Gender Differences In Schizophrenia

Schizophrenia is a recurring disorder and is defined by abnormal in five areas in general, including hallucinations, delusions, disorganized things, disorganized or abnormal motor behavior, and negative symptoms (APA, 2013; McNally & McCarley, 2016). However, would there be any differences between males and females in terms of age-at-onset for the first episode and symptoms? Are there any reasons behind those differences?

To begin with, males and females are experiencing different rates of incidence and prevalence, age-at-onset for the first episode and diagnostic issues (Abel, Drake, & Goldstein, 2010; Aleman, Kahn, & Selten, 2003; APA, 2013; McGrath, J., Saha, S., Chant, & Welham, 2008). For the rates of incidence and prevalence, although there is a similar prevalence of schizophrenia among males and females, the onset of females is a few years later than males (Angermeyer & Kühn, 1988; Jones, 2013; Kirkbride et al., 2012; Li, Ma, Wang, Yang, & Wang, 2018; Nowrouzi et al., 2015). Besides, there would be multiple incidences of schizophrenia onset peaks for both males and females across the lifetime. For males, the early twenties would be the highest incidence onset frequency and the second peak would be in the mid-thirties; for females, the pattern of peaks is similar to males, on the other hand, the third peak occurs in the early sixties (Abel et al., 2010; Drake, Addington, Viswanathan, Lewis, Cotter, Yung, & Abel, 2016). Besides, comparing between males and females, males would be a higher rate of onset from the first two peaks, however, females would be higher frequency rates of onset in late middle age which described as the third peak. In terms of the prevalence of schizophrenia, according to American Psychiatric Association (2013), the rates of schizophrenia as a lifetime developing disorder is approximately 0.3% to 0.7%. However, no gender differences show in terms of prevalence (McGrath, Saha, Chant, & Welham, 2008).

Moreover, studies of differences in age-of-onset are the most stimulating into account of the gender differences in schizophrenia. Males develop schizophrenia at the age between 18 and 25; while females develop schizophrenia at the mean age between 25 and 35. Thus, the age-of-onset distribution for males and females is considered as non-isomorphic, in the other words, the distribution is not the same or similar. As discussed before, females seem to have the third peak in the age-of-onset of schizophrenia, i.e. the third major prevalence of females in late middle age. This could be understood by the reduction of estrogens after menopause which would be discussed later on (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012).

Besides the incidence and prevalence of schizophrenia, differences are also shown in terms of symptoms presentation. According to Li and his colleagues (2016), differences in symptoms show in positive, negative, and cognitive symptoms. For males, more negative symptoms would be appearing for males with schizophrenia and more server clinical features comparing to females with schizophrenia, including social withdrawal, substance abuse, and undermine or contradictory emotional issues. On the other hand, females with schizophrenia would often show more in mood disturbance as well as affective symptoms, for instance, depressive symptoms. Besides, while comparing between males and females, males are more presenting negative symptoms, violent behavior, and disorganized, while females are showing more depression and social anxiety (Li et al.,2016; Riecher-Rössler, Butler, & Kulkarni, 2018). Apart from the positive and negative symptoms, males also reported to be more serious cognitive

deficits them females, including immediate and delayed memory (Li et al., 2016). However, there is no gender difference in cognitive deficit in terms of language, visuospatial, and attention. With the higher risk for schizophrenia in males, males with schizophrenia are generally first perceived negative and cognitive symptoms. On the other hand, females with schizophrenia are generally the first to record positive and affective symptoms.

To order to understand the reasons behinds those differences, I would like to separate two main factors, biological, and social, and environmental factors. Biological factors are about the brain structure, hormone hypothesis, and sex chromosome hypotheses; on the other hand, social and environmental factors are about social functioning and substance abuse.

