

Can we close the barn door before the horses get out?

A case study of high genetic loading and subsequent development of psychosis

We would like to report on a 10 year old girl who was referred to a genetic study of schizophrenia in the Afrikaner population because of a high familial genetic loading. This patient subsequently at the age of 16 years was diagnosed with a psychotic disorder. The initial presentation at 10 years of age as well as the course of illness until the diagnosis of psychosis was made will be reported on. Possible predictors of the ultimate development of psychosis will be highlighted and the continuous follow-up of a high-risk case is emphasized.

"A" was a 10 year old grade 4 pupil at a private school when she was referred to us. The mother was diagnosed with schizoaffective disorder, bipolar type and the father with paranoid schizophrenia. Anne's birth and milestones of development were normal. She was raised by a family member. Between 2 – 3 years of age she regressed emotionally, was not sleeping and eating well.

She experienced the following early deviant behaviour during the first 10 years of her life:

- Fear of the dark,
- Struggled to socialize,
- Experienced periods of extreme sadness,
- Daydreaming, and
- Odd behaviour.

She was extremely fussy about the food she would eat. At one stage she was complaining of a terrible taste in her mouth and said she tasted her mother's illness. At school she struggled with reading, spelling and concentration. She failed her grade 2 school year. After the death of her mother and a close friend she became depressed and her school functioning declined even more. A child psychiatrist diagnosed a major depressive disorder and ADHD. She was prescribed citalopram 10 mg daily and methylphenidate. She became hyperactive on the antidepressant, which was subsequently discontinued. The methylphenidate was continued as the teacher could not cope with her in the classroom. She was lost for follow up for 5 years.

At 16 years of age she presented to the state psychiatric services with further information: her highest level of school education was grade 7. She was staying at home with her caregiver. She could not function as a helper at a nursery school. Her menarche was at 11 years of age and she had a bisexual sexual orientation. She started smoking marijuana at 13 years of age and was involved in poly-substance abuse. This was discontinued 5 months prior to this consultation. She was raped at 14 years of age by an older male. Since she started abusing marijuana she was experiencing psychotic symptoms (persecutory delusions & auditory hallucinations). These symptoms worsened over a three year period of time. Her mood was depressed and never had mania for more than a few days. Her self care was poor. She just wanted to sleep.

The following working diagnosis was made at that stage:

- Schizoaffective disorder – bipolar type
- Poly-substance abuse in a patient with borderline personality traits

The duration of untreated psychosis (DUP) was noted as 2+ years. When this patient was evaluated at 10 years of age she was not psychotic. It was suggested that she be observed on a regular basis for the further development of a psychiatric disorder. She was seen as a high risk for the development of psychosis in the future for the following reasons:

- There was a strong family history of psychosis
- Presence of early deviant non psychotic behaviours
- There were odd psychotic like thoughts e.g. tasting her mother's illness
- A possible manic switch on citalopram

Each of these factors led to the subsequent development of psychosis: empiric risk estimates are used for multi-factorial disorders, in which the inheritance patterns are unknown and do not appear to follow the typical mendelian pedigree patterns. Currently, the major genes contributing to mental illness remain to be conclusively established and genetic testing is not yet available. For this reason, recurrence risk estimates are based on empiric risks. (typically, risks based on data from available family studies).¹ By their very nature, empiric risks are summary estimates and thus would not be expected to apply directly to

Correspondence

Prof. JL Roos
email: Erna.fourie@up.ac.za

individual families. Genes may confer risk for a disorder, but the expression of the phenotype and the probability of the disorder occurring may be difficult to predict.¹ When providing recurrence risk for schizophrenia one should provide a range of risks, gathered from multiple sources. Comparisons with general population risks should be offered.² Empiric risks are usually available for simple family relationships.^{3,4} If two affected parents suffer from schizophrenia a child will have an approximate empirical risk of 45% to develop schizophrenia.^{3,4} Early deviant patterns of non-psychotic behaviour in children in their first ten years of life, who go on to develop schizophrenia have been constantly reported in high-risk, prospective and retrospective behavioural studies of schizophrenia.⁵ These aberrant behaviours constitute valid endophenotypes for the disease indicating early neurodevelopmental abnormalities.

Deviant childhood behaviour can be grouped into 3 clusters:

- Social functioning impairment cluster
- Mood/anxiety cluster and
- Cognitive impairment cluster

"A" scored high on most of these clusters. The odd thoughts she experienced (e.g. tasting her mother's illness) may have been part of the prodromal phase of schizophrenia. Currently available screening tools have been able to identify a group of patients who are at ultra-high risk of developing schizophrenia, but such tools are nonspecific. Only 25% to 50% of the individuals identified by these tools as being at risk will go on to develop a psychotic disorder within 1 or 2 years.⁶ Of the prodromal symptoms depressive symptoms occur on average 5 years before first admission. Depression can be seen as an integral part of the disease process leading to psychosis. A significant decrease in psychosocial functioning especially in young people may be the first sign of severe mental illness.⁷

What about her possible manic switch whilst being treated with citalopram? The STEP-BD study has confirmed the association of rapid cycling with antidepressant use, supporting the viewpoint that these agents can worsen overall illness, causing more mood episodes (including depression), in patients with a rapid-cycling course.⁸ This switching had a definite influence on this patient's diagnosis and further management.

Patients using marijuana should be warned about the risk for developing schizophrenia and monitored closely. This use is associated with a two fold increase in the odds of developing schizophrenia and related disorders.^{9,10} Recent reviews suggest that marijuana is a partial causal factor.¹¹ The association between marijuana use and the onset of psychosis is stronger for people with a predisposition for psychotic disorders. Onset of use before the age of 16 has a much stronger effect than if the cannabis use started at a later age.¹¹ It can be concluded that early marijuana use is a risk modifying factor for psychosis related outcomes.⁹

There is an emerging body of evidence that suggests that the early stage of schizophrenia might provide an opportunity for interventions, even very simple ones that may help to prevent the development of full blown schizophrenia. Studies suggest that delayed treatment leads to poorer long-term outcomes for patients with schizophrenia. The DUP here was more than 2 years.

The goal of prevention of first episode of psychosis is to develop a model of care similar to that used in cardiovascular

disease, in which patients with risk factors that increase the likelihood that they will experience cardiac events are identified early and treated to prevent such occurrences.⁶ What could have been done for this patient prior to the development of frank psychotic symptoms? Physicians should engage such patients, monitor their condition and provide support. Family targeted therapies can help protect these at-risk individuals who appear to be very vulnerable to stress. The family's role is to buffer the individual from stresses in the community. Simple and safe treatments must be the first priority. Psycho-education on substance use in vulnerable patients is of paramount importance. Treat what is already a problem and do not use antipsychotics before the onset of psychosis.⁶

It has been hypothesized that schizophrenia is a neurodevelopmental disorder in which brain development begins to go awry at around 12 or 13 years of age. Earlier interventions may help to stop progression and improve outcomes which had been described as: "trying to close the barn door before the horses get out".¹² We were accurate with our clinical predictions of this patient at 10 years of age, but the question may be asked: "Did we do enough to close the barn door before the horses got out?"

JL Roos, M Lombard, A Ladikos

Department of Psychiatry, University of Pretoria, Pretoria, South Africa

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