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Present situation on the causes and treatments of tourette syndrome

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Abstract. Tourette Syndrome (TS), a neurological disorder classified as the most complex form of tic disorder in the DSM-5, has remained a prominent concern for the adolescent population. Owing to its complexity and the unknowability of its physiology, it currently has no cure. Through the review of two family studies, two twin studies, one Genome-Wide Association Study, and two other reviews, firm evidence for additive genetic influences and non-shared environmental influences was found, suggesting TS's high heritability. Specific genetic factor (SNP-rs2504235), environmental (pre-and peri-natal) factors, and the interaction between these factors were evident from the studies as well. Through the analysis of these findings, one coping strategy was emphasized over the two existing classes, pharmacological and non-pharmacological, of typical treatments: preventative approaches under the assistance of advanced technology like genetic testing. The inability of the now available treatments to cure TS and their respective side effects cause them to be less desirable than prevention as early actions were shown to be effective in hindering the disorder's deterioration and persistence.

Keywords: tourette syndrome, genetic factors, environmental factors, treatments.

1. Introduction

Tourette Syndrome (TS) is a complicated neurological disorder that causes individuals, mainly children and adolescents, to exhibit involuntary, abrupt, and repetitive movements or vocalizations named "tics". Being classified into the neurodevelopmental disorders in the DSM-5, TS is recognized as the most complex form in the spectrum of tic disorders, including Tourette's disorders, persistent motor or vocal disorder (lasted more than a year), and provisional tic disorder (lasted less than a year) [1]. The overall international prevalence of TS is, according to Robinson and his team in their cross-country review, approximately 1%. On a country level, TS's prevalence in adolescents is 0.96% in South Africa, 0.7-3.8% in the United States, 0.76-2.9% in the United Kingdom, 0.4-0.56% in China, 0.5% in Japan, and 0.6% in Sweden [2]. These percentages make Tourette Syndrome the main obstacle concerning the population in adolescence, and thus requires an urgent address.

The prominent factor that leads to its lack of cure is tic disorders' unidentified cause: it is only known to be caused by a combination of genetic and environmental factors. However, there is no means to thoroughly cure this disease to date, and the major treatment to alleviate TS and other tic disorders currently involve pharmacological and nonpharmacological approaches [3]. This paper aims to examine previous studies-- two family studies, two twin studies, one Genome-Wide Association

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Study, and two comprehensive reviews--from a quantitative approach and evaluate various factors that are considered to contribute to the diagnosis of TS, thus suggesting better effective and suitable treatments.

2. Family studies

The use of family studies in demonstrating family resemblance started as early as the late 18th century; the comparison and contrast between family members helped provided causes for the epigenetic variation. In 1991, Pauls and his team from the Yale University School of Medicine published their findings of TS as a familial disease. They selected 86 probands, 338 biological relatives, 21 adopted relatives that are genetically unrelated, and 22 relatives of subjects not diagnosed with TS as the control group. Utilizing the "pre-coded structured interview" that the team specifically designed for the study, all relatives, differentiated by adults and children, received two versions of the interview to collect information on their "presence of obsession and compulsions", "senselessness or repugnance of those symptoms", etc. [4] The probands also underwent another interview to guarantee they attain the DSR-3 criteria for TS. Then, by comparing and analyzing the rates of TS among first-degree relatives of the probands and the control subjects, it can be noted that the first-degree relatives yield 10 to 100 times higher rates than the controls. The significantly elevated prevalence rate in the biological relatives of the patients over the general population provides support for the genetic evidence of TS.

To further extend from the previous data, another family study was manipulated over a large population basis as it selected 4826 patients diagnosed with Tourette Syndrome or Chronic Tic Disorder (CTD) in the Swedish National Patient Register over 40 years, from 1969 to 2009. After that, the first-, second-, and third-degree relatives of the selected probands were compared with the biological relatives of unaffected control individuals among the natural population at a 1:10 ratio, and they were matched by sex, age, and country of residence in order to eliminate potential bias to a certain extent. As a result of the study, the hereditary risk is present, which can be inferred from the calculated tetrachoric correlation with the proband -- the first-degree relatives, who are 50% genetically similar to the probands, exhibit a significantly higher risk of having TS than the second- and third-degree relatives, who are 25% and 12.5% genetically similar to the probands, respectively. In fact, full siblings' correlations (0.40) are approximately double that of maternal half-siblings (0.22). By summarizing these numbers, the study could conclude the trend that as genetic similarity decreases, the correlation between two individuals also decreases, which suggests a strong heritability. According to Statistics Sweden, 90% of Swedish children tend to live with their mothers instead of fathers after parental separation like divorce. In other words, there is a much greater possibility for the probands to share an environment with their maternal half-siblings in comparison with their paternal ones. However, this additional source of shared-environmental influence does not make maternal half-siblings significantly more susceptible to TS than paternal half-siblings, who are 0.13 correlated to the probands. This moderate difference of 0.09 indicates that the shared environmental influence does not play a very important role in the development of TS. In addition, the ACE model used by the study summarizes into that "the variance in liability of TS or CTDs was largely attributable to additive genetic factors (0.72; 95% CI, 0.42-1.00), with a negligible effect of shared environment (0.03; 95% CI, 0.00-0.16)" [5]. The non-shared environment, on the other hand, is modestly attributive, accounting for the remaining 0.25 of the variance in liability of TS.

