

Research Progress on the Cause of Schizophrenia

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Abstract: Schizophrenia is often considered one of the most common and influential psychotic disorder. The purpose of this article is to explore the differences in gender and age in schizophrenia. The outcome of the idea that early onset of schizophrenia is characterized by more genetic influence, and siblings should be the focus as higher risk will be presented. The difference between male and female schizophrenia is emphasized with the different mechanisms causing it, and the possible reason behind it. The conclusion includes that females are found to be more influential in general, while they are more genetically influenced, males are more environmentally influenced. Contradicting evidence of existing papers will be presented and discussed. Possible attempts of understanding environmental factors of schizophrenia will be included. Connections between marital status, housewife percentage, This paper also seeks to provide a general sum up of treatment of schizophrenia, and how would the difference of gender and age possibly impose a more implicit way of therapy and more evidential prevention of schizophrenia.

1. Introduction

In the entire human history, diseases are considered greatly responsible for the death of people. Studies have been concentrated on flu and cancer in terms of illnesses. Breakthrough of these illnesses has indeed brought new treatment and largely improved human healthcare, sustaining human lives. People often think that diseases only include physical diseases, and do not think that mental diseases include them. However, psychotic disorders have been largely ignored. Focuses and attention on psychotic diseases do not match with the high incidence rate of general psychotic disorder. There is always resistance against the presence and recognition of psychotic disease. People pay few visits to a psychologist when confronting stress or other problems requiring relief. Parents are reluctant to accept that their child is diagnosed with a psychotic disorder. Understanding psychotic disorders, and providing improved treatments of these diseases can be the future scope of health.

Since schizophrenia not only has a serious impact on the patient, but also brings a heavy economic burden to the family and society, the etiology of the disease has attracted much attention. Psychotic disorders are usually caused by the presence of mental dysfunction in several parts of the brain. Its genetic and neurobiological backgrounds are different, and its pathogenesis is still being studied so far. In the field of behavior genetics, schizophrenia has been the most frequently studied psychotic disorder. This is likely to be the result of the high prevalence as well as the high incidence rate every year: prevalence is considered to be generally 1 percent of the total population at any given time internationally, and the incidence rate stands at around 1.5 people every year [1], as evidence of schizophrenia is very likely the most influential psychotic disorder. In people over 18 years of age, the disease accounts for about 1.1%, persists throughout the life of the patient, and poses a significant burden on global public health [2]

But the exact etiology of psychotic disorders is remained not understood, only judge the relevant pathological features of mental illness. Its main pathological characteristics include: once the patient has the disease, there will be disturbances in perception, behavior and death emotion, and will be resistance to certain environments. Moreover, schizophrenia is a very complex disease. Most patients develop severe cognitive impairment due to strong shocks to their thinking and emotions. If timely treatment is not taken to control the condition, the patient's condition will become more and more

serious over time, directly threatening the patient's life safety [3]. As technology advances, there are approaches to understanding the factors influencing these psychotic disorders, including the classical adoption and twin study, also known as quantitative genetics. The new method of genetic study, known as genome-wide association study, its occurrence characterized by the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, was soon employed by many researchers. The goal of this essay is to summarize the past studies of schizophrenia, several important quantitative genetic studies and gene-specific studies. There will also be attempts to draw hypotheses and explain the evidence of these studies, which are to some extent contradicting.

Quantitative genetics, including adoption and twin studies, employs a method of finding the correlation between different family members. It is generally considered that psychotic disorders can have different sources, genetic influence (A), shared environmental influence (C), non-shared environmental influence (E). The exact percentage of these influences is estimated by comparing different groups of family members. Classic quantitative genetics study includes twin studies, since homozygous twins have exactly the same gene, though this idea is being debated [4], all their differences must be accounted for the difference of the environment; adoption studies, which shows how the difference of correlation of gene would influence aspects of disorders, marked by an essay in 1966 [5], primarily done because separation of genetic from environmental influences could be achieved by studies of adopted individuals [6]. Besides this, other mechanisms such as genetic-environment interplay, including genetic and environmental correlation, genetic-environment interaction are also recognized by past studies. Psychotic disorders have shown the different extent of these influences and mechanisms. Schizophrenia, as one of the most studied psychotic disorders, is considered to have high heritability in general. The investigated topic soon diverges into studies of schizophrenia between gender, across ages, considering other multiple factors such as immigration status, marital condition, income level, etc.

