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Serological Evidence of Herpes Simplex Virus-1 (HSV-1) Infection among Humans from Bandung, West Java Province, Indonesia

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Abstract

BACKGROUND: *Toxoplasma gondii*, Rubella virus, Cytomegalovirus, and herpes simplex virus (TORCH) infection is still a significant burden in developing countries since they potentially increase perinatal death and decrease life quality by causing congenital disorders. As part of TORCH and as one of the most common infections in humans, HSV Type 1 infection also should receive attention. HSV-1 infection induces an immediate reactive oxygen species (ROS) production, indicate that ROS plays beneficial effects in several biological functions, including innate immunity and antiviral responses. HSV-1 preferentially replicate and establish latency in different subtypes of sensory neurons and in neurons of the autonomic nervous system that are highly responsive to stress hormones, including cortisol.

AIM: The objective of the study was to detect the latent HSV-1 infection in adults population and its effect on ROS and cortisol levels.

PATIENTS AND METHODS: Subjects were enrolled with consecutive-sampling methods among the adults population age 18–40 years old, with no health complaints. We collected their blood to examined IgG HSV-1, ROS, and cortisol levels.

RESULTS: A total of 57 subjects with 27 subjects were reactive IgG HSV-1 (herpes group) and 30 subjects were non-reactive IgG HSV-1 (non herpes groups). Mean of cortisol and ROS was 223.2904 nmol/L and 2.23337 IU/mL, respectively. There was a very weak correlation between HSV-1 infection with ROS and cortisol.

CONCLUSION: There is a positive effect of latent HSV-1 infection in the adult population on cortisol ROS levels.

Introduction

Herpes simplex virus (HSV) infection as one of *Toxoplasma gondii*, Rubella virus, Cytomegalovirus, and HSV (TORCH) infection can causes perinatal infection and potentially contributes morbidity and mortality in neonates [1]. Abortus, intrauterine growth restriction, intrauterine fetal death, prematurity, early neonatal death, low birth weight, and cerebral palsy can be caused by perinatal infection. A significant burden of TORCH infection still occurred in developing country since they potential increase perinatal death and decrease quality of life by causing congenital disorders or clinical disturbance due to HSV infection which reactivates from its latent period [2], [3], [4]. HSV-1 is infectious for lifetime, but mostly subclinically and asymptomatically [5], but HSV-1 often causes symptoms with mild-to-severe degrees of disease [5], [6]. The transmission of HSV from mother to fetus during pregnancy is less common, about 85% of perinatal transmission can occurs during the intrapartum period [6]. Primary infections of HSV-1 mostly occur during infancy and childhood, after maternal antibody has disappeared in the 1st year of life. HSV-1 enters periods of latency in the trigeminal or cervical ganglia. Reactivation of HSV-1 is triggered by known factors such as exposure to sunlight and ultraviolet (UV) radiation, fever, trauma, diminished cellular immunity, emotional stress, and other unknown molecular mechanisms, then caused recurrent incidents of viral shedding at the skin and oral mucosa through lesions and sores [4].

The prevalence of HSV-1 and HSV-2 in the United States was found in people aged >12 years as 27.1% were seronegative for both HSV. The prevalence of HSV-1 at one referral hospital in Indonesia was 66.67% [7]. The 51% were positive only for HSV-1 and 5.3% were positive only for HSV-2; 16.6% were coinfected with HSV-1 and HSV-2 [8]. HSV Type 1/2 belong to the human herpes viruses, in spite of the fact that a large proportion of women at childbearing age are seropositive to these viruses, especially to HSV, primary or secondary infections with these viruses may occur during pregnancy [9]. A percentage of 70–85% of neonatal HSV infections are caused by

HSV-2, whereas the remaining cases are due to HSV-1. The HSV-2 infection carries a graver prognosis than that caused by HSV-1 [7], [9]. In the next life, most people did not complain about the symptoms, but some have common recurrent oral ulceration due to HSV infection [10]. Almost all herpetic ulcerations are caused by HSV-1 and the reactivation of the orolabial infection is common. Primary HSV-1 infections usually occur in young children and it is estimated that about 90% of the adult population has antibody titers directed against HSV-1 [11].

