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Obstructive Sleep Apnea Risk Level Affect Executive Function Rather than Attention

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Abstract

Obstructive sleep apnea (OSA) is a kind of sleep disorders which is associated with cognitive impairment, either independently or by its strong association with metabolic syndrome. OSA affected attention and executive functions. Since the diagnosis of OSA had limitation, the assessment of OSA risk level by using STOP-BANG Questionnaire instrument in common population is important. This was a cross-sectional study aimed to investigate the effect of OSA risk level determined based on STOP-BANG Questionnaire score to attention and executive functions in 82 subjects. The demographic and clinical characteristics data obtained were age, gender, level of education, hypertension, body mass index (BMI), neck circumference, OSA risk level, and attention and executive functions. Attention function was assessed by using Forward Digit Span and Trailmaking Test A (TMT-A) instruments, while executive function was assessed by using Backward Digit Span and Verbal Fluency Test instruments. The demographic and clinical characteristics data showed significant higher proportion of male gender, large neck circumference, and hypertension in high risk OSA group. The OSA risk level significantly impaired the executive function but did not impaired attention function.

Introduction

Obstructive Sleep Apnea (OSA) is a highly prevalent sleep disorder. It is characterized by symptoms of intermittent snoring, sleep disruption, excessive daytime sleepiness and observed apneas during sleep (Zhang & Si, 2012). Recently, the clinicians pay more attention on OSA since it was known to be closely associated with metabolic syndrome (Xu et al., 2015; Drager et al., 2013), therefore, increase the risk of cardiovascular disease (Kim et al., 2015). The global prevalence of OSA is 22% in male and 17% in female population (Franklin & Lindberg, 2015). Thus, OSA is more common in male rather than female. The data of the prevalence of OSA in Indonesia is not available yet.

Most recent studies showed that OSA impaired the cognitive functions, more prominent on attention and executive functions (Choraghe & Pillai, 2016; Canessa et al., 2011; Krysta et al., 2017). It can be explained partially by the effects of intermittent hypoxia as the consequence of OSA in triggering endothelial dysfunction of cerebral vasculature, free radical formation, microglial activation and inflammatory process in brain tissue that lead to neurodegeneration process (Daulatzai, 2012). Activated microglia is the main source of oxidative stress in brain that will continuously induce neuro-inflammatory process that cause significant neuronal damage and result in

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neurodegeneration (Yang, Wang, Feng, Cao, & Chen, 2013). In fact, the neurodegeneration process can occur in any parts of the brain where the pathologic process as described above take place. The neurodegeneration process that occur in gray matter area located in prefrontal cotex, an important structure carrying out attention and executive functions, will impair those cognitive function in various degree, ranged from mild cognitive impairment to severe dementia (Joo et al., 2010). This process will be more evident with the existence of metabolic syndrome, which consists of hypertension, diabetes mellitus, dyslipidemia, and central obesity (Drager et al., 2010). Previous studies showed that OSA had close association with hypertension (Konecny et al., 2014), diabetes mellitus (Nannapaneni et al., 2013), dyslipidemia (Adedayo et al., 2014), and central obesity (Romero-Corral et al., 2010). Large neck circumference is one of the parameters of central obesity, representing the upper-body visceral fat deposition (Li et al., 2014). Previous study involving 149 subjects showed that large neck circumference can be used as the predictor of the presence of OSA and, together with hypertension, it can be used as predictors of the severity of OSA in snoring patients (Kim et al., 2015).

The gold standard for the diagnosis of OSA is the examination of polysomnography. This examination need a well-trained professionals, expensive and time-consuming, so its availability and feasibility for diagnosis confirmation is limited (Aurora et al., 2011). Therefore, assessment of OSA risk level using simple screening instrument in the level of population is needed. The STOP-BANG Questionnaire is a simple instrument which is useful for the assessment of OSA risk level. This instrument is had been validated as the screening tool for identification of OSA risk level, either in common population (Chung et al., 2016) or hospitalized patients population (Nagappa et al., 2015; Doshi et al., 2015). This instrument was had been applicated in Jakarta (Gunawan et al., 2013).

