

A Case of Triplets Concordant for Schizophrenia: Psychopathological Considerations

Dimitris G. Dikeos¹, George B. Mitropoulos², Ersi Tsopanaki², Maria Typaldou¹, Dimitra Gorgoli³, Ioannis Papoulidis⁴, Christos Garnetas², George N. Papadimitriou¹

¹First Department of Psychiatry, Athens University Medical School, Athens, Greece

²Fourth Inpatient Department, Psychiatric Hospital of Attica, Athens, Greece

³Psychiatric Department, General Hospital of Nea Ionia, Athens, Greece

⁴Eurogenetica SA, Thessaloniki, Greece

Abstract

A case of monozygotic triplets suffering from schizophrenia is presented. The three brothers had grown in a strikingly common environment and they developed an almost identical psychotic symptomatology at the age of 19. We thoroughly assessed their symptomatology using the structured interview Schedules for Clinical Assessment in Neuropsychiatry, blindly to results of zygosity testing. Brain MRI scans were also performed. The patients' psychopathology included trichotillomania in the context of an elaborate pseudo-philosophical world view, which led them to grandiose self-perception; withdrawal and social isolation; decline in every aspect of functioning; finally, physical aggressiveness. The vast majority of symptoms were practically identical and the MRI findings did not differ substantially among the three siblings. This case, by showing that the clinical presentation of the disease was similar in three men having in common both genes and environment, provides support for the hypothesis that, once the disease develops, the type of schizophrenic symptoms is almost exclusively influenced by genetic and environmental factors.

Key words: triplets, monozygotic, schizophrenia, hoarding, trichotillomania

Introduction

The likelihood for the development of schizophrenia depends on genetic and environmental factors. Concordance rates of monozygotic twins raised in the same environment, however, do not exceed 50% [1] denoting that at least half of the risk for the disease is most probably due to stochastic events. Once developed, the clinical presentation of the disorder is by no means uniform; variation among individuals is presumed to be dependent on genes, environment or random events of an unknown nature. The study of genetically identical siblings with regard to phenotypical similarities and differences can offer valuable insight into the factors which determine uniformity and variety of schizophrenic symptoms.

Although reports of twins suffering from schizophrenia are fairly common in the literature, the same does not apply for reports of triplets or quadruplets. So far, nine cases of triplets concordant or discordant for schizophrenia or schizoaffective disorder have been reported in the English psychiatric literature [2-7]. A set of quadruplets suffering from schizophrenia was first reported in 1963 and is since known as the Genain quadruplets [8].

We present the case of a set of male triplets suffering from schizophrenia and we examine the similarities and differences that the three brothers present regarding their psychopathology, personality traits and neuroimaging features. Possible genetic and environmental influences are also discussed.

Case report

The triplet brothers were admitted at age 23 in three separate departments of the Psychiatric Hospital of Attica. Their involuntary admission had been asked for by their parents.

Symptomatology was very similar among the three brothers and dated from the beginning of senior high school at age 16. They first manifested trichotillomania which was compulsive and made them feel guilty and ashamed, instead of relieving their anxiety. They gradually developed a puritan and ascetic attitude towards life, they avoided sex, and they took up excessive physical training. They started quarreling with their

parents and other people and they became transgressive by committing impulsive shoplifting.

Until the end of senior high-school they had never been separated from each other living in an apartment of their own next to that of their parents. After finishing high-school they took exams and entered university departments, each at a different city. Their studies, however, were interrupted three years later, their academic achievement being a shadow of their brilliant performance as schoolboys. Eventually, they all decided to return to their common home; there, they jointly developed a fairly elaborate pseudo-philosophical worldview of clearly delusional dimensions. They had no social contacts, they fed themselves according to peculiar dietary rules, and they didn't wash, holding that each man has a "system of self-cleaning". More notably, they didn't cut their hair, as they preferred to pull them off instead, hair by hair, considering this to be the only way for the hair to be renewed. They exhibited hoarding behavior and their apartment ended up being full of plastic bags with recycle garbage, which they collected scrupulously during their rare nocturnal excursions and never disposed of.

It was not long before they spoke with scorn of their old friends and acquaintances, of their studies as being completely meaningless, and of modern life-style as being inferior and "petit bourgeois". They even gave up sports and reading, and they ended up spending countless hours on a sort of improvised group meditation. They believed that, in contrast to all other people who lived "will-lessly" and "mechanically", they themselves had accomplished a superior way of life, which they ought to teach to others, even if that meant becoming violent. What we have here is that kind of radical certainty which Jacques Lacan considered to be an essential feature of psychotic delusion [9].