HSV-1 epidemiology is transitioning in Asia with lower seroprevalence in youth. Yet, 50% of children and 75% of adults are infected. HSV-1 is playing a role as a sexually-transmitted infection explaining one-fifth of genital herpes and 6% of genital ulcer disease [12]. HSV is one of the most widespread infections in humans, affecting 60–95% of the adult population worldwide [13]. The seroprevalence of HSV-1 varied by race/ethnicity [6]. HSV-1 are lifelong infections [14]. Many infections stimulate other cellular activities, such as reactive oxygen species (ROS), which are by-products of cellular respiration that can promote oxidative stress and damage cellular proteins and lipids [15]. ROS have long been known to be a component of the killing response of immune cells to microbial invasion, and it is emerging early during HSV infection, and act as an important regulator of some of intracellular signaling pathways leading to cytokine and chemokine expression. ROS directly interact with signaling components or induce other post-translational modifications such as S-glutathionylation, thereby altering target [16]. The previous study also found that HSV-1 infection of neural cells causes oxidative stress that is required for efficient viral replication [17]. Production of ROS plays beneficial effects in several biological functions, including innate immunity and antiviral responses. Many data have been accumulated over the past years showing that treatment with anti-oxidants could be beneficial against infections caused by different viruses [18].

HSV-1 infects and establishes latency in peripheral neurons, from which they can reactivate to cause recurrent disease throughout the life of the host and this situation might influenced the occurrence of emotional stress. Stress is associated with the exacerbation of clinical symptoms and the induction of recurrences in humans [19]. A case of recurrent intraoral HSV-1 (RIH) infection with emotional stress as a predisposing factor found in a patient with anti-HSV-1 IgG showing the reactive result [20], [21], [22]. In the long-term stress, the response will be induced by cortisol, which binds to glucocorticoid receptors to regulate metabolism and suppression of the immune system [23]. HSV-1 transmits the adult person to the others by physical and non-sexual contact during childhood and adolescence. Most HSV-1 infections are subclinical and many people carrying this type of virus are not aware they are infected [24].

HSV-1 infection can be chronicand characterized by reactive IgG HSV-1 for about 10 years. This entity is potentially lowering the quality of life when people who have had this latent infection experience some exacerbation. The exacerbation of HSV-1 infection is in connection with a high level of ROS [16]. The previous studies have found that stress factors characterized by high ROS levels can trigger neurological disorders caused by microglial reactivity reactions associated with HSV-1 [16]. There are no community-based studies about cortisol and ROS profile in HSV-1 latent infection. Avoiding the stress factors is almost impossible; however, at least by knowing ROS and cortisol profile in HSV-1 patients, we would be able minimizing the exacerbation event by giving some antioxidant or lifestyle modification, and the important thing is to prevent disease caused by TORCH infection, especially in women when planning to have children. This study aims to detect latent HSV-1 infection and to determine its effect on ROS and cortisol levels in adult population.

Patients and Methods

Case definition

We collected healthy peoples in adults population and examined the serum for IgG HSV-1 to get the information regarding HSV-1 infection.

Inclusion and Exclusion Criteria

Serum samples were obtained randomly from voluntary healthy-subjects (it does not have any clinical manifestation of HSV infection or other diseases) attending Hasan Sadikin Hospital Bandung. Ages of the patients ranged from 18 to 40 years old.

Diagnostic tests

Human serum samples were tested for specific anti-HSV-1 using a commercially available ELISA test (Vircell® kit). All serum was also examined with Human ROS ELISA kit and cortisol kit (Cobas®).

Statistical analysis

The data were analyzed by independent t-test and Spearman correlation analysis using SPSS 21.0.

Ethics statement

Patients who consented to participate in the study signed an informed consent.

The study was conducted with the approval of the Ethical Health Committee of Universitas

Padjadjaran. Assessment of type-specific serologic outcome of HSV-1 in Bandung was conducted between October and December 2018.

Results

The research subjects were 57 healthy adults with more female than male, and most subjects were in the age range 18–40 years. Examination of serum IgG HSV-1 showed that 27 subjects were reactive and the rest were not (Table 1).