Although various treatments of the psychotic disorder have been presented, an explicit understanding of environmental factors is always lacking. Few explicit treatments for differences of age and gender have been observed. This is especially worth pointing out as it has been observed that the cause of schizophrenia might significantly differ across gender, the theory is that males and females can face different types of risk and thus females can be largely influenced by genetics, while males are mostly influenced by the environment.

2. Family Studies About Age Onset and Gender

2.1 Inverse Proportional Relationship of Inheritability and Age

A Swedish study using the Multigeneration Register had to take into account a total of 19029 females and 21199 males with psychotic symptoms [7]. The huge sample size, and the use of SIR rate for statistics, allowed many environmental variables to be addressed, including gender, age, immigrant status, employment status, education, income. The main finding was that the risk of parental transmission has been generally decreasing as offspring gets older, showing an inverse proportional relationship between age and heritability. However, since environmental influence from the parents can also be considered as a decrease through time, this idea remains debatable.

People showing fewer symptoms as they age may due to the loss of parental influence, and general family members as well, when they become more social. Offspring tend to show an increase in their communication with peers as they develop their social wellbeing when they become older. Therefore, the decreased risk of schizophrenia might be due to the decreased average environmental influence instead of the decreased heritability.

For the difference of paternal influence and maternal influence shown by the same study, the percentage of housewives in Sweden in those years may be related to this idea. This makes sense as women that spend more on work are more influential to the entire family, and thus the children. This hypothesis coincides with the results in this paper [8]

It is worth pointing out that environmental influence on family members depends on the extent of mental dysfunction, as part of the influence of family members. However, females are recorded to show less mental dysfunction compared to males. This appears to be the case for language dysfunction [9], for odor acuity [10]. Odor acuity is found to be correlated with cognitive ability, to a great extent, although the previous study also found that correlation itself between odor acuity and general cognitive performance significantly differs for gender. This to some extent lowers the significance of taking odor acuity as an indicator of cognitive ability. Yet, in general, odor acuity is considered an important factor for understanding schizophrenia [11].

Concerning evidence correlated to the particular environmental influence of families in Sweden, there are also other findings by this study [8]. One often found environmental influence that correlated with the onset of schizophrenia, marital status, including divorce rate, has been recognized as one of the highest in Europe since World War 2, peaked at 40 percent. It is important to stress that the divorce rate indicates not only a possible one parent environment for the child, but also as an index for the general happiness in a family of this country. Children may have to observe frequent quarrels between parents and possible violence. A possible indicator of high schizophrenia risk environment also includes the willingness of having a child, while Sweden has shown a rapidly decreasing rate of a married couple having a child since the 1930s. If family members were less willing to have a child in the first place, they are less likely to give the attention and love their children required. These are all possible environmental influences of schizophrenia in Sweden. However, the evidence does show a high rate of marriage-like couples living together instead of marriage in Sweden, which decreases the significance of using divorce rate as an indicator of family dissolution, since a number of families were not living together as married in law.

In addition, it is important to address that males with schizophrenia are considered to have more negative symptoms in general. This includes substance abuse and males are more likely to be introverted in social conditions, also a more severe cognitive deficit in general. Whereas females tend to show more delusion, the extent of these delusions decreases as the age of onset goes up [12].