As noted earlier, the previous studies had confirmed the negative effect of OSA to the cognitive functions. This effect probably occurred either independently or by its role in the pathogenesis of each component of metabolic syndrome, especially hypertension, with subsequent cognitive impairment. Since hypertension has high prevalence, especially in rural area, it can be the most important risk factor for OSA that contribute to cognitive impairment (Rosjidi et al., 2017). This was the first study which was conducted to investigated the effect of OSA risk level to the attention and executive functions in normal subjects and previously never been diagnosed as OSA.

Method

This was a cross-sectional study in normal subjects attending car free day event routinely held every Sunday in Mataram, Indonesia, and were recruited consecutively. The inclusion criteria were subjects aged 40 years and older, voluntary participated, fully conscious, literate, and speaking in Indonesian Language. The exclusion criteria were subjects who were previously diagnosed as OSA and/or decided to discontinue their participation in this study. This study was conducted in the period of February to April 2017 after getting approval from local ethical clearance committee. This study was approved by Komisi Etik Penelitian Kesehatan Universitas Mataram with the ethical clearance number 81/UN18.8/ETIK/2017.

The data collected were demographic and clinical characteristics of the subjects, OSA risk level and attention and executive functions. The demographic and clinical charahcteristics data were gained from a structured and detailed interview, physical examinations, and laboratory examinations. The data gained from a structured and detailed interview were age, gender, level of education, hypertension. The data collected from physical examinations were body mass index and neck circumference.

The OSA risk level was assessed by using STOP-BANG Questionnaire instrument consisted of eight structured questions which confirmed the existence of snoring, tiredness, observed episodic apnea, hypertension (pressure), body mass index (BMI)>35 kg/m^2, age 50 years old and older, neck circumference >40 centimeters, and male gender. Each of structured questions was scored 1 when the answer was "YES" and was scored 0 when the answer was "NO." The total score of STOP-

BANG Questionnaire will determine the stratification of OSA risk level, defined as either low risk or high risk of OSA. A STOP-BANG Questionnaire total score of 0 to 2 indicated low risk of OSA whereas a STOP-BANG Questionnaire total score 3 to 8 indicated high risk of OSA (Chung et al., 2008).

Assessment of attention and executive functions were performed by using selected neuropsychological testing. Attention function was assessed by using Forward Digit Span and Trailmaking test-A (TMT-A) instruments (Adamis et al., 2016; Salthouse, 2011). Subjects were considered for normal when they were able to repeat 5 or more numbers in the same order as the series of number examiner said in the examination of Forward Digit Span and also were able to finished the task as accurately as possible in 90 seconds or less in the examination of TMT-A (Kelompok Studi Neurobehavior PERDOSSI, 2016).

Executive function was assessed by using Backward Digit Span dan Verbal Fluency Test (Faria et al., 2015; Torralva et al., 2009). Subjects were considered for normal when they were able to mention 4 or more numbers in the reverse order as the series of number examiner said in the examination of Backward Digit Span and also were able to mention 18 or more animal names in 60 seconds in the examination of Verbal Fluency Test (Kelompok Studi Neurobehavior PERDOSSI, 2016).

Statistical analysis of the comparison of clinical and demographic characteristics between 2 groups of OSA risk level were based on chi-square and Mann-Whitney U tests. Statistical analysis of the comparison of both attention and executive functions between 2 groups of OSA risk level were based on chi-square test. The result of tests were statistically significant if p>0,05.