Table 1: Characteristics of subjects

Variable	n	%
Sex		
Female	42	73.7
Male	15	26.3
Age (year)		
18–25	24	42.1
26–40	33	57.9
IgG HSV-1		
Reactive*	27	47.4
Non-reactive	30	52.6
Total	57	100

*IgG antibody levels may be reported as Non-reactive (no detectable antibody) or Reactive (antibody is detectable within the positive range of the assay).

Twenty-seven subjects showed reactive for IgG HSV-1 levels (herpes group) and 30 subjects found no reactive HSV-1 infection (non-herpes group) (Figure 1).

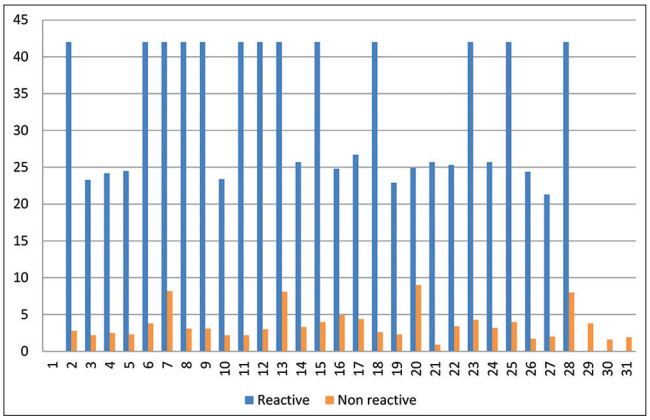

Figure 1. IgG HSV-1 levels in herpes and non-herpes groups

ROS levels in herpes group are in range 0.64–10.04 IU/mL and 0.56–6.19 IU/mL in non-herpes group Figure 2.

Table 2: Difference test between ROS in herpes and non-herpes group

ROS * (IU/mL)	Groups		p-value
	Herpes (n = 27)	Non-Herpes (n = 30)	
Mean (SD)	2.55 ± 2.30	1.95 ± 1.20	0.620
Median	1.41	1.43	
Range	0.64–10.04	–6.19	

*Mann–Whitney test.

Cortisol levels are in range 92.7–380.2 and 118–696.4 nmol/L in herpes and non-herpes group, respectively. Mean was 201.1 and 243.3 nmol/L (Herpes and non-herpes groups, respectively). Median was 214.8 and 209.9 nmol/L in herpes and non-herpes groups, respectively Figure3.

There was no significant difference between ROS in the herpes group and the non-herpes group (Table 2). Correlation test showed that there was a very weak correlation between HSV1 IgG, cortisol, and ROS levels in all subjects (Table 3).

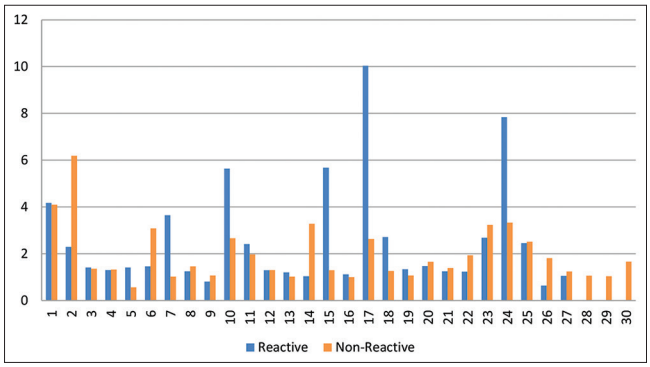

Figure 2. ROS levels in herpes and non herpes groups. Mean were 2.55 and 1.95 (Herpes and Non-Herpes Group, respectively), whereas median were1.4 in both groups.

The Rank Spearman correlation value between HSV-1 IgG (Index) and cortisol (nmol/L) is −0.148 (r = −0.148). The correlation between IgG HSV-1, cortisol, and ROS levels was very weak Table 3.