Although general symptom difference across gender has shown positive evidence to the precious claim of correlation between difference of environmental influence from parents across gender, cognitive ability difference between gender does not support this claim. Males tend to be less social, which gives them less chance to influence their child, while females would show less introverting symptoms. It is also worth noting these environmental influences can be indirect. This means that the psychotic dysfunction does not influence the family members, but when they are unable to take familial responsibilities, other members of the family must take over. This may create an environment correlated with schizophrenia. Such an environment includes a lower family income while the infected parents have to take extra treatments. This influence is considered directly proportional to the importance of the members of the family.

Since males and females have equal familial responsibility generally in Sweden compared to other countries, it would be able to explain why the low extent of psychotic dysfunction does not match with the high influence of females.

2.2 Difference of Paternal Influence and Maternal Influence

For the same paper, another discover is the difference between paternal influence and maternal influence. Data indicates that schizophrenia mothers generally influence offspring greater than schizophrenia fathers, no matter the gender of the child, with about 2-3times SIR rate in general, compared with schizophrenia fathers. If the heritability of schizophrenia for mothers and fathers is generally the same, which they are normally considered since exactly half of the gene comes from the mother and the other half from the father. This is a suggestion of higher maternal environmental influence.

Another finding worth mentioning was that immigration status is found to be correlated with schizophrenia to some extent. As a factor that few studies took considered, brought new inspiration to quantitative genetics.

Female being more influential generally for schizophrenia : Another Danish twin study [13] consists of the twin pairs born from 1969 to 2011, a total amount of 31524 among which 788 schizophrenia spectrum disorder and 471 diagnosed as schizophrenia. Age of the onset of schizophrenia was the major concern of this paper, narrower age gaps are also identified: below 18, 18-22, 22-26, 26-30, and over 30. It is found that the range of onset for schizophrenia spectrum disorder is generally broader than the narrowly defined schizophrenia (Figure 1). The researcher soon computed that risk of schizophrenia on the second twin if the first twin had schizophrenia will be higher up to 4.7 times in general. Concerning gender, this paper also shows the influence from the first twin to the second twin is greater for females than males, while few difference was found concerning the second twin's gender.

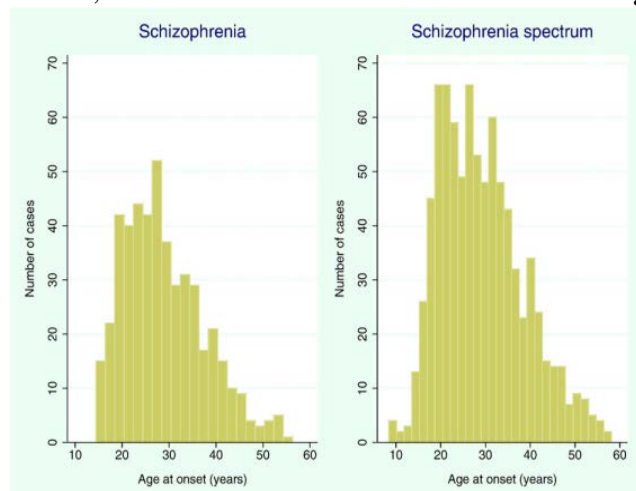


Fig 1 Distribution of onset for schizophrenia and schizophrenia spectrum [13].

Females below the age of 22 have a hazard ratio of 8.66, while for males below 22 is 2.53. However, the hazard ratio for a general monozygotic female is 5.26, the male is 6.91. The situation becomes not significantly different for the schizophrenia spectrum. This result is to some extent contradicts the previous assumption, that higher environmental influences from the female with schizophrenia are due to larger contact between housewives and their children. The result stated that female is generally more influential for these disorders, does not depend on the higher rate of interactions between the child and mother, direct or indirect. The statistics from the paper also showed that early males are likely to have more environmental influence, while females have a more genetic influence. The other approach, genome-wide association study of schizophrenia had found conclusions to some extent contradict with the quantitative genetic research regarding gender. For these studies, it is found that some alleles were significantly related to the time of the early onset of schizophrenia, but these alleles were for males instead of females [14-15]. Some alleles were found to have no significant difference across gender, and some gene that was thought to affect the development of neurons and cause schizophrenia has been found not influential.

