

SCHIZOPHRENIA SPECTRUM PSYCHOSIS IN A CROATIAN GENETIC ISOLATE: GENEALOGICAL RECONSTRUCTIONS

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SUMMARY

Background: Schizophrenia spectrum psychosis is a chronic mental disorder, based on a range of genes whose expression can be altered by different environmental factors.

Subjects and methods: In this archival and demographic study of genetic isolate we show an incidence of schizophrenia spectrum psychosis in a minority population and transmission of schizophrenia spectrum psychosis through several generations of two families in an isolated rural area of Dalmatia from the second half of 19th and the first half of 20th century.

Results: The incidence of schizophrenia spectrum psychosis was between 0.58 and 2.58 per 1000 inhabitants. The genogram of Family 1 shows that out of 182 descendants in six generations, there were 27 people with schizophrenia spectrum psychosis. Schizophrenia spectrum psychosis occurred in two men who were born from a relationship of a mother with her relative. The genogram of Family 2 shows that 19 out of 86 descendants in five generations suffered from schizophreniform psychosis.

Conclusion: The high occurrence of schizophrenia spectrum psychosis in an isolated village in central Dalmatia is in accordance with the results of earlier studies in that region. The fact that psychosis occurs in varying frequency, without obvious regularity, can be explained by the irregular expression of risk genes as well as by exogenous factors which may affect the activity of the key chromosome areas. Occurrence of psychosis in people born from incestuous relationships indicates the importance of genetic factors in the development of the disorder.

Key words: psychosis – schizophrenia – genogram – incest - isolated rural area

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INTRODUCTION

Schizophrenia (SCH) is a chronic mental disorder, with a prevalence of 0.6-7.1‰ and annual incidence ranging from 0.11 to 0.70 per 1.000 (Kaplan 1998). In Croatia, the incidence of SCH in the population older than 15 years is 0.26-0.29 ‰ (Folnegović-Šmalc et al. 1990).

Numerous theories have tried to explain the development of this disorder. Genetic studies have unequivocally shown that it is a disorder with a hereditary basis. Most probably, it is a case of polygenetic inheritance, based on a range of genes whose expression can be altered by different environmental factors and whose variability

contributes to the total risk of the disorder (Šagud 2008). Multiple genes of small effect, grouped in the same chromosome areas, are suggested to lead to a predisposition for SCH. Chromosome areas shown to be associated with SCH are 1p36, 6p22-24, 8p12-22, 1q21-22, 10q25.3-26, 10q22, and 22q11.2. However, recent studies exploring these questions have yielded contradictory results (Guo et al. 2007, Roy et al. 2007, Nunokawa et al. 2007, Kohn et al. 2004). Genetic mechanisms of the disorder may be related to the synthesis of dysbindin, neuregulin, RGS4, prolin dehydrogenase and abnormal membrane phospholipid metabolism (Fischbach 2007, Reif et al. 2007, Duan et al. 2007, Buretić-Tomljanović 2008). Due

to the decrease of genetic distance, the risk of SCH is higher among the relatives of people with SCH. Studies exploring the frequency of SCH in large number of families have shown that SCH occurs significantly more often among families with a positive anamnesis for SCH in the first generation (Kendler 1993, Onstad 1991). In studies of monozygotic and dizygotic twins, heritability was estimated between 82- 85% (Cannon 1998, Cardno 1999).

A search of the Medline database did not reveal any study exploring the occurrence of SCH among family members born in an incestuous relationship.

The purpose of this study is to show a transmission of schizophrenia spectrum psychosis through several generations of two families in an isolated rural area of Dalmatia, Croatia.

SUBJECTS AND METHODS

A demographic field study was conducted in a small isolated village in Dalmatia with a high incidence of psychosis. In the next closest village there lived people of different confession and the inhabitants of these two villages never married each other.

To estimate the incidence of psychosis, we used the data on the number of inhabitants between 1890 and 1991. We used all available sources: church books with the records of born and deceased people in the Mirlović Zagora parish (Stošić 1941), as well as the books “Villages of Šibenik County” and “Konjevrate and Mirlović Zagora – parishes of Šibenik diocese” (Gulin 2005).

(Data on schizophrenia spectrum psychosis for the first three generations were obtained from the family members who had drawn up their family trees).