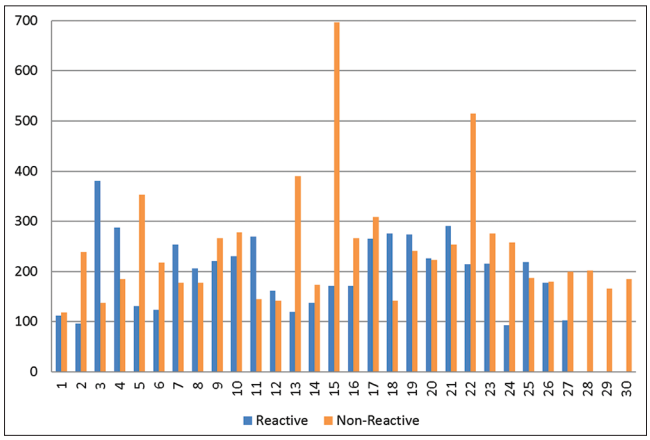

Figure 3. Cortisol levels in herpes and non-herpes groups

Discussion

This study found that mostly HSV-1 patients are female, resemble with the data from the WHO [25]. Seroepidemiological study of HSV-1 conducted in Turkey revealed that as many as, 62% of females were HSV-1 positive [24]. Data from a nationwide population-based survey in Australia also showed that women (80%) had a significantly higher prevalence of HSV-1 than men (71%) (adjusted RR 1.12).[26] A study

Table 3: The correlation between IgG HSV-1, Cortisol, and ROS Levels

Correlation	r*	Force Correlation	p-value
IgG HSV-1 and Cortisol (nmol/L)	−0.148	Very weak	0.271
IgG HSV-1 and ROS (IU/mL)	0.047	Very weak	0.727

*The Rank Spearman correlation value.

prevalence of HSV-1 in persons aged 14–49 in the United States during 2015–2016 found that the number of female is higher (50.9%) than males (45.2%) [16].

The age range showed in this study was 18–39 years old due to the inclusion criteria, different from the previous study in Turkey that showed in the group aged 15–19, seropositivity was significantly higher than in 19–24 years old (p = 0.0333) [24]. A study in Australian people found that the prevalence of HSV-1 was highest in the 65–74 years age range (85%) and in comparison with the youngest age group (25–34 years), the RR of HSV-1 seropositivity was 1.25 [26]. Another study also found that the prevalence increased linearly with age, from 27.0% among those aged 14–19 to 41.3%, 54.1%, and 59.7% among those aged 20–29, 30–39, and 40–49, respectively [24].

IgG HSV-1 showed in range 0.9–42 index, with the mean levels were 17.5018 mg/mL from all subjects (57 subjects) with mean levels of IgG HSV-1 are 32.9 and 3.6 indexes in herpes and non-herpes group, respectively. According to the validation protocol for the user in kit instruction (Vircell® kit), samples with equivocal results must be retested and a new sample obtained for confirmation. Samples with indexes below 9 are considered not having IgG or IgM (depending on the procedure) specific antibodies against HSV-1 and 2. Samples with indexes above 11 are considered as having IgG or IgM (depending on the procedure) specific antibodies against herpes simplex Type 1 and 2 [27]. Individuals with HSV infection produce virus-specific IgG antibodies that are usually apparent for life even during the periods of latency thus, if HSV IgG antibodies are detected in a particular person it indicates that the person is infected with HSV and are capable of transmitting the virus to others [28]. This study was conducted in a healthy or non-asymptomatic population. It turned out that 27 out of 57 subjects examined showed reactive results for IgG HSV-1 levels, this means that they have been infected with HSV and can pass it on to others even though they did not know this condition before the examination. We conducted this initial research to determine the community's condition in Bandung related to HSV-1 infection, and the results show that as many as, 47.4% are infected with HSV-1. These results are lower than previous data which states that HSV-1 infection affects 60–95% of the adult population worldwide [13].