Results and Discussion

Previous studies of cognitive functions were conducted to the subjects diagnosed with OSA after being confirmed by polysomnography examination, defined as Apopnea-Hypopnea Index (AHI) of 5 or more (Choraghe & Pillai, 2016; Canessa et al., 2011; Krysta et al., 2017). Since the use of polysomnography examination has limitation as mentioned earlier, the need of an applicable simple instrument in general population for determining the OSA risk level is important. This was the first study investigating the effect of OSA risk level to two domains cognitive function, attention and executive functions, in 82 subjects (n=82). As noted earlier, STOP-BANG Questionnaire is a validated instrument for this purpose. In the recent study, subjects were divided into two groups of OSA risk level, high risk level group (n=37) and low risk level group (n=45), based on STOP-BANG Questionnaire score and stratification.

STOP-BANG Questionnaire are consisted of three questions that confirm the existence of clinical symptoms of OSA and five parameters which represent the risk factors for OSA. These five parameters are hypertension (pressure), BMI >35 kg/m^2, age 50 years old and older, neck circumference >40 cm, and male gender. Among these parameters, the frequency of male gender, hypertension, and neck circumference >40 cm are significantly higher in high risk level group compared to low risk level group of OSA (table 1). Pathophysiological, OSA, male gender, hypertension, and large neck circumference are interconnected. A study conducted in OSA patients showed that the higher proportion of male gender was associated with the higher comorbidities in these gender (Valadares et al., 2015). Male gender increased the risk of OSA since it has low estrogen level compared to female gender that contribute to increase of oxidative stress, endothelial dysfunction, and preferential adipose tissue deposition in the viscera and around pharynx (Geer & Shen, 2009). These oxidative stress and endothelial dysfunction could contribute to the development of hypertension, whereas preferential adipose tissue deposition in the viscera and around pharynx could contribute to large neck circumference, one of the hallmarks of central obesity (Lam et al., 2010). As stated earlier, large neck circumference is representing the upper-body visceral fat deposition and, therefore, becoming one of the parameter of central obesity (Li et al., 2014). Large neck circumference is associated with the increase of the development of hypertension (Alfie et al., 2012). Both large neck circumference and hypertension can be used as predictors for

the severity of OSA (Kim et al., 2015). Large neck circumference results a smaller lumen of pharynx and, therefore, contributes to intermittent upper airway collapse with the result of snoring and hypoxia during sleep as seen in OSA (Romero-Corral et al., 2010). A study conducted in Turkey which was also involving OSA patients showed that large neck circumference was a risk factor for OSA and it was also associated with the high degree of OSA (Ahbab et al., 2013).

A BMI > 35 kg/m^2 is also an important risk factor for OSA, especially in male (Deng, Gu, Li, Liu, Li, & Gao, 2014). Therefore, BMI >35 kg/m^2 is becoming one of the STOP-BANG Questionnaire components. It is also associated with the development of hypertension, another important risk factor for OSA, and cognitive impairment (Korneliani & Meida, 2012). In this study, there was no significant difference in the frequency of BMI >35 kg/m^2 between high risk and low risk level group of OSA. This result was probably associated with very low proportion of subjects with BMI >35 kg/m^2 (table 1).

Intermittent hypoxemia occurred in OSA triggers the sympathetic activities, leading to the serial processes of cerebral vasoconstriction, endothelial dysfunction and blood-brain barrier disruption (Dewan et al., 2015). These processes will result in both structural and functional changes of the cerebral vasculature as well as brain tissues. A study that involved subjects undergoing brain *Magnetic Resonance Imaging* (MRI) examination showed the decrease of gray matters volume in entorhinal, posterior parietal, and frontal lobe which were correlated to cognitive impairment (Canessa et al., 2011). Neurons of those regions are hypoxia-sensitive, thereby, chronic intermittent hypoxia occurred in OSA are contributed to the neuronal damages in those regions by activating the microglia. Once activated, the microglia will be sustainably up regulating their surface molecules, such as complement receptors, reactive oxygen and nitrogen species, proinflammatory receptors and major histocompatibility complex simultaneously and releasing various soluble factors which have proinflammatory and potentially cytotoxic characteristics (Yang et al., 2013). Neurons in those regions are important for two important domains of cognitive function, attention and executive functions (Joo et al., 2010). It is still unclear whether subjects at high risk level of OSA but never been diagnosed as OSA showed those cognitive impairment since the existence of vascular risk factors that underlie the process as described above in these subjects increase the risk of OSA. The recent study showed that frequency of subjects showing executive disorder was significantly higher in high risk level group rather than low risk level group of OSA, but there was no significant difference of attention disorder between groups (table 2). However, the effect of OSA risk level to attention and executive functions could be variably among different populations in different regions. It is influenced