Violence was manifested gradually in the course of months, mainly towards their parents who for many years had remained mere spectators to their children's decline. Verbal and physical aggressiveness were of such magnitude, that the parents were persuaded to ask for the compulsory admission of their sons, who would not consent to a formal psychiatric evaluation.

During admission in three separate departments of the hospital, the symptomatology did not ameliorate before drugs took effect, indicating that all three brothers suffered independently of each other, their case not being a shared psychosis.

Apart from the common features presented so far, there have been subtle differences among the three men, both in personality traits and in the way their psychopathology was manifested. Both similarities and differences are summarized in Table 1. What follows is a detailed description:

“The fists”

Triplet A was more perfectionist than his brothers and did more regular physical exercise. He was the strongest physically and he undertook the heaviest tasks. He was regarded by the others as “the fists” of the team. It was he who initiated the physical assault first towards their father and later towards their mother, acting “on behalf” or “in defense” of his brothers who were present merely shouting abuse, leaving triplet A to act physically. Triplet A also hit a neighbor “defending triplet C”. At age 16 he had the tendency to put his hands on his mother’s breasts. He was the one who started spending many hours in the bathroom pulling off hair from his pubis; the others followed, but less committedly. He was more interested in and influenced his brothers on matters of diet and he scrutinized the ingredients of foods. As a student, he was the best of all three, except in the last year of high school and during the preparation for the university entry exams when triplet C did better. During a joint post-discharge interview with the triplets he turned out to be the most eager participant, the most willing to compromise and adhere to treatment (despite his lack of insight), volunteering to persuade the reluctant triplet C to do the same. Post-discharge he appeared to have a better relationship with their parents, and he even tried to resolve any friction between them and his brothers. He was also the only one who did not rule out the possibility of a future job. He is described by his parents as being the most sensitive, emotional, shy, poetical, easily frustrated and the less humorous of their children. Explicitly he had a heterosexual orientation without having ever dated a girl, he had never masturbated and he had had sex only once with a prostitute.

Being the most ascetic (along with triplet C) he spent several hours trying to break a meditation record.

“The brains”

Triplet B was the most sociable and communicative before adopting his brothers’ withdrawn lifestyle in early adulthood. He had the best relationship with their parents. At school he was popular, being a member of the students’ council. He had a few dates with girls, and he was the most active sexually both in terms of masturbation and visiting brothels. At school he was a good student, although his parents thought he was a little “slow”. His academic performance was slightly inferior to that of triplets A and C. Upon entering the university he was admitted to a faculty that he didn’t like much and which was of an “inferior status” compared to those of his brothers. He gave up his studies 6 months before the other two decided to do the same. Nevertheless, he had always been a little more inclined than his brothers to artistic matters, being better informed on music, cinema etc. During their “ascetic” period he was the dirtiest, not having had a proper bath for nearly a year. His brothers readily acknowledged him as their team’s “representative”, “brains” and “headquarters”. When they became aggressive he provided theoretical rather than physical support. According to his parents he had the most irritable character. Post-discharge he was the only one to discontinue his medication and become depressive and suicidal to the degree that he had to be readmitted for further treatment. He appeared to remain the most faithful to their prior lifestyle and to its assumed superiority, regretting its abrupt end and wishing to write memoirs.

“The crazy”

Triplet C was the most introvert and remote. During the last year of high school he tried harder, did better in the final exams and was admitted to Law School. After adopting his brothers’ retired lifestyle, he was the one who lost the most weight, to the extent of becoming almost “dematerialized” and “reminding of Auschwitz” (according to his parents). He was the most devoted trichotillomaniac, pulling off the hair of

his head until he was virtually bald. At the same time he was the cleanest and tidiest; he swept the floor and put away the fallen hair, despite the fact that he had been the laziest child. He was the most reckless when risky behaviour was at issue. When it came to aggressiveness, he was eager to start the fight, being the “craziest” and the most quarrelsome, at least verbally. In sexual matters, even in adulthood, he remained in an “infantile stage”, according to his parents. His asceticism was comparable only to that of triplet A’s (neither had ever masturbated and their only sexual experience was one visit to a brothel).

Material and methods

E.T. and C.G. interviewed all three brothers when they were first brought to the emergency room of the hospital. At the time, none of the triplets was under medication. All subsequent interviews, neuroimaging and genetic testing were done at the 1st Department of Psychiatry of Athens University Medical School, Eginition Hospital, after informed consent was obtained from patients and parents regarding the use of information for publication purposes. Proper approval was obtained by the Ethical Committees of both Psychiatric Hospital of Attica and Eginition Hospital.