In terms of biological factors, differences in brain structure could explain the differences between gender. Some studies suggested that schizophrenia, although it is not considered as the category of neurodevelopmental disorder in DSM-V by APA (2013), is related to fetal and early postnatal origins (Abel et al., 2010; Goldstein & Walder, 2006). It is believed that gender differences in brain abnormalities in schizophrenia are proposed at the early period of sexual differentiation of the brain, i.e. fetal and early postnatal development. For males with schizophrenia, in the understanding of the gender difference about the brain structural abnormalities of schizophrenia, there are greater abnormalities than females with schizophrenia (Abel et al., 2010; Nopoulos, Flaum, & Andreasen, 1997). Under MRI study and post-mortem study, males with schizophrenia reported to be larger lateral and third ventricles, which functioned as filling of cerebrospinal fluid and protection of brain (Saladin, 2004), and anterior temporal horn; smaller medial temporal volumes, for instance, hippocampus, which responsible for retrieval condition including recall of episodic, semantic, and autobiographical information (Banich & Compton, 2011); amygdala, which plays an important role in effective information and emotional expression (Banich & Compton, 2011); Herschel's gyrus, a primary auditory cortex; superior temporal gyrus which also contains auditory cortex responsible for processing sounds (Bigler et al., 2007); and overall smaller volume in the frontal and temporal lobe (Abel et al., 2010). Besides, abnormalities of left-lateralized were also reported in males with schizophrenia rather than females. More general brain destruction show in males than females with schizophrenia about the greater sulcal volume and smaller thalamic size in which the thalamic size is considered to be positively associated with the volume of the frontal and temporal lobe (Brickman et al., 2004). A smaller volume of the superior temporal gyrus, the site of the auditory association cortex, was also found in males with schizophrenia. On the other hand, there is also some abnormality in females with schizophrenia in terms of the brain structure comparing with males with schizophrenia. The volume of heteromodal association areas, which mainly focus on integrating sensory data, motor feedback, and promote learning and creates thought, expression, and behavior, is smaller among females with schizophrenia than males including dorsolateral prefrontal cortex, superior temporal gyrus and orbital prefrontal cortex (Abel et al., 2010; Buchanan et al., 2004; Narr et al., 2004). However, in terms of cognitive symptoms, similar abnormalities are reported in the dorsolateral prefrontal cortex, which responsible for executive functioning, for instance, decision making, working memory, social cognition, and neurotransmitter functioning, for both males and females with schizophrenia (Abel et al.,2010; Phan, Quo, & Wang, 2006). On the other hand, short-term and long-term memory deficits are more likely to be contributed to males with schizophrenia instead of females (Han et al., 2012).

Besides the influence of different brain structure, hormone hypotheses also suggest a way to explain the difference between males and females with schizophrenia in terms of schizophrenia symptoms and age-of-onset. Gender differences in schizophrenia involve gonadal hormones (Li

et al. 2016). Estrogen, for instance, act a possible role in protecting from and against schizophrenia pathology in females. In the other words, the late age-of-onset and the incidence peak around late middle age, so-called menopausal age, of females are supporting the estrogen hypothesis. During menopausal age of the female, lack of estrogen shows a high relationship with the severity of psychotic symptoms including schizophrenia symptoms (Grigoriadis & Seeman, 2002; Li et al., 2016). For instance, in Grigoriadis and Seeman's study in 2002, the female with schizophrenia were having more severe schizophrenia symptoms during menstrual cycle with a low estrogen phase. On the other hand, in the case of males with schizophrenia, there is a negative correlation between plasma estrogen levels and schizophrenia symptoms. Besides estrogen, the primary female sex hormone, testosterone, a major male hormone, also act as an influences in schizophrenia in terms of the symptoms (Ko et al., 2007; Lo et al. 2016). There is an association with a negative correlation between levels of testosterone and the severity of schizophrenia symptoms. Low levels of testosterone and serum testosterone level often associated with greater severity of negative symptoms of patients with schizophrenia (Sisek-Šprem, Križaj, Juki?, Miloševi?, Petrovi?, & Herceg, 2015). Not only gender hormone, estrogen, and testosterone, presenting influence to schizophrenia, oxytocin also influence the symptoms of schizophrenia. Oxytocin is a hormone generally produced in the hypothalamus and released by the posterior pituitary (Standring, 2015). Oxytocin plays a role in reproductive function (Li et al., 2016; Yang, Wang, Han, & Wang, 2013). In males or females with schizophrenia, oxytocin levels may elevate the psychotic symptoms (Lee, Macbeth, Pagani, & Young, 2009). Sensorimotor gating by the prepulse inhibition of the startle reflex which reducing the intense sensory stimuli of the sudden, in other words, weakening the sensory stimulus. This sensorimotor gating is so-called an attentional mechanism to reduce the distract stimuli. A deficit in the sensorimotor gating would generate feature of schizophrenia symptoms. It was also reported that males and females with schizophrenia with a higher level of oxytocin would develop fewer schizophrenia symptoms with improved cognitive (Cochran et al, 2013; Li et al., 2016). As a result, regulating central dopamine and hence performing antipsychotic effects would be believed as the function of oxytocin in terms of schizophrenia.