This family study has its strength in its large population base and a time longitude of 40 years; besides, it is recognized as the first study that is statistically capable of measuring the familial risk of tic disorders for the proband's relatives that are across three degrees, varying in genetic and environmental similarities. However, in light of the limitations, this study's selected sample from Sweden's National Patient Register cannot represent all TS patients since only the cases diagnosed by specialist physicians were selected; in other words, only more severe forms of the diseases were considered, and milder cases might get neglected. Besides, the research team failed to distinguish between TS and CTD because most Swedish professionals tended to use them interchangeably.

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3. Twin studies

Twin studies, generally considered as the experiment of "nature", allow for the disentanglement of the non-shared environmental influences from shared environmental influences and genetic influences of the trait of interest. Because of this characteristic, twin studies enable a different pathway of calculating heritability and environmentality from family studies. Besides, one twin study could attain the sample inadequacy of the previous family study as it collected self-reported data instead of physician-monitored one. It analyzed the data reported by 7311 families from the Netherlands Twin Register, with a total of 8323 adult monozygotic and dizygotic twins and 7164 family members (parents and siblings) of them. Due to the fact that it clarifies the definition between probable TS and probable CTD, its measurement of heritability can be exclusively attributed to TS, which makes up for one shortcoming of the family study. This research first estimated the prevalence of tic disorders among the sample, then used the genetic Structural Equation Modeling (SEM) to calculate the heritability of tic disorder under four definitions: "probable TS, probable chronic (motor or vocal) tic disorder, probable transient tic disorder, or probable tic disorder 'Not Otherwise Specified'" [6]. As the result, the heritability of tic disorder measured from the model has a range from 0.25 to 0.37, with overlapping wide confidence intervals across the four definitions. However, since the pervasiveness of the severe tic disorder (Tourette Syndrome) was low, their calculated confidence intervals for heritability were wide, and the authors speculated that their narrow sense heritability could be as large as 0.56, the upper bound of the confidence interval. Besides, in agreement with the family study in Sweden, there is no evidence for shared-environmental or non-additive genetic factors. Specifically, the liability for the tic disorder can be mainly attributed to additive genetic factors and non-shared environmental influences. This research first estimated the prevalence of tic disorders among the sample, then used the genetic Structural Equation Modeling (SEM) to calculate the heritability of tic disorder under four definitions: "probable TS, probable chronic (motor or vocal) tic disorder, probable transient tic disorder, or probable tic disorder 'Not Otherwise Specified'". [6] As the result, the heritability of tic disorder measured from the model has a range from 0.25 to 0.37, with overlapping wide confidence intervals across the four definitions. However, since the pervasiveness of the severe tic disorder (Tourette Syndrome) was low, their calculated confidence intervals for heritability were wide, and the authors speculated that their narrow sense heritability could be as large as 0.56, the upper bound of the confidence interval. Besides, in agreement with the family study in Sweden, there is no evidence for shared-environmental or non-additive genetic factors. Specifically, the liability for the tic disorder can be mainly attributed to additive genetic factors and non-shared environmental influences.

Nevertheless, this twin study also exhibits some drawbacks, including the bias that might be present in the self-report data collection process. Also, the process is not administered by professional clinicians, which could possibly lead to the misclassification of disorders. However, this drawback could be remedied by the first study since professional administration is applied in it.