We had the opportunity to interview the three boys and their parents repeatedly since their admission at the Psychiatric Hospital of Attica. During these subsequent interviews the three brothers were receiving antipsychotic drugs (triplets A and C were on 20mg Sertindole daily, and triplet B on 240mg Ziprasidone plus 15mg Aripiprazole daily). During their hospitalization G.B.M., E.T. and C.G. were the therapists of triplet A, and they also interviewed triplets B and C who were hospitalized in separate wards and were treated by other therapists. Their parents were asked to provide a copy of the obstetrical files concerning the perinatal history of the triplets.

Psychiatric diagnosis and assessments

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) structured interview was administered to the triplets

by D.D. as an independent assessor. Diagnosis was made according to DSM-5. Detailed symptomatological assessment was based on the clinical interview, notes of hospitalization and on SCAN ratings; symptoms were rated as present or absent and, if present, by their relative intensity, blind to zygosity testing.

For the determination of zygosity, DNA was isolated from whole blood leukocytes from all three siblings and their parents, and comparative analysis was based on fourteen highly polymorphic markers.

Structural MRI was performed with axial, sagittal and coronal images of slices 6mm thick examined in a variety of sequences (T1, T2, T2-TSE, FLAIR), as appropriate.

Results

Psychiatric diagnosis and symptomatology

According to the SCAN structured interview DSM-5 criteria for schizophrenia were met for all three siblings. A detailed symptomatological assessment of clinical features (divided in: age of onset, pre-treatment symptoms, loss of functioning and post-treatment symptoms) and premorbid traits are presented in Table 1.

The age of onset and the majority of symptoms of the disease (unusual thought content, pseudo-philosophical preoccupation, bizarre behavior, disruption of social relations, absence of insight, self-esteem/grandiosity) as they presented before any treatment were identical for the three siblings. For one premorbid trait (timidness) and two pre-treatment symptoms (violent behavior and eating peculiarity) triplet A was worse than his siblings. Triplet B fared worse than his brothers in academic performance (pre-treatment), and he had a generally worse clinical course after treatment, as reflected in persistence of residual positive symptoms and development of post psychotic depression.

Regarding their premorbid condition, as described by their parents and assessed retrospectively, triplet C fared worse than his brothers in seven out of the nine examined traits.

Genetics

Phenomenologically the three brothers looked quite similar to each other. Zygosity testing showed that all brothers were monozygotic (all marker alleles were identical for the three siblings; error probability was less than 0,001).

Structural MRI

The brain MRI scans of both triplet A and triplet B were normal. Triplet C had a few pointed focal lesions in the lower part of the basal ganglia, compatible with slight local enlargement of the perivascular subarachnoid space, as well as a small vague focal lesion of a few millimeters in diameter without any specific imaging features at the right frontal lobe next to the horn of the collateral ventricle.

Gynecological/Perinatal history

The triplets' mother was pregnant at the age of 23. The pregnancy was not scheduled and the couple was married only after that. The most probable date of conception was at the end of April. During the summer the mother followed her usual sports activities, which were somewhat intense. It was not before October that it was found out by ultrasonography that she was carrying triplets. From then on and until delivery phenobarbital was prescribed to her by her gynecologist as a means of preventing uterus contractions. The triplets were born after a pregnancy of 33 uneventful weeks at the beginning of January by cesarean section; triplet B was pulled out first, followed by triplet C and then by triplet A. The babies were normal and they didn't have to remain in an incubator; they were only kept at the department for premature babies for 5 days before going home with their parents, with the exception of triplet B who had to undergo a bubonic hernia operation before being taken home 5 days later than his brothers.

Discussion

In this paper a set of male monozygotic triplets is presented, all of which met DSM-5 criteria for schizophrenia. In the three subjects the age of first manifestation and what we would

consider as "core" features of the disorder, i.e. unusual thought content, pseudophilosophical preoccupation, bizarre behavior, disruption of social relations, absence of insight, and a sense of grandiosity were identical. Only slight differences were noted in terms of personality traits and other features of psychopathology, as detailed in Table 1. In summary, triplet C fared somewhat worse than his brothers premorbidly, while triplet B did worse in terms of academic pre-treatment functioning and post-treatment course.