- Data on the first three generations who lived in the village between the end of the 19th century and the 1950-ies were collected from the oldest living member of the family, who at the time of the interview was 94 and in a good mental state despite his very old age. The descriptions of diseased people were transferred by oral tradition and he heard them from the senior members of his family. Based on his descriptions, diseased people could be categorized into four groups. Most of those

people (10 from the first three generations) would get ill after the 20th year of life. Previously unobtrusive, they would suddenly become withdrawn, very silent, shy and timid, unwilling to communicate with others and unable to do any kind of work. For those reasons, they could be only entrusted to watch the sheep. The second group consisted of 8 people who got ill in their late 20s. They were not able to do even the simplest work, used to run away, hide from others, and would not talk to anyone. They also did not care about hygiene and were very dirty. Their speech was incoherent, they would loudly talk to themselves, sometimes scream or sing for no reason. Sometimes they even behaved aggressively. The third group consisted of 5 persons who were different from the others from their birth, they behaved strangely from the beginning, as if “they were not very clever”. Their symptoms were similar to those observable in persons from the second group. They would be recognized as ill very early, in their teenage years, so no one of them ever got married. The fourth group consisted of only two persons who had a characteristically asocial, bizarre behavior and both ended their lives by suicide. One of them was a woman who showed some symptoms of illness even before her labor, but after she delivered a child her illness got worse and she threw herself into a draw well. The other one was a man who also took his own life, but the details about that event could not be ascertained.

The descriptions of illness that begins in the early adult age, characterized by a cessation of communication, social isolation, deranged behavior, perception disorders (talking to oneself) and thinking disorders (incoherent speech), would correspond to the diagnostic category of schizophrenia spectrum psychosis, according to the 10th revision of the International Classification of Diseases and Related Health Problems.

For the three generations of people who were living in the village since 1950s, the diagnosis of SCH was found and confirmed in the archive of hospital admissions at the psychiatric ward of the general hospital in Šibenik. We also used the testimonies of general practitioners who worked in the village during 1970s and 1980s, one of them being a coauthor of this study.

Data problems

Problems with the data collection in this study are related to the trustworthiness of recollections of the oldest living villager and the oral tradition on which they were based. Making a diagnosis retrogradely also poses significant methodological problems, since it is not possible to perform a more detailed diagnostic assessment of the described symptoms. The data collection was further complicated by the fact that some medical records were destroyed during the war in 1992.

In this article we show the genograms of two families descended from two women with schizophrenia spectrum psychosis who moved into the village to marry with two men who lived there. Genograms consist of six generations, with all

members of both families included. The incidence of psychosis was calculated based on the number of village inhabitants given in the literature (Stošić 1941, Gulim 2005). Among the members of other families in the village there were no identifiable cases of schizophrenia spectrum psychosis. The study was approved by the ethics committee of the Clinical Hospital Split.

RESULTS

The incidence of the schizophrenia spectrum psychosis per 1000 inhabitants was between 0.58 in the second half of 19th century and 2.58 in the 1930s (Table 1).

Table 1. Incidence of schizophrenia spectrum psychosis in Croatian Genetic Isolate

Year	Number of Villagers	Generation	Family 1		Family 2		Psychosis Total	Incidence
			N	Psychosis N (%)	N	Psychosis N (%)		
1890	513	1.	6	2 (33.00)	4	1 (25)	3	0.58
1910	620	2.	11	0 (0.00)	13	5 (38.46)	5	0.81
1931	699	3.	37	15 (40.54)	23	3 (13.04)	18	2.58
1953	750	4.	42	2 (7.14)	23	8 (34.78)	10	1.33
1971	565	5.	75	9 (12.00)	23	2 (8.70)	11	1.95
1991	329	6.	11	0 (0.00)	/	/	0	0.00

The genogram of Family 1 shows that out of 182 descendants in six generations, there were 27 people with schizophrenia spectrum psychosis. In the first generation, the mother with psychosis gave birth to six children – two daughters and four sons. Both daughters suffered from psychosis (33%). One of the diseased daughters had four daughters and two sons, and one of these sons had five sons of his own. In the second generation no one had psychosis. In the third generation, out of 37 descendants, 15 (42.86%) had psychosis – 12 men and three women. In the fourth generation, there were a total of 42 descendants and 17 of them were women. Psychosis occurred in two men (7.14%), one of them being born from a relationship of mother with her third-generation relative. Out of 77 descendants in the fifth generation, 9 people (12%) – four men and five women – had psychosis. In the sixth generation, only 11 persons were followed up and none of them had psychosis (Figure 1). Ten of them have moved out of the village, and three of them emigrated to another country or even continent.

The genogram of Family 2 shows that 19 out of 86 descendants in five generations had psychosis. In the first generation, three sons and one daughter was born. One of the sons was diseased and he had five children: three sons and two daughters. Out of these five, two sons and a daughter were diseased. Two healthy brothers in the first generation had six children – four daughters and two sons, with only one daughter that was diseased. The sister from the first generation gave birth to a healthy son and a daughter with psychosis. Therefore, in the second generation, five out of 13 descendants had psychosis. In the third generation there were 23 descendants, out of whom 12 were men. All three persons with psychosis in this generation were also men. In the fourth generation, there were 23 descendants (13 men), out of whom eight (six men) had psychosis. In the fifth generation, there were 23 descendants – 12 men and 11 women, out of whom two persons, both of them men, had psychosis (Figure 2).