Besides, the dopaminergic system also explains part of the gender differences in terms of schizophrenia. The different activity level of neurotransmitters and receptors reflecting on different positive and negative schizophrenia symptoms. Abnormalities in the dopaminergic system are shown in both males and females with schizophrenia (Banich & Compton, 2011; Kesby, Eyles, McGrath, & Scott, 2018; Li et al. 2016). In general, there would be two main families of receptors, i.e. D1-like, which increase the production of cyclic AMP, a second-messenger, and located on postsynaptic sites; and D2-like, which decrease the production of cyclic AMP and located on both postsynaptic and presynaptic sites (Banich & Compton, 2011). For males and females with schizophrenia, increased subcortical synaptic dopamine content and basal dopamine synthesis capacity were found (Bloemen et al., 2013; Egerton et al., 2013). Besides, positive symptoms were found to be related with the increased subcortical dopamine synthesis (Banich & Compton, 2011). Dopaminergic neurotransmission is also related to inflect attention, effectiveness of executive functioning, and positive affect in which differences between males and females in terms of the dopaminergic system also shown (Riccardi, Park, Anderson, Doop, Ansari, Schmidt, & Baldwin, 2011). For females, in terms of cognitive functioning, higher baseline extracellular levels of dopamine release are recorded with higher d-amphetamine which induced dopamine release; meanwhile, positive affect had found correlating with dopamine release in substantia nigra which mediating dopaminergic function with effect (Riccardi et al., 2011).

Apart from the above, sex chromosome hypotheses are also proposed to explain the gender difference among schizophrenia. To understand the gender differences, sex chromosomes, i.e. XX and XY, maybe a role to investigate in the effect of neurodevelopment and sharing the sex-specific cognitive function (Bache & DeLisi, 2018; Li et al., 2016). Via the sex chromosome hypotheses, the genetic predilection of schizophrenia could be considered with abnormal X chromosome and exuberance of schizophrenia have shown in Klinefelter's males i.e. XXY and triple X females (Bache & DeLisi, 2018). With this abnormal number of X-chromosomes, it is suggested that incidence in motor impairment and psychosis symptoms would be higher than in normal populations (Hong & Reiss, 2014; Li et al., 2016). In the other words, a higher prevalence of psychosis would be shown in a person with an excess sex chromosome. Besides the abnormal X chromosome of males and females with schizophrenia, there are some other chromosome-related facts that could explain the differences among them. For instance, G/G genotype of the catechol-O-methyltransferase (COMT) gene on chromosome 22q11, CAA and TATC polymorphism of the Nogo gene, and GPR50 gene on chromosome Xq28 was associated with females with schizophrenia only (Goldstein et al., 2013; Shifman et al.,2002; Tan et al., 2005; Thomson et al., 2005). On the other hand, chromosome 8p22 and chromosome 17p11.2-q25.1 were reported as abnormal only in males with schizophrenia (Williams et al., 2003; Xie et al., 2011).