Table 1. Demographic and Clinical Characteristics of Subjects

Categories	**OSA Risk Level**		***p-value***
	Low Risk (n=45)	**High Risk** (n=37)	
Age ≥ 50 years old n(%)	27 (32.93)	28 (34.15)	0.133
Gender			
Male n(%)	13 (15.86)	26 (31.71)	0.000*
Female (n(%)	32 (39.02)	11 (13.41)	
Level of education (Mean, ±SD)	13.93±3.08	12.78±3.86	0.274
Hypertension n(%)	9 (10.98)	22 (26.83)	0.000*
Neck circumference >40cm n(%)	2 (2.43)	10 (12.20)	0.004*
BMI > 35 kg/m^{2}n(%)	0 (0.00)	2 (2.44)	0.201

*Significant difference (p<0.05)

OSA = Obstructive Sleep Apnea; BMI = Body Mass Index

Tabel 2. Attention and Executive Functions between Groups of the Risk Level of OSA

Cognitive Domains	**Risk level of OSA**		***p-value***
	Low Risk (n=45)	High Risk (n=37)	
Attention			
Normal n(%)	30 (36.59)	20 (24.39)	0.264
Impaired n(%)	15 (18.29)	17 (20.73)	
Excutive function			
Normal n(%)	23 (28.05)	8 (9.76)	0.006*
Impaired n(%)	22 (26.83)	29 (35.36)	

*Significant difference ($p<0.05$)

by demographic and clinical characteristics of subjects. As showed in a *meta-review* in which some studies showed that OSA affected those both cognitive domains, whereas other studies showed significant effect only on one domain, either attention or executive function (Bucks et al., 2013).

Metabolic syndrome, characterized by hypertension, diabetes mellitus, dyslipidemia, and central obesity, can also impair cognitive functions, especially the domain of memory and executive functions in non-dementia population and males were more susceptible than females (Cavalieri et al., 2010). The mechanisms underlying the pathogenesis of cognitive impairment among subjects with metabolic syndrome are cerebral vascular endothelial dysfunction and microglial activation that result in oxidative stress and neuro-inflammation (Yates et al., 2012). These mechanisms are similar to those found in OSA as described above. As noted earlier, this study showed that the frequency of subjects with hypertension and large neck circumference, one of the hallmarks of central obesity, were significantly higher in high risk group compared to low risk group of OSA (table 1). Thereby, executive disorder found significantly higher in high risk group of OSA as showed in this study was seemingly related to the existence of hypertension and neck circumference as the component of metabolic syndrome, but it is still need further investigation. However, previous studies showed that both large neck circumference and hypertension can interfere cognitive function either independently or by their interaction with other component of metabolic syndrome (Chen et al., 2018; Iadecola et al., 2016).

Conclusions

The OSA risk level significantly affected executive function but not attention function. Demographic and clinical characteristics of subjects which were significantly different between high OSA risk level and low OSA risk level groups were gender, large neck circumference, and hypertension. Since large neck circumference and hypertension, the components of metabolic syndrome, can cause cerebral similar pathophysiologic process as seen in OSA, including oxidative stress and neuro-inflammation in certain areas of the brain that subserve cognitive functions, the effect of OSA risk level on executive function in high OSA risk level group in this study might be related to large neck circumference and hypertension which had higher proportion in this group. However, this relationship still needs further investigation.

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