0
Not serious	186	100
Interval to onset of neurological AEFI (n = 186)		
<1 day	141	75.8
1-7 days	44	23.7
>7-14 days	1	0.5

Note: AEFI: Adverse Events Following Immunization

The mixed category for neurological AEFI type is a combination of Central Nervous System AEFIs and Peripheral Nervous System AEFIs, while for neurological AEFIs that cannot be classified (excluding CNS AEFIs, PNS AEFIs, and Mixed AEFIs), they are grouped in the Non-specific category.

Table 3 displays the results of the bivariate analysis done on several variables for the occurrence of neurological AEFIs.

The results of logistic regression of several factors for the occurrence of neurological AEFIs are presented in Table 4.

All subjects had a non-serious neurological AEFI with 186 events so there was no further analysis for the relationship between internal and external factors and the severity of the neurological AEFI. When the data was further analyzed to see the relationship between neurological AEFIs and their impact on work, we found that the relationship was not statistically significant. The same results come from the attitudes towards AEFIs and vaccinations (Table 5).

Table 3. The Relationship between Internal & External Factors with Neurological AEFI

Variable	Neurological AEFI				p-value
	Yes		No		
	n (%)	Median (min-max)	n (%)	Median (min-max)	
Age, years		34 (24-61)		35 (24-58)	0.47a
Age group					
21 – 35 years	100 (53.8)		28 (54.9)		
36 – 45 years	62 (33.3)		11 (21.6)		0.09b
≥46 years	24 (12.9)		12 (23.5)		
Gender					
Male	28 (15.1)		13 (25.5)		0.08b
Female	158 (84.9)		38 (74.5)		
Occupation					
Doctors	9 (4.8)		4 (7.8)		
Nurses	64 (34.4)		30 (58.8)		0.002b
Other Health Workers	113 (60.8)		17 (33.3)		
History of allergy					
Yes	71 (38.2)		11 (21.6)		0.03b
No/do not know	115 (61.8)		40 (78.4)		
History of neurological disease					
Yes	53 (28.5)		12 (23.5)		0.48b
No/do not know	133 (71.5)		39 (76.5)		
History of metabolic disease					
Yes	19 (10.2)		7 (13.7)		0.48b
No/do not know	167 (89.8)		44 (86.3)		
History of COVID-19 infection					
Yes	51 (27.4)		20 (39.2)		0.10b
No/do not know	135 (72.6)		31 (60.8)		
Type of Vaccine					
Viral-based	106 (57.0)		42 (82.4)		0.001b
Non-viral-based/other	80 (43.0)		9 (17.6)		
Number of vaccine doses					
3	178 (95.7)		50 (98.0)		
2	6 (3.2)		1 (2.0)		1.00c
1	2 (1.6)		0 (0)		

Tabel 4. The Logistics Regression Results of Several Factors Affecting the Occurrence of Neurological AEFIs

Variable	p-value	95%CI	OR
Age group			
21 – 35 years	0.29	0.231 – 1.555	0.6
36 – 45 years	0.04	0.101 – 0.921	0.3
≥46 years			Ref
Gender			
Male	0.58	0.305 – 1.951	0.8
Female			
Occupation			
Doctors	0.19	0.592 – 13.449	2.9
Nurses	0.01	1.387 – 6.152	2.9
Other Health Workforce			Ref
Allergy history			
Yes	0.18	0.778 – 3.793	1.8
No/do not know			
COVID-19 infection history			
Yes	0.14	0.259 – 1.203	0.6
No/do not know			
Type of Vaccine			
Viral-based	<0.0001	0.100 – 0.517	0.3
Non-viral-based/other			

Note: 95%CI: Confidence Interval 95%; OR: *Odds Ratio*

Table 5. The Relationship between Neurological AEFI and Attitude Towards AEFI and Vaccination

Variable	Attitude towards AEFI		p-value	95%CI	OR	Attitude towards Vaccination		p-value	95%CI	OR
	Accept	Anxious or angry				Support	Not support or in-doubt			
Neurological AEFI										
Yes	156 (83.9)	30 (16.1)	0.14	0.148 – 1.320	0.4	150 (80.6)	36 (19.4)	0.11	0.168 – 1.221	0.4
No	47 (92.2)	4 (7.8)				46 (90.2)	5 (9.8)			

Note: AEFI: Adverse Events Following Immunization; CI95%: Confidence Interval 95%; OR: Odds Rati

Discussion

These neurological AEFIs does not necessarily have a causal relationship with vaccines. AEFI is an adverse or undesirable medical event that occurs after the administration of a vaccine but does not necessarily have a causal relationship with the vaccine itself.[5]