On the other hand, apart from biological factors, social and environmental factors may also take into account gender differences. Environmental factors may show a significant role in explaining the hidden pathophysiology of schizophrenia. For instance, infections, nutritional deficits, and neurotoxins are influencing brain development and causes of a psychotic disorder (Brown, 2011). Substance abuse would also be understood as one of the environmental factors. The relationship is shown between psychosis symptoms and substance misuse in which the rates are higher in the first-episode psychosis patients (Stilo, Di Forti, & Murray, 2011). Although not all addictive drugs are found to have the ability in inducing psychotic symptoms, repeated use of stimulants, for instance, cocaine and amphetamine, would activate the sensitization of the dopamine system. In the other words, the dopamine system would be dysregulated and lead to developing psychotic symptoms. as discussed before, the gender difference was shown in terms of the dopaminergic system, different severity of the symptoms would be considered (Riccardi et al., 2011). Besides, the use of cannabis was also found to be correlated with the increasing levels of psychotic symptoms. In the other words, cannabis would be considered as one of the risk factors for psychotic disorder. The use of cannabis would increase the risk of development in later psychotic symptoms or disorders regards of psychosis awareness. age-of-onset of psychotic disorder for the cannabis user would be earlier than those nonusers (Stilo, Di Forti, & Murray, 2011). Early use of cannabis is also reported to be correlated to impeded cortical maturation in males with a high risk of schizophrenia development and probably increase the rate of disorder development. In early adolescence, males were found to be more heavily relying on cannabis when compared to females, and thus to be at risk in schizophrenia development (French et al., 2015). The differences might also be explained in terms of the testosterone level in early adolescence, in which testosterone production would be related to aggressive norm-violating behavior and thus, drug use (Tarter et al., 2009). Besides, in the social factors or psychosocial factors, the social functioning would also generate the gender differences in schizophrenia. Females with schizophrenia shows had better social functioning when comparing to males with schizophrenia as females reported better social support while males would have more criticize than females. Males with schizophrenia also report presenting greater social isolation and social withdrawal comparing with females with schizophrenia (Barajas, Ochoa, Obiols, & Lalucat-Jo, 2015; Gogos, Ney, Seymour, Van Rheenen, &

Felmingham, 2019). Besides, stress and trauma also consider as social factors. Traumatic life events seem to increase the risk of developing schizophrenia and affecting the severity of schizophrenia symptoms, for instance, different kinds of abuse and childhood experience. Some studies were reported that females with schizophrenia have a history of traumatic events more frequently than males with schizophrenia, in which females report a greater risk of schizophrenia after traumatic events when comparing to males. Besides, childhood abuse would also reported in females with schizophrenia and presenting more schizophrenia symptoms and depressive symptoms but not for males (Riecher-Rössler, Butler, & Kulkarni, 2018). For stress handling, females with schizophrenia were reported to be greater emotional reactivity for daily stress which may also influence by the estradiol levels.

All in all, the gender difference is shown in schizophrenia development in terms of age-of-onset, and the development of the symptoms. The difference in the incidence rate and prevalence rates is always reported in a gender difference of schizophrenia. Different age-of-onset also reported for earlier in males and later in females, and females would have another peak for the late middle age. Differences are also shown in schizophrenia symptoms between males and females with schizophrenia, i.e. males with schizophrenia would have a higher tendency in suffering negative symptoms while females would be more chances in suffering positive symptoms instead. These differences could be explained in terms of biological and social factors. By the understanding of brain structure, hormones, and chromosomes, differences in the age-of-onset and symptoms presentation could be explained the gender difference. Besides, social factors, for instance, the social structure or substance abuse, could also explain the gender differences. With the help of biological factors and social factors, it would be easier and clearer to understand the reasons behind the gender differences in age-of-onset and symptoms presentation. To have a full picture of understanding the causes of schizophrenia, with the help of many other perspectives related to the explanation of gender differences, risk factors, and protective factors would be useful in the prevention, assessing, and intervening of schizophrenia with targeting in different gender.