It is worth noting that these findings are only “to some extent contradicting” and further increase the uncertainty of the exact etiology of schizophrenia. Quantitative genetics has always been a statistical approach, conclusions that do not match can simply be because of the lack of our understanding of genes. In the future, we can expect more gene found association with schizophrenia that fits the discovery of quantitative genetics.

The second Danish study [13] showed that early males are likely to have more environmental influence, while females have a more genetic influence. This conclusion can be used to explain the previous findings but does not perfectly explain the previous data. If females and males differed in the mechanism of causing schizophrenia, possible that females are more influenced by genes while males are more environmentally influenced, thus when a female is diagnosed with schizophrenia, the high risk gene of schizophrenia would cause a higher correlation of schizophrenia between them and their family members. While environmental influence can be non-shared and personal, the gene does not. Males would be influenced by schizophrenia which has a generally high heritability, while with the

environmental influence of their sibling, they are more likely to be diagnosed with schizophrenia. However, if the mechanism differed for gender in terms of causing schizophrenia, then females should have a higher correlation between female offspring as the same mechanism is presented. However, a previous study [7] shows that females have a higher influence on their children, regardless of their children's gender.

3. Summarized Schizophrenia Treatments

Common schizophrenia treatments includes psychosocial treatments [16], antipsychotic drugs [17]. Anti-psychotic drugs have been summarized into first generation antipsychotic drugs (FGAs), and second generation antipsychotic drugs (SGAs). All FGAs have strong relation with the effect on dopamine D2 receptors, which is considered to be a neuron largely related to schizophrenia, adopted by many studies [18]. However, FGAs were not effective in general, most patients have found no effect or few response. Clarification on the effectiveness of comparing SGAs and FGAs has been debated, though none of them made pursuit cognition and quality of life, which now have more attention. Different agents have been classified and carefully evaluated and discussed, effectiveness differed across symptoms, receptors of the brain.

On the other hand, early psychosocial treatments employed simple punishment and reward methods, while soon afterward, processes such as demonstration, prompting, role-playing has been included. Many medical records have shown that patients were able to follow instructions. Apart from the direct contribution of treatment, psychosocial therapy also provide information on cognitive ability, social capability, etc.

However, it is recognized that classical family studies do very little contribution to the development treatments of schizophrenia, but are rather good at preventing it. One thing that can be noted for sure was schizophrenia mothers was generally more influential for offspring, according to the finding of quantitative genetics. This means that offspring with schizophrenia mother were particularly requiring measures to prevent it.

4. Conclusion

Conclusions that can be derived from the contradicting results of these studies would be a hypothesis of variation of environmental influence. Schizophrenia females are found to be more influential than males, yet schizophrenia was found to be more related with some genes on males than females. Also, the idea of "early males are likely to have more environmental influence, while the female has more genetic influence." is also being disputed as some alleles significantly related to schizophrenia was found on males instead of female. Attempts to relate the environmental influence of schizophrenia with marital status, and explore the causes of schizophrenia more deeply. Therefore, the cause of schizophrenia is very complicated. With the detection of the whole genome, more and more genes related to schizophrenia have been studied, and more and more experiments have been conducted to explore them. But with the deepening of research, different conclusions will inevitably lead to new discoveries. However, the causes currently studied include family heredity, the patient's own factors, and the patient's excessive stimulation, the interference of psychological factors, the influence of the social environment, the influence of autoimmunity and metabolic levels, and the growth of the fetus when the mother is pregnant. Under the influence of drugs, etc. The emphasis on schizophrenia and continuous research can guide people to prevent it and find more effective treatments. And adopting effective treatment plans as soon as possible can control the patient's condition, reduce the incidence of the patient, and enhance the patient's social adaptability and resistance to problems.

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