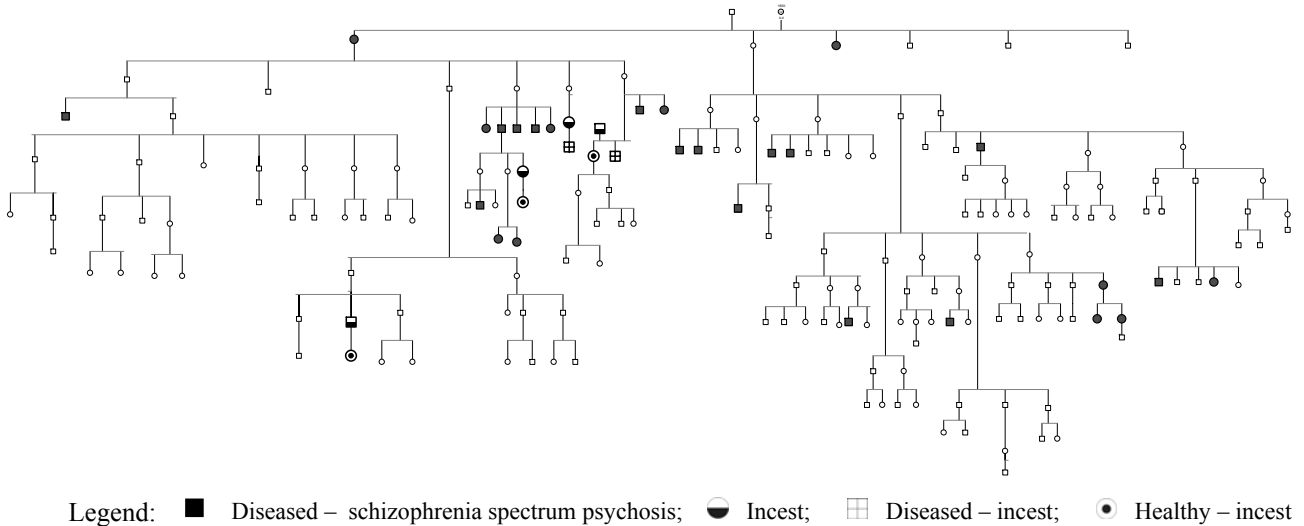


Figure 1. Genogram of the Family 1

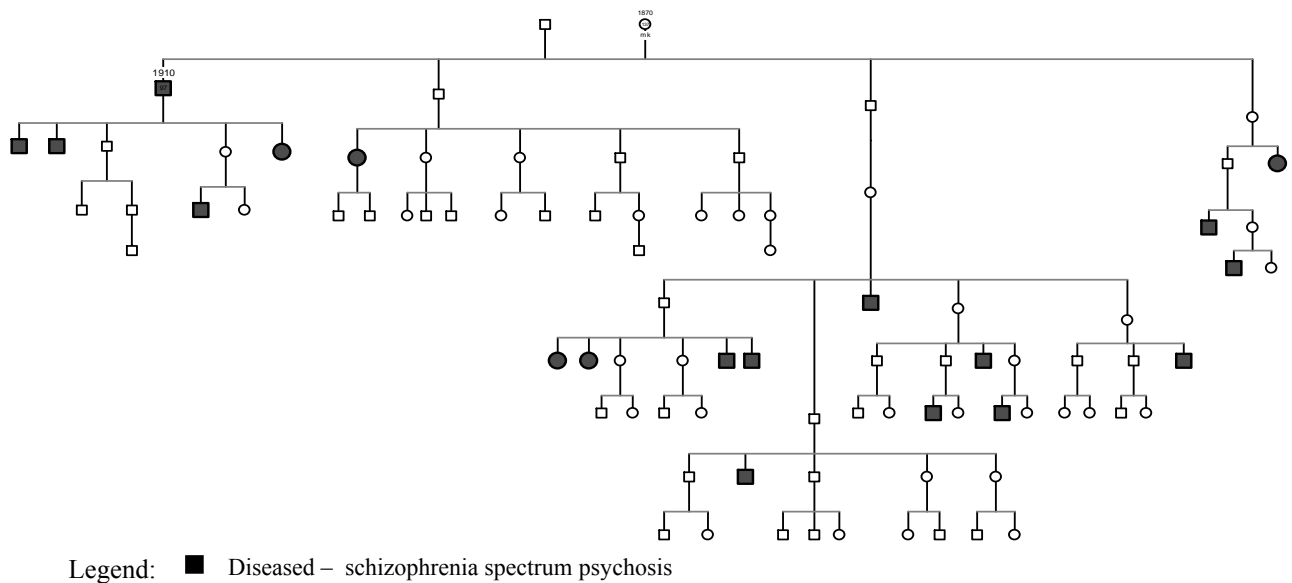


Figure 2. Genogram of the Family 2

Incestuous relationship

In the Family 1 incestuous relationship occurred four times – once in the third generation, twice in the fourth and once in the fifth generation. In the third generation, out of 15 diseased people, one man was born from an incestuous relationship of mother with her third-generation relative. He was the only child from that marriage. In the fourth generation, incest occurred in two marriages in which three children were born, two of them being healthy, and one of them ill. In the fourth generation there were only two ill persons, one of them born from an incestuous relationship. In the fifth generation, a healthy child was born from an incestuous relationship of a mother with her third-generation relative.

DISCUSSION

Results of this study demonstrate a high incidence of schizophrenia spectrum psychosis in an isolated village in central Dalmatia. The incidence of schizophrenia spectrum psychosis over the six generation was two to four times higher than in the general population of Croatia, where it is 0.21 to 0.22 per 1000 people. It was also higher than that found in ethnically small groups in London, where the incidence was 12-38 cases in 100,000 inhabitants (Boydell 2001). These findings indicate that the isolation of a population is associated with the frequency of occurrence of schizophrenia spectrum psychosis.

Genograms of the described families showed that marrying of two diseased women into an

isolated rural community resulted in the spread of the disease that previously did not exist there. In every generation of the observed families, the number of people with psychosis greatly exceeded that in the general population. This finding confirms the results of previous studies that a higher risk of SCH is present in the families with a positive anamnesis for that disorder (Kendler 1993, Onstad 1991).

The fact that schizophrenia spectrum psychosis occurs in varying frequency, without obvious regularity, in different generations of the same families, can be explained by the irregular expression of risk genes. It is also an indication that some exogenous factors may affect the activity of the key chromosome areas. These factors that result in a varying genetic expression are still not precisely determined.

Our findings corroborate the results of other studies which showed the importance of heredity in the occurrence of schizophrenia spectrum psychosis, from 82-85% (Cannon 1998, Cardno 1999). The fact that some diseased people in our study were born from incestuous relationships argues in favor of the significance of genetic factors in the etiology of psychosis. Unfortunately, we could not compare our results with the findings of other studies, since our Medline search did not yield any study exploring the possible association of psychoses and incestuous relationships.