Since both studies being mentioned set up their investigation in Europe, the result of the studies could not extend to patients that are not Europeans. Therefore, another study this is conducted in a country outside Europe is required to be incorporated. A twin study that approached the inheritance of Tourette Syndrome quantitatively was published in 1985. In comparison with the previous two studies, this investigation had a smaller scale, recruiting only 43 pairs of same-sex twins (30 monozygotic twins and 13 dizygotic twins) with at least one twin in each pair diagnosed with TS from the U.S. Tourette Syndrome Association. Based on the zygosity and sex of the twin pairs, the concordance within each pair was estimated respectively. Among the pairs that are fully concordant for TS -- both twins are diagnosed with TS -- monozygotic (MZ) twins obtain a prominently higher concordance rate (0.533) than dizygotic (DZ) twins (0.077). Again, this is an indication of the strong genetic influence because MZ twins are roughly 50% more similar than DZ twins, and thus they yield greater concordance on TS symptoms. Among the twin pairs that are "at least partially concordant", where one twin in each pair is diagnosed with TS, the other twin either is affected by TS as well or only possesses simple tics. This broadens the criteria of the concordance and also leads to an increase in the

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concordance rate for both MZ and DZ twins. Nevertheless, the same pattern still exists, where MZ twins have a significantly greater correlation for TS than do the DZ twins, manifesting the important contribution of inheritance. On the other hand, it can be inferred that the effect of sex is not prominent in the concordance since the rate does not differ greatly in both the "fully concordant" groups (MZ: 0.520 vs. 0.600; DZ: 0.100 vs. 0.000) and the "at least partially concordant" groups (MZ: 0.760 vs. 0.800; 0.300 vs. 0.000) [7].

By analyzing the family study and twin studies, it can be concluded that the majority of variation among individuals' Tourette Syndromes conditions can be attributed to additive genetic influences and non-shared environmental influences.

4. Specific factors and their interaction key

In the recent decade, the advancement in technology actualizes psychiatrists' conception of specifying the various causes of Tourette Syndrome instead of generally classifying them into genetic and non-genetic. For instance, to identify the specific genetic factors that are responsible for the development of TS, the Genome-Wide Analysis Study (GWAS) could be applied. In 2019, a large group of researchers conducted a meta-analysis of "4,819 Tourette's syndrome case subjects and 9,488 control subjects" [8]. In the end, the analyses recognized one genome-wide significant locus, rs2504235, the top SNP lies within an intron of FLT3 on chromosome 13, responsible for encoding FMS-like tyrosine kinase 3. Besides, this location was also tested to be fully statically significant.

On the other hand, among the studies that examine particular environmental factors for the development of TS, the prenatal environment is proven to play an imperative role [9]. Hoekstra and his team have summarized a list of prenatal environmental factors that were found to be correlated with the development or severity of TS in past studies. These involve pregnancy complications like older parental age, delivery complications like frequent delivery difficulties, and neonatal complications like lower Apgar score at 5 minutes, etc. Therefore, it is plausible to conclude that the conditions of TS can be attributed to a myriad of prenatal factors.

Knowing that certain locations on people's genes and pre-and peri-natal factors are responsible for the onset and severity of TS, it is reasonable to suggest that some of them interact and together exert an effect on the condition of TS. In 2021, an article written by Abdulkadirr and his team reported on the presence of genotype-environment (G×E) interaction between the prenatal environment and a top Tourette Syndrome GWAS SNP, rs6539267. In this research, the scientists sampled 586 patients diagnosed with tic disorders (458 with TS), measured the pre- and peri-natal adversity level as the indication of the prenatal environment, and selected 196 top SNPs from a previous GWAS study [10]. Among these 196 investigated SNPs, rs6539267 is found to exhibit the G×E interaction since the change in its genotypes is associated with different levels of lifetime tic severity under the same cumulative pre- and peri-natal adversity score. In other words, different genotypes elicit different interactions with their environment, causing various magnitudes of tic severity. For this reason, the CC genotype on rs6539267 has the steepest and most positive slope as shown on the graph plotted against lifetime tic severity and cumulative pre-and peri-natal adversity score.