Regarding brain structural MRI, the only finding worth mentioning is that triplet C had a few non-specific focal lesions in the frontal lobe and basal ganglia. This is in contrast to a previously reported set of concordant schizophrenic triplets who showed MRI findings which were more uniform and conventional for schizophrenia [6,7]. In another set of triplets the affected sibling was negative for MRI findings [4].

Heritability seems to account for at least some of the common MRI findings in schizophrenia [10-13]. Regarding localization of lesions, frontal lobe volume reduction has been found to be associated with negative symptoms [14]. In the set of triplets we describe none of the characteristic structural neuroimaging features of schizophrenia was found. The only marginally abnormal finding of triplet C, cannot be considered to be etiologically associated with the disease. Similarly, the uneventful congenital hernia operation to which triplet B was subjected when a week old, cannot be taken to account for the development of the disease. One could not exclude, however, that the finding of triplet C might be related to his worse premorbid functioning, and that the perinatal operation of triplet B might be connected to his lower academic achievement and his worse post-treatment course.

According to the risk factor model, schizophrenia is caused by the additive interaction of genetic factors and of environmental factors, most important of which are gestational and birth complications, viral infections and drug abuse; unknown stochastic factors are also considered to play an important role in the probability of whether the disorder will manifest itself or not [1, 15-17]. Despite the fact that genetic influences on psychiatric disorders seem to transcend clinical boundaries [18], twin and family studies, as well as emerg-

ing indications from molecular genetics, have suggested that once a psychiatric disorder develops, its clinical features and course strongly depend on genetic factors [19-21]. Cultural and societal factors which sometimes affect the content of positive psychotic phenomena [22] did not appear to be of particular relevance in the case of these patients. The triplets we describe share a common genome and they have not been exposed to any of the known environmental risk factors (excluding multiple pregnancy); they also seem to have shared all possible environmental influences, having lived until early adulthood under strikingly similar conditions.

Our paper shows that the identity of “core” schizophrenic symptomatology in the three men was strongly determined by their common genes and common environmental conditions. The fact that differences in the clinical symptomatology among the siblings were of limited magnitude points to the assumption that the major part of the variety with which schizophrenia manifests itself among different people is the result of the variety in genes and environmental influences, and that stochastic events may be important in the development of schizophrenia, but do not substantially influence the presentation of its symptomatology.

Clinical features
1. Age of first manifestation of dysfunction: A=B=C
Symptoms pre-treatment
2. Unusual thought content: A=B=C
3. Pseudophilosophical preoccupation: A=B=C
4. Bizarre behavior: A=B=C
5. Disruption of social relations: A=B=C
6. Absence of insight: A=B=C
7. Self-esteem/grandiosity (pre-treatment): A=B=C
8. Violent behavior: A>B=C
9. Eating peculiarity: A≥B=C
10. Poor rapport with parents (pre-treatment): A=C>B
11. Obsessive-compulsive behavior: A=C>B
12. Weight loss: C>A=B
General functioning pre-treatment
13. Hindering in academic performance: B>A=C

14. Inadequacy of preparation for the university entry exams: A=B>C
15. Lacking self care: A=B>C
Symptoms post-treatment
16. Postpsychotic depression and suicidality: B>A=C
17. Residual positive symptoms: B>A=C
18. Poor rapport with parents (post-treatment): B=C>A
Premorbid traits
19. Restricted affect: C>A=B
20. Irritability: C>A=B
21. Reckless behavior: C≥A=B
22. Diminished sociability in childhood/adolescence: C>A>B
23. Diminished interest in sex: C≥A>B
24. Lack of artistic interests: C≥A>B
25. Asceticism: C≥A>B
26. Timidness: A>B=C
27. Obsessive preoccupation with sports: A=B>C

Table 1. Comparison of the clinical features and premorbid (personality) traits among the three siblings (A, B and C)

References

- Murray RM, Castle DJ. Genetic and environmental risk factors for schizophrenia. In: Gelder MG, Andreasen NC, López-Ibor JJ, Geddes JR (eds) *New Oxford Textbook of Psychiatry*. Oxford University Press, Oxford, 2009.
- Langsley DG, Burton TP, Griswold M, Walzer H, Spinka RB. Schizophrenia in triplets: A family study *Am J Psychiatry*, 120:528-532, doi: 10.1176/ajp.120.6.528
- McGuffin P, Reveley A, Holland A. Identical triplets: Non-identical psychosis? *Br J Psychiatry* 1982, 140:1-6, doi: 10.1192/bjp.140.1.1
- Anonymous. Monozygotic male triplets discordant for psychosis (letter). *Br J Psychiatry* 1991, 159:734-735, doi: 10.1192/bjp.159.5.734c
- Härnryd C, Jönsson E, Greitz D, Nyman H, Sedvall G. A set of male monozygotic triplets with schizophrenic psycho-