This study is limited by the lack of a control group and by a relatively small number of participants. A further limitation of the study relates to the fact that data needed for the construction of family trees were collected by talking with people and looking into incomplete medical documentation. It was not always possible to objectively establish the diagnoses of SCH, as there are no medical records from the end of 19th and the beginning of 20th century. We therefore had to rely on the narratives of people, which may have been biased or imprecise. The term “schizophrenia spectrum psychosis” was used because we could not make an exact diagnosis, given the fact that the symptoms were reconstructed on the basis of family members’ narratives.

The strength of this study is that we explored the occurrence of schizophrenia spectrum psychosis in a relatively long period (from the end of 19th century up to the present time) in a rural community that experienced no significant immigration. Given the massive migration currents

during the last 150 years, it is almost impossible to find such an isolated community, except in rare ethnic areas. Another strength of this study is that included a family with a history of incestuous relationships, which is rarely described in the scientific literature.

Further research may focus on genetic analysis of descendants of the families observed in this study, compare the found frequency of SCH with that in the families without the positive anamnesis for SCH, and follow up those members of the observed families that did not develop the full clinical picture of SCH, but suffered from some of the SCH-spectrum symptoms.

CONCLUSION

The high incidence of schizophrenia spectrum psychosis in an isolated village in central Dalmatia from the end of 19th century up to the present time in a rural community is in accordance with the results of earlier studies in central Dalmatia. The fact that schizophrenia spectrum psychosis occurs in varying frequency, without obvious regularity, can be explained by the irregular expression of risk genes as well as by exogenous factors that may affect the activity of the key chromosome areas.

The strength of the study is that it shows the occurrence of schizophrenia spectrum psychosis in children from incestuous marriage relationships, which is rarely described in the literature and indicates a significant role of genetic factors in the etiology of psychoses.

Further research may focus on the genetic analysis of descendants of the families observed in this study, and compare the found frequency of schizophrenia spectrum psychosis with that in families without a positive anamnesis for this psychosis.

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