5. Treatment

Until now, there is no therapy that can utterly cure Tourette Syndrome, but studies have provided evidence for some treatments to be effective at mitigating the extent of tics caused by TS. The first main category of treatment is through a pharmacological approach. One of the prevalent medications is typical neuroleptics like haloperidol and pimozide, which functions by exclusively blocking the dopamine system (Eddy et al.). Other medications include atypical neuroleptics (risperidone, clozapine) that target modulate serotonin (5-HT), norepinephrine, and/or histamine neurotransmission and DA agonists (levodopa, aripiprazole) that are partial or full at dopaminergic receptors [11,12]. In an experiment manipulated at the Yoshiko Nomura Neurological Clinic for Children, 303 children from 5-18 years old with various severity of TS received pharmacological treatments. By comparing the participants who took the medication (a small dose of levodopa and/or aripiprazole) with those who

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did not take it, the subjects that took the treatment showed a higher rate of improvement (18.3%) and marginally shorter duration of symptoms (-0.70 years), as reported by the author Nomura. The drawback of medication is the exhibition of side effects. For instance, in the case of neuroleptics, its common side effects include weight gain and drowsiness, and some patients might "experience excessive sedation leading to difficulty in performing cognitive tasks"; its greatest health concern is the potential incurrence of hyperprolactinemia (amenorrhoea, galactorrhoea, and gynaecomastia) and extrapyramidal symptoms (dystonia, parkinsonism, akathisia, and tardive dyskinesia) that may be persistent after ceasing the treatment [13].

The second category of treatment is the nonpharmacological approach, which is strongly recommended by the American Academy of Neurology and the European Society for the Study of Tourette Syndrome since they are "more effective and safer" [14]. This refers to behavioral therapy such as habit reversal, a mature technique that guides patients to identify tics out loud and learns behaviors that are incompatible with tics. In a small-scale study conducted by Woods and his colleagues, the effectiveness of habit reversal therapy has been demonstrated---86%-96% improvement is observed in all four children with motor tic disorders and a 38%-96% reduction in their vocal tic frequency [15,16]. However, the limitation of habit reversal therapy is also noticeable: the replacement of one type of tic with another type of tic; for instance, the original vocal tics are replaced by other motor tics. There are other nonpharmacological approaches that are considered more "invasive", such as Botulinum toxin injections and Deep Brain Stimulation (DBS), requiring further examination.

Owing to the presence of prominent disadvantages in the two categories of treatments mentioned above and the inability to 100% cure tic disorders, methods with greater effectiveness should be considered. The quantitative analysis of the heritability and environmentality of TS brings up greater emphasis on "prevention" over "cure"; in other words, there is emerging importance of having actions before the diagnosis. Current technology is increasingly growing mature; it allows for comprehensive health checks to be achieved, providing insights into the potential disease risks of the taker through the breakdown of family ancestry and genetic review. This sheds light on several possible preventions: as studies showed that TS is highly heritable and chromosome 13 is especially correlated with its severity of it, using DNA genetic testing beforehand and utilizing specific treatment to block the expression of the gene can possibly mitigate the seriousness of tic disorders. Besides, by controlling the pre-and peri-natal factors that are proven to be positively correlated with the severity of TS due to G×E interaction, such as older parental ages and delivery difficulties, the possible contribution of the onset of TS or the interaction with other genetic factors that contribute to TS can be avoided to a certain extent.

This suggestion still has its limitations. According to Zacharias from Purdue University, "But the pattern of inheritance is complex; there could be a few genes with substantial effects, or many genes with smaller effects and environmental factors could play a role." The complicated nature of the causes of TS adds to the difficulty of locating direct treatment, which made complete prevention of this disorder currently unattainable. However, genetic testing still allows for the risk of the syndrome to be discovered early and thus enables treatment to prevent further deterioration and persistence into adulthood [17].

6. Conclusion

Through analyses of various types of studies, it can be safely concluded that: 1) Additive genetic and non-shared environmental influences account for most of the individual differences in the liability for TS; 2) SNP-rs2504235 correlated the most with TS severity; 3) The prenatal environment contributes to the severity of TS; 4) Interaction between the genotype and the prenatal environment is present and influences the severity of TS. Still, limitations are present in these studies, with a prominent one being the sample's emphasis on severe cases and neglect of milder ones since patients in more emergent status have a higher propensity of participating in the studies. Aside from that, the relatively small number of studies that targeted tic disorders is another weakness of the present conclusion. However,

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studies conducted through different perspectives were selected and made up for each other's inadequacy to a certain extent. Furthermore, the concordance between conclusions reached by each study and the evidence given by other related articles support the current direction.

Despite, there being no current treatment that can completely eradicate the symptoms of TS or the risk of it, both pharmaceutical and nonpharmaceutical methods have their advantages and limitations respectively, and thus should be prescribed in consideration of the actual condition. The quantitative analysis of TS emphasizes the importance of taking preventative approaches. Besides, it proposes that technological advancement allows certain genetic and environmental factors can be controlled beforehand to reduce the risk of TS worsening or persisting. Further studies are still necessary, but the analysis of current reports marks a promising prospect.

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