- ses. Nature or nurture? *Eur Arch Psychiatry Clin Neurosci* 1995, 245:1-7, doi: 10.1007/bf02191537
5. Torrey EF, Bowler AE, Taylor EH, Gottesman II. *Schizophrenia and Manic-Depressive Disorder: The Biological Roots of Mental Illness as Revealed by the Landmark Study of Identical Twins*. Basic Books, New York, 1994.
 7. Jönsson E, Härnryd C, Johannesson T, Wahlström J, Bergenius J, Bergstedt H et al. Further studies on a male monozygotic triplet with schizophrenia. Cytogenetical and neurobiological assessments in the patients and their parents. *Eur Arch Psychiatry Clin Neurosci* 1997, 247:239-247, doi: 10.1007/bf02900301
 8. Rosenthal D. *The Genain Quadruplets*. Basic Books, New York, 1963.
 9. Lacan J. *The Seminar of Jacques Lacan. Book III. The psycho-ses 1955-1956*, Norton, New York, 1993, pp.75-76.
 10. Rijdsdijk FV, van Haren NE, Picchioni MM, McDonald C, Touloupoulou T, Hulshoff Pol HE, et al. Brain MRI abnormalities in schizophrenia: same genes or same environment? *Psychol Med* 2005, 35:1399-1409, doi: 10.1017/s0033291705005167
 11. Kaymaz N, van Os J. Heritability of structural brain traits an endophenotype approach to deconstruct schizophrenia. *Int Rev Neurobiol* 2009, 89:85-130, doi: 10.1016/s0074-7742(09)89005-3
 12. Hulshoff Pol HE, van Baal GC, Schnack HG, Brans RG, van der Schot AC, Brouwer RM, et al. Overlapping and segregating structural brain abnormalities in twins with schizophrenia or bipolar disorder. *Arch Gen Psychiatry* 2012, 69:349-359, doi: 10.1001/archgenpsychiatry.2011.1615
 13. van Haren NE, Rijdsdijk F, Schnack HG, Picchioni MM, Touloupoulou T, Weisbrod M, et al. The genetic and environmental determinants of the association between brain abnormalities and schizophrenia: the schizophrenia twins and relatives consortium. *Biol Psychiatry* 2012, 71:915-921, doi: 10.1016/j.biopsych.2012.01.010
 14. Ettinger U, Schmechtig A, Touloupoulou T, Borg C, Orrells C, Owens S, et al. Prefrontal and striatal volumes in monozygotic twins concordant and discordant for schizophrenia. *Schizophr Bull* 2012, 38:192-203, doi: 10.1093/schbul/sbq060
 15. Tsuang M. Schizophrenia: genes and environment. *Biol Psychiatry* 2000, 47:210-220, doi: 10.1016/s0006-3223(99)00289-9
 16. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry* 2002, 159:1080-1092, doi: 10.1176/appi.ajp.159.7.1080
 17. Pulver A, Pearlson G, McGrath J, Lasseter VK, Swartz K, Papadimitriou GN. Schizophrenia. In: King RA, Rotter JI, Motulsky AG (eds) *Genetic Basis of Common Diseases*, Oxford University Press, New York, 2002.
 18. Smoller JW. Disorders and Borders: Psychiatric Genetics and Nosology. *Am J Med Genet Part B* 2013, 162B:559-578, doi: 10.1002/ajmg.b.32174
 19. Fanous AH, Kendler KS. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. *Mol Psychiatry* 2005, 10:6-13, doi: 10.1038/sj.mp.4001571
 20. Hare E, Glahn DC, Dassori A, Raventos H, Nicolini H, Ontiveros A, et al. Heritability of age of onset of psychosis in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2010, 153:298-302, doi: 10.1002/ajmg.b.30959
 21. Takahashi S. Heterogeneity of Schizophrenia: Genetic and Symptomatic Factors. *Am J Med Genet Part B* 2013, 162B:648-652, doi: 10.1002/ajmg.b.32161
 22. Mitropoulos GB, Gorgoli D, Houli D, Korompili K, Lagiou C, Gerontas A. Psychosis and societal prescriptions of gender; a study of 174 inpatients, *Psychosis* 2015, 7:324-335, doi: 10.1080/17522439.2015.1020333