Velocardiofacial syndrome case report:
Is this a homogeneous genetic subtype of Schizophrenia?

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Summary

In this case report of a 21-year-old Afrikaner male, a diagnosis of velocardiofacial syndrome was made on clinical grounds. Later a FISH analysis test for 22 q 11 microdeletion confirmed this clinical diagnosis.

Specifically two independent studies have reported that 25 - 31% of patients with the 22 q 11 microdeletion met diagnostic criteria for schizophrenia or schizo-affective disorders, while the microdeletion occurs in the population at a rate of 0.025%, it has been found in 2% of adult schizophrenic patients and in 6% of cases with childhood onset schizophrenia.

The complete history, physical and psychiatric examination of the 21-year-old male schizophrenic with velocardiofacial syndrome is described.

It is likely that the 22 q 11 region harbours genes that alone, or in combinations, are causally implicated in schizophrenia in certain proportions of patients. Uncovering of one or more genes that predispose to schizophrenia in this region will lead to a better understanding and management of this homogeneous subtype of schizophrenia.
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INTRODUCTION

Schizophrenia has been called "arguably the worst disease affecting mankind". The worldwide lifetime prevalence of the disorder is ~ 1%[1]. Studies carried out over the last 50 years have demonstrated conclusively that the genetic constitution of an individual plays a large role in determining whether he or she will develop schizophrenia[2,3]. Attempts to dissect out the individual genes that may play a role in the onset of this disease have met substantial difficulties, primarily because the mode of inheritance of the disease is complex and likely involves interaction among multiple genes and environmental factors[4]. The nature of such interaction, the number of susceptibility loci, the risk ratio conferred by each, or the extent of locus heterogeneity, all remain unknown. Thus, conclusive identification and replication of a chromosomal region that harbours a susceptibility locus has not been forthcoming.

Technological advances as well as progress in genetic analytic methods will facilitate the discovery of genes influencing susceptibility to mental disorders. It seems clear that ultimate success will require large-scale data collection efforts to obtain samples of sufficient power for the detection of susceptibility loci of relatively small effect.

It is likely that the requirement for large sample-sizes can be relaxed if the target population presents less heterogeneity at the susceptibility loci, as may be the case for populations founded by a relatively small number of individuals (genetic isolates), such as the Afrikaner population. Several diseases occur at unusually high frequencies among the South African Afrikaners (as much as 5-10 times higher than in most other population groups), such as variegate porphyria, Huntington's chorea, Familial Hypercholesterolemia, Fanconi Anaemia and myotonic dystrophy[5-9].

Moreover, when a founder effect occurs and a mutant allele is introduced within a population with limited admixture, the frequency of a mutant allele can increase rapidly during a few generations. For this reason a collaborative project between The Rockefeller University in New York and the University of Pretoria / Weskoppies Hospital on genetic studies of schizophrenia was initiated in 1997. More than 175 families have been recruited up to now. The ongoing collection of schizophrenic patients of Afrikaner origin in Genetic Studies of Schizophrenia will be described in detail elsewhere (C Sobin et al, manuscript in preparation).

The notable increase in the number of published studies on velocardiofacial syndrome over the past 3 years is likely attributable to data suggesting that the syndrome may represent a homogeneous genetic subtype of schizophrenia[10]. The concurrent breakthrough in genetic research of the complete sequencing of chromosome 22 will undoubtedly fuel additional investigations of the syndrome and its genetic underpinner[10].

A 7 microdeletion of chromosome 22 q 11 is associated with variable phenotypic expression that often

includes learning disabilities, palatal abnormalities, congenital heart defects, and mildly dysmorphic facial features[12]. One of the first clues that psychiatric symptomatology may also be associated with this microdeletion was a report of expressionless face, monotonous speech, and flattened affect among children with the microdeletion[13]. In light of the evidence for suggestive linkage for schizophrenia on chromosome 22[14], patients with the 22 q 11 microdeletion were evaluated for psychiatric symptoms or disorders, and a relatively high frequency of severe mental illness has since been reported. Specifically two independent studies have reported that 25 - 31% of patients with the 22 q 11 microdeletion met diagnostic criteria for schizophrenia or schizo-affective disorders[15,16], while the microdeletion occurs in the population at a rate of 0.025%, it has been found in 2% of adult schizophrenic patients[17] and in 6% of cases with childhood onset schizophrenia[18]. In addition, several studies have described 22 q 11 microdeletions among schizophrenic patients of various ethnic origins[19]. These studies collectively suggest that the morbid risk of schizophrenia for a patient with a 22 q 11 microdeletion may be approximately 20-30 times the general population risk of 1% and that the rate of 22 q 11 microdeletions in schizophrenia, although relatively low, may be approximately 80 times the estimated general population rate. It therefore seems likely that the 22 q 11 region harbours genes that alone, or in combinations, are causally implicated in schizophrenia in certain proportions of patients.

In this case study a diagnosis of velocardiofacial syndrome was made on clinical grounds (see history and physical examination). Later a FISH analysis test for 22 q 11 microdeletion confirmed this clinical diagnosis. As approximately 10% of individuals with velocardiofacial syndrome apparently lack the deletion, negative results do not exclude a clinical diagnosis of velocardiