

Gene and environment interaction in familial suicidal behavior

A single family with 4 committed suicides

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ABSTRACT

إن وجود حالات مسبقة للانتحار في تاريخ الأسرة يعد من المؤشرات المقلقة التي تزيد من خطر الانتحار. نستعرض في هذا المقال حالة نادرة لأسرة سوف ندعوها بالأسرة (م) والتي انتحرت فيها 4 أفراد في مدة قصيرة وذلك من منظور العلاقة بين الجينات والبيئة ومدى تفاعلها مع بعضهما. لقد انتحرت الأب في هذه الأسرة مع أربعة من أبنائه في فترة زمنية لم تتجاوز 5 سنوات، كما أن الانتحار قد حصل في عدد من أفراد الأسرة الآخرين. ويظهر من خلال هذا البحث بأن زيادة خطر الانتحار في الأسرة قد نجم من بعض العوامل البيئية والجينية، كما يُرجح تأثير كلا منهما على زيادة هذه المشكلة. وتشمل العوامل البيئية كلا من: تدني مستوى التعليم، واعتماد أفراد الأسرة الذكور على الأفيون، والبطالة، والفقر، وعدم القدرة على الحصول على المساعدة والاستشارة النفسية. لقد أظهر تحليل النمط الجيني للتنوع الشكلي A218C بين أفراد الأسرة الناجين من الانتحار بأن كانوا حاملين للجينات من النمط الجيني CC وAC في هيدروكسيليز تريبتوفان. وخلال هذا المقال قمنا بمناقشة العلاقة التفاعلية بين البيئة والجينات ومدى تأثيرهما على الانتحار.

Family history of suicide is among the strongest predictors of suicide risk. From the context of gene by environment interactions, this manuscript presents a case study of the "M" family, which experienced 4 committed suicides within a short time period. Over the course of 5 years, the father and 3 sons committed suicide. Suicidal ideations developed in several other members of the family. The family's suicide risk appears to have stemmed from both environmental and genetic factors, and likely from an interactive effect between both. Environmental factors included low level of education, opium dependency among male family members, unemployment, and poverty, and limited access to mental health services. Genotype analyses of A218C polymorphism among surviving family members revealed that all individuals were associated with the gene variation (genotypes CC

and AC) in tryptophan hydroxylase. The genetic by environmental interaction influence is discussed.

Saudi Med J 2011; Vol. 32 (10): 1073-1077

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Received 5th March 2011. Accepted 28th May 2011.

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Suicide is a major mental health problem worldwide, with some estimates suggesting suicide is responsible for one million deaths annually across the globe.¹ Several theories have been proposed to explain the etiology of suicide, with genetic explanations, environmental explanations, and a combination of genetic and environmental factors emerging as the most prominent theories.²

Genetic predisposition. Suicide has long been thought to have some genetic etiology. Two avenues of genetic transmission have been proposed.³ First, it may be that suicide is transmitted genetically on its own, independent of the influence of mental disorders.⁴ Theorists have proposed, for example, that genetic inheritance of serotonin system processes tryptophan hydroxylase (TPH1 gene) may explain part of the inheritance properties in suicide.⁵ Another possibility is that suicide is genetically passed not independently, but through its association with genetically-inherited psychiatric disorders such as affective/mood disorders (depression, bipolar disorder) and substance use

disorders.^{4,5} Note that the 2 explanations for the inheritance of suicide risk are not mutually exclusive. Suicide may have genetic inheritance both because it is independently passed through genetic lines and because it is passed through its concordance with genetically-linked psychiatric disorders like mood disorders and substance use disorders.⁵

Environmental factors. One theoretical basis for the role of environmental factors for suicide comes from social learning theory, which proposes that individuals learn by modeling trusted others. Thus, suicidal tendencies might be learned from parents, peers, or television and movie actors who are trusted and admired.⁶ Familial suicidal behavior may result from a process of learning from the environment, whereby vulnerable individuals imitate suicide attempts of their relatives. The higher risk for suicide in persons exposed to suicide attempts in parents with mood disorders offers evidence of this theory.^{7,8}

Gene and environmental factors interaction. This approach hypothesizes that suicide attempts are the outcome of a genetic by environment interaction.^{9,10} This model, sometimes labeled the stress-diathesis model, suggests a predisposing diathesis, largely driven by genetics, is present in each individual. When environmental factors – stressors – are added to an underlying diathesis, suicide ideation, or action may occur. A high predisposing diathesis could lead to suicide attempts in the context of minor environmental stress. With a low predisposing diathesis, suicide may only occur in the context of major environmental stress. Evidence from persons with familial heritability who do not attempt suicide, and those without familial heritability who do attempt suicide, supports the genetics by environment interaction explanation for suicide etiology.^{9,10} Considering suicide as a multidimensional problem influenced by both genetics and the environment can guide suicide prevention strategies. That is, prevention programs could target environmental factors, which may be more amenable to change, and in doing so would reduce genetically-influenced risk.

Case Report. In view of the above-mentioned theory, we consider a family case study in which 4 individuals committed suicide. The case is presented with the objective of considering underlying genetic and environmental etiological risks for the suicide attempts in the family. In March 2009, a client told her psychiatrist that she knew a family in her neighborhood who “attempted suicide frequently”. She anxiously reported that 4 family members had committed suicide and expressed concern for the mental health of the other family members. The psychiatrist recommended the client bring the family to his office.

A few days later, the family of 8 individuals came to the psychiatrist’s office and were interviewed one by one. The following history was acquired from those interviews. Mrs. M’s family lives in a small rented house in a small city in Kermanshah province, Iran. Mr. and Mrs. M. had 10 children, 5 boys and 5 girls. Three of the boys and Mr. M. are currently deceased, all victims of suicide within the past 5 years. Mrs. M. is 50 years old and illiterate. She married Mr. M. at the age of 15. As is typical in the culture, she is dressed in black to indicate mourning. Her surviving children range in age from 17 to 32. The family was currently experiencing substantial financial difficulties. They live primarily off governmental social support. Mrs. M presents with anxiety on the future of her family and depressed mood, but also some signs of resilience and a desire to remain strong to protect her children.

During a lengthy interview, Mrs. M. related the story of 4 successive suicides in her family. The first occurred about 5 years ago, when S, the second-oldest boy in the family, died. He had migrated to Tehran, the capital city, for employment; he was working in construction. S. had only a primary education and was 25 years old when he died. The suicide occurred a few months after his migration to Tehran, and was completed by opiate overdose. She reported that S had opiate dependency, depressed mood, and aggressive behavior problems. She emphasized that the oldest boy, who lived with S, told her that his brother was very depressed and had talked about suicide. He had no history of psychiatric treatment. His suicide was traumatic for the family.

Six months after his death, as the family still mourned, S_j, the oldest boy in the family, committed suicide by hanging. Like his brother, he had a primary education, was dependent on opiates, and was working as a construction worker. At the time of his death, S_j was 30-years-old. He was married but had no children. Four months after S_j’s death, and 10 months after S’s, the family met with another disaster. Mr. M, the boys’ father, successfully committed suicide by opiate overdose. An illiterate 53-year-old man, who like his sons worked in construction, Mr. M. had been dependent on opiates since adolescence. His death was the third committed suicide in the family within a year, and caused severe trauma for all family members. Mrs. M explained that she explained Mr. M’s suicide as death due to myocardial infarction to her neighbors, but that in fact he had committed suicide. He routinely used opium by inhalation, but had purposefully eaten a large quantity of it in a suicidal gesture. She explained that he was very depressed, especially after the suicides of his 2 sons (note that in rural Iranian culture, the death of a son is a great disaster for parents).

Psychiatric interviews revealed that all 9 surviving family members experienced suicidal ideation after Mr.

M's death. They remained a cohesive family, and Mrs. M. initiated substantial efforts to prevent further suicides by working on the farm, supporting her children, and displaying culturally-appropriate grieving practices. In fact, Mrs. M. showed impressive resilience, claiming that she thought to herself, "I should protect my family. If I would attempt suicide, my family foundation would be destroyed." Consistent with cultural practices, Mrs. M. did not remarry.

The surviving family – Mrs. M, 3 boys and 5 girls – experienced 4 years without loss. During those years, they had financial stress. It was a very difficult situation. Financial providers of the family had died, they were grieving, and they withdrew socially due to the stigma and mourning customs in their culture. In December 2008, about 4 years after Mr. M.'s death, a fourth tragedy occurred when the third-oldest boy, Sk, committed suicide by hanging. He was 24-years-old at the time of his death. He worked in construction, was married, and had a 3-year-old girl. Mrs. M., who had shown remarkable resilience, described her mood at the time of Sk's death, "the suicide story has started again". Mrs. M asked the psychiatrist to help prevent suicide among her other children. She said, "It is very painful for me that the 3-year-old child of my boy hangs her mother's scarf on her neck and plays, "I want to kill myself like my daddy". "I am very afraid; I cannot sleep a wink every night. I have to hide everything that can be used for suicide attempts - even my scarf. Help me, please" she said. The psychiatrist tried to comfort the mother and asked her to let him interview her surviving children, 2 boys and 5 girls. She agreed. The following information summarizes the interviews with the surviving children, in order from oldest to youngest.

L is an illiterate 32-year-old girl. She has mild-moderate mental retardation, as indicated by unclear speech patterns, disturbed gait and movement, and failure to attain any formal education. Her IQ has not been formally assessed. She does not appear to comprehend the family history of suicides. Her mother provides full-time care for L, and this daughter represents one reason why Mrs. M. feels the need to remain resilient and healthy.

Sa is a 29-year-old man with secondary education. He is married and works as a temporary laborer when short-term jobs are available. He has opiate dependency and insomnia. He reports no history of actual suicide attempts, but frequent suicide ideation (by hanging), which increases when he cannot sleep well. He believes that opiate dependency and unemployment caused his father's and brothers' suicide attempt; thus, he attributes their suicides to environmental factors rather than genetics. He was treated for opiate addiction with

medication (olanzapine 5 mg and fluoxetine 20 mg daily) and referral to a Narcotics Anonymous (NA) group. He expressed a desire to overcome his addiction "because I want to live with my wife and my family, and I do not want to suffer from my brothers' fate". He currently continues treatment in the NA group.

Z is a 25-year-old woman with a high school education. She is the first girl of the family to marry and has a 3-year-boy. Prior to her marriage, she reports 3 suicide attempts. She reports no current suicide ideation. She expresses grave concern for the mental health of other family members.

Sr is a 23 year-old-man with a high school education. He is single and works as a temporary worker. Like his brothers, he suffers from opiate dependency and from insomnia. He expresses frequent suicide ideation by hanging, but refuses hospitalization. He was treated with medications (olanzapine 5 mg and fluoxetine 20 mg daily) and referred to an NA group. His current mental health status is addressed below.

T is a 21-year-old girl studying in the university. She says that she has uncontrolled recurrent suicide ideation by hanging, but has not had made any suicide attempts. She describes educational failure, which she attributes to depressed mood. She was treated with antidepressant medication.(fluoxetine 20 mg daily). On monthly follow-up mood improvement was seen. There is no report of active suicide ideation.

F is an 18-year-old girl studying in high school. She reports suicide ideation and was treated with antidepressant medication (fluoxetine 20 mg daily). In addition to prescribed drugs, F received supportive psychotherapy with focus on leisure time activity, walking, and development of social contacts. On monthly follow-ups, her mood was improved and mental health status deemed stable. There is no report of active suicide ideation.

Zi is a 17-year-old girl studying in high school. She recently attempted suicide by drug overdose but survived. She reports no current suicide ideation. She complains of insomnia and was treated with medication (fluoxetine 20 mg at morning and Trazodone 50 mg at night) to improve mood and sleep. She also received supportive psychotherapy, which has resulted in improved mood and functioning. Mrs. M was also asked about family history. She reported no known history of suicide attempts or depressed mood in previous generations of her family or Mr. M's family.

To evaluate genetic factors in suicide risk, the family visited a medical genetic lab for testing. All family members provided informed consent. Using standard procedures, genomic DNA was isolated from peripheral blood. Intron 7 of the TPH gene was studied

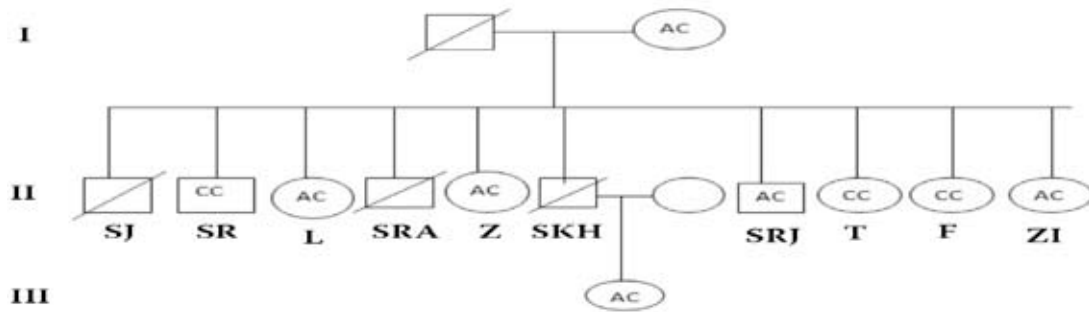


Figure 1 - Pedigree of the family.

to examine whether the 218A→C polymorphisms may be associated with completed suicide in the family. The target sequence encompassing the A218C variation was amplified by polymerase chain reaction (PCR). The PCR products were digested with used anti-Na-H exchanger 1 restriction endonuclease enzyme. After digestion, 2 alleles were observed, 218C (600bp, 250bp) and 218A (850bp).

Figure 1 shows a pedigree of the M family. Circles represent female and squares male. Boxes that are crossed represent deceased individuals. Except their son SKH's wife (empty circle), who had no genetic relationship with the others, 2 alleles of 218C and 218A were detected for all family members. Information is unavailable for the 4 deceased individuals who committed suicide. Mendel's laws suggest during gamatogenesis step half of allele randomly will be received by offsprings, so now we can explain this pedigree. Here, the mother of the family shows (AC) heterozygose genotype but the father has unknown genotype. Based on information from the offspring, we can predict the genotype of the father might be either CC or AC. In the second generation, we have 3 persons with CC hemozygous genotype. We know one C originates from the mother, but the other belongs to the father. In summary, the pedigree supports the existence of a genetic predisposition for suicide in the family.

Since the suicide events, Mrs. M's family has continued to attend monthly psychiatric visits. In addition to monthly psychiatrist visits, the family now has readily-available access to call a psychiatrist in emergency situations. Mrs. M. also reported recently that suicide ideation subsided in the family for several months. However, about a year after their first psychiatric contact, Sr attempted suicide by hanging. He survived and was admitted to a psychiatric ward due to strong suicide ideation. Electroconvulsive therapy and drug therapy were initiated, along with supportive psychotherapy. After a 6-week hospitalization, monthly follow-up sessions were initiated. Mrs. M. reports Sr is abstaining from opium use. Other family members are

psychiatrically stable, and no active suicide ideation and attempt or an active phase of psychiatric disorders such as depression is reported.

Discussion. Before we discuss the theoretical aspects this case study raises, we mention the uniqueness of this family. To state the obvious, 4 suicides in a single family over the course of 5 years, and not simultaneously, is rare. In fact, we are not aware of any similar cases. Beyond the curiosity (and tragedy) of the suicides, however, it is not the uniqueness of this family that offers valuable information. Instead, rare cases such as the M family are most useful to identify high risk groups and consequently influence development of suicide prevention programs. What led to the suicide deaths in this family? Several factors likely contributed. The family suffered from many known environmental risk factors for suicide, including low socioeconomic status, limited financial resources, illiteracy/poor education level, male gender, limited access to mental health services, and rural domicile.² They also suffered from a cultural tendency in Iran to view suicide as a secret and shameful problem that should be hidden. The victims had substance use problems, and may have had other undiagnosed mental illnesses. A few had very significant personal life stressors at the time of their death – a recent move to a new city in one case, and the recent loss of 2 children in another case. Finally, the M family victims had environmental influences of modeling the suicide attempts of relatives.^{7,8} It is perhaps not coincidental that all 4 victims were male family members struggling with substance abuse, unemployment, and life stressors. Two committed suicide by overdose and 3 – including the recent unsuccessful attempt – by hanging.

Genetic factors also likely contributed to the chain of suicides in the M family. Our genetic analysis offered evidence of genetic transmission of familial suicidal behavior. Although genetic analysis of the 4 deceased individuals was unavailable, the AC genotype was detected in 6 of the 8 surviving family members, and CC in 3. The role of TPH1, which affects the serotonin

system in aggregation of familial suicidal behavior, was strong in the M family. Genetic transmission of substance use disorders, and perhaps also of mood/affective disorders, likely also played a role in the genetic component of suicide in the M family.⁹

Consistent with prevailing opinions in the literature, we might conclude that the M family suicides resulted from a combined gene by environment interaction etiology. There is evidence of strong genetic heritability within the family, and they also suffered from multiple environmental risks. Stated mathematically, the family was influenced by 2 parallel vectors for suicide – genes and environment. Alone, the parallelism led to a stronger vector for suicidality; together, they created an interactive and probably multiplicative effect.^{9,10} Future work should continue to consider how gene by environment interactions influence suicide risk. In particular, it would be useful to examine whether genetics and environmental factors simply add together to create risk – that is, having 2 factors increases risk in a linear manner over having just one factor – or whether the 2 factors might have a multiplicative effect, such that having both genetic and environmental risk factors creates multiplicatively or exponentially greater risk than having just one. Such future work will require more sophisticated research designs than this case study. Epidemiological research offers one possible avenue of exploration. This case study offers several lessons for development of suicide prevention strategies. First, it suggests that high risk individuals – such as the members of this family – must be targeted for intervention. Such intervention should target accessible change, such as environmental factors that might increase suicide risk. Second, it demonstrates the importance of broad mental health access. Individuals like this family, who live in rural Iran, have poor access to any mental health treatment. Third, it raises cultural issues. Initiating mental health treatment with low-income rural individuals in Iranian culture is challenging. There are significant cultural barriers to overcome, as suicide and mental illness are topics that are shameful and not discussed in the culture. Help-seeking for the mental health service is not common.

Finally, the case study highlights the need for post-suicide family interventions. Adverse consequences of suicide on the family may include survivor's grief, interruption in social relationships, and emotional problems in children.⁸ The consequences may be particularly noticeable in children; the symbolic act of the little girl who imitated her father's suicide attempt is among the most tragic and concerning aspects of the suicide impact on the M family. Children have undeveloped cognitive processing systems, and it is not clear how they comprehend traumatic events such as

family suicides. Would psychiatric or psychological care have prevented the suicides in this family? We can never know, but we can hypothesize that it may have helped. The lack of accessibility to mental health treatment for this family, and for so many similar individuals globally, must not be overlooked. Psychiatric interventions with surviving family members, managed despite the large distance between their home and an appropriate medical center, was helpful, especially for Mrs. M.

In conclusion, familial suicidal behavior can be viewed as a multidimensional problem. Genetic and environmental factors interact to create etiological risk. Further, research designed to examine the effect of interaction is recommended. Cultural aspects of treatment, accessibility to proper mental health care, and poverty complicate prevention. Given its strength as a predictor of suicide, however, familial suicidal behavior must be considered in treatment and prevention prioritizing.

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