This study showed that the mean ROS was 2.23337 IU/mL, 2.55 ± 2.30 IU/mL, and 1.95 ± 1.20 in total subjects, herpes, and non-herpes groups, respectively. ROS is produced when our cells create energy during food metabolism and several internal and external factors, including food and drinks, oxygen, exposure to microbial infections, extensive exercise, pollutants/toxins such as cigarette smoke, alcohol, and ionizing, UV radiations, pesticides, and ozone [29]. Oxidative stress, primarily due to increased generation of ROS and reactive nitrogen species (RNS), is a feature of many viral infections, including HSV infection. ROS and RNS can be initiated within cells by redox reactions associated with normal physiologic processes or by enzymatic and non-enzymatic mechanisms associated with pathologic processes [30], [31]. ROS level in the herpes group was higher than the non-herpes group, but it was not statistically significant with p = 0.620. Viral infection triggers the production of ROS [32], [33], includes HSV-1. ROS are used by the immune system as weapons against pathogens. Although the current paradigm predicts that ROS production contributes to the elimination of pathogens, it is becoming clear that for viruses, bacteria, and protozoans, ROS production can contribute to increasing pathogen burden [34], [35].

This present study found that the cortisol level was 223.29 ± 101.84 nmol/L from the total subjects. This result differs from the previous study, which showed the mean of serum cortisol level 459.6 ± 235.2 nmol/L from 14 healthy persons taken at 8 am. Our research was conducted at 8–10 am. This can affect the cortisol level in serum because cortisol as a marker of hypothalamic–pituitary–adrenal axis functioning and follows a diurnal rhythm and, therefore, the time of day at which it is sampled will affect its level [36], [37]. Cortisol levels in our study showed average level, which is 8.04 mcg/dL (1 mcg/dL = 0.036 nmol/L), the average level of cortisol ranges between 6 and 23 micrograms per deciliter (mcg/dL). However, many laboratories have different measuring techniques, and what is considered normal may vary [38], [39]. All subjects did not have any emotional stress or other condition that can influence the exacerbation of clinical symptoms, and this condition also supported our examination.

Statistically, the trend of correlation between IgG HSV-1 and ROS was weak with a negative correlation direction. It means that IgG HSV-1 levels are inversely proportional to the ROS level. IgG HSV-1 and cortisol also showed a weak correlation. These results might be influenced by the sample size, time, and cost. This result reflects that ROS plays a key role in HSV-1 infection. Subjects with high titer specific antibody (IgG) to HSV-1 will have a lower risk of HSV-1 infection. Hence, this result resembles our hypothesis that ROS will increase in subjects with HSV-1 infection who have symptoms and decrease healthy subjects and HSV-1 infection without any symptoms. The subjects become healthy, or without any symptoms, because we just take a cross-sectional study. All of the cortisol levels in our study were normal. We know that once humans are infected with HSV-1, the IgG will be increased, and the virus becomes dormant. Cortisol level will increase in stress condition and our subjects were healthy-immunocompetent people, so neither they have not experienced increasing cortisol level nor the higher level of ROS. These results (normal ROS and cortisol level and high IgG HSV-1 level) are appropriate with our hypothesis that ROS and cortisol levels will decrease in

HSV-1 infected subjects without any sign of infection. Our findings have some application impact that people who have high IgG HSV-1 level should maintain their good physical and psychological condition to avoid increased cortisol and ROS levels. The people who have been infected by HSV-1 or have reactive HSV-1 IgG in their blood should minimize their exhausted physical condition or psychological disturbance. We know that it will be impossible to avoid those conditions in all of life, so we can suggest they consume anti-oxidant to lower ROS while they experienced physical exhaustion or psychological disturbances. The previous studies showed that some herbal medicine like Curcuma could lower the ROS and cortisol levels [40], [41].

The correlation between IgG HSV-1, ROS, and cortisol was not statistically significant. The correlation was not statistically significant between IgG HSV-1. This may be because ROS and cortisol are not biomarkers that can be found in chronic or latent infections, but in infections or inflammation that are acute in nature. This present study had limitations includes small sample size, and cross-sectional design, we will perform some cohort design so that we can follow cortisol and ROS level of every HSV-1 infected person in more than 1 time and various clinical condition, it would be better if we performed two conditions; cortisol and ROS level while the people with physical/psychologic stress condition and those level without physical/psychological stress.

Conclusions

This study showed that HSV-1 in an adult population often acts as a latent infection. This entity is potentially exacerbated when the ROS level is high. According to this study, adults with latent HSV-1 infection showed normal cortisol and ROS level. Antioxidants supplementation and regular exercise are necessary for stabilizing ROS levels. Hence, exacerbations can be minimized.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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