According to WHO, AEFIs are grouped into 5 categories, namely, (1) reactions related to vaccine products, AEFIs can be caused or triggered by components contained in the COVID-19 vaccine such as vaccine antigens, adjuvants, solvents, buffers, and others; (2) reactions related to vaccine quality defects, such as the failure of IPV vaccine manufacturers to inactivate the poliovirus which can cause paralysis; (3) reactions related to incorrect immunization procedures, such as the occurrence of infection transmission due to contaminated multidose vials; (4) anxiety reactions, such as the occurrence of vasovagal syncope during or after COVID-19 vaccination; and (5) coincidental events, where the AEFI is caused by other things, such as headaches due to toothache or the presence of a brain tumor that occurs at the same time as the COVID-19 vaccination. If there is a serious AEFI, it will be investigated to find out whether the AEFI is directly related to the vaccine.[3]

The results of this study showed that of all the AEFI events experienced by 97 subjects, 78.5% were neurological AEFIs. The most common types of neurological AEFIs experienced were muscle pain (16.0%), hypersomnolence (15.4%), and fatigue (14.7%). Similarly, the previous study by Tran et al reported that the most frequently reported side effects or neurological symptoms of AEFIs were muscle pain, followed by fatigue/drowsiness, body aches, and headaches.[6]

Our study found that the nursing profession is at a higher risk of experiencing neurological AEFIs than the other groups. As a health workforce, we can expect that nurses are aware of the AEFIs when they experience one and report it. However, we believe that the higher percentage of neurological AEFIs among nurses might be influenced by their heavier workload before and after the vaccination. Additionally, they have a higher chance of being exposed directly to various pathogens during their work shift. A relatively similar result was reported by Grimshaw et al. They also found that neurological AEFIs are common among nurses ($p < 0.0001$).[3]

In this study, the types of viral-based vaccines included Sinovac-CoronaVac and AstraZeneca, while the type of non-viral-based/other vaccines included Moderna. In this study, subjects with viral-based vaccines had a lower chance of experiencing neurological AEFIs than those with the other type. The difference in the components of each vaccine will allow the reactogenicity of different vaccines. In addition, in this study, the majority of the Sinovac-CoronaVac vaccine was used as the primary dose so that it would provide a different reactogenicity than the Moderna vaccine as a booster dose.[7]

The Sinovac-CoronaVac vaccine (whole virus attenuated/inactivated virus) consists of several components such as vaccine antigens, adjuvants in the form of aluminum hydroxide salts, as well as solvents and buffers. Systemic reactions have rarely been reported in vaccines with aluminum hydroxide salt adjuvants. The benefits of aluminum hydroxide salt adjuvants are that they can increase antibody levels, reduce vaccine antigen doses, and make the immune response last longer and stronger. This vaccine is not always able to induce an immune response (immune response sometimes does not last long) at the first dose, so it requires a booster.[8] Clinical trials 1 and 2 in China from Sinovac-CoronaVac reported systemic reactions in the form of muscle aches, joint pain, fatigue, fever, and headache.[9]

Moderna vaccines (mRNA-based vaccines) are the latest technology in vaccine development and are theoretically safe. Synthetic mRNA that resembles viral mRNA will not enter the nucleus, so it will not change human DNA.[10] Moderna vaccine efficacy is 94.1% and Moderna vaccine recipients have higher reactions.[11]

There are 35.5% of the health workforce with neurological AEFIs in our study who cannot perform their work optimally. This finding is important and should be anticipated in the future since the performance of doctors and nurses is very important in terms of health quality assurance, including patient satisfaction.[12]

The majority (83.9%) of the health workforce's attitudes when experiencing neurological AEFIs are accepting the event. Research conducted by Shrestha et al showed that 41.4% of the health workforce who experienced AEFI received and did not take any medication to relieve symptoms.[13] The majority (80.6%) of the health workforce still support the government's vaccination program. This is in line with survey-based research on the health workforce in France in 2021 where the majority of respondents still support COVID-19 vaccination (73.1%).[14] We believe that this finding can be explained by the fact that most of the neurological AEFIs are mild.

Based on the results of the analysis in this study, there is nosignificant relationship between neurological AEFIs and the impact on work, individual attitudes towards AEFIs, and individual attitudes towards COVID-19 vaccination.

There are some weaknesses in our study. There were cases of neurological AEFI that were unclear or difficult to identify based on a questionnaire, such as cases of weakness, so they were grouped into the non-specific neurological AEFI. However, the percentage is only 1.6%

(Table 1). Confirmation and diagnosis from a neurologist to classify the neurological events experienced, such as weakness, will be required for this study and further research.

Conclusion

Neurological AEFI is commonly found among the health workforce who have received the COVID-19 vaccination. This finding should be anticipated in designing vaccination protocols and education for the health workforce as they play a critical role in managing the COVID-19 pandemic nationwide. However, the neurological AEFI only has a little impact on the work and attitudes towards vaccination of the health workforce in this study. The mild form of neurological AEFIs experienced by all subjects might explain this finding.

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Conflict of Interest

We declare that there is no conflict of interest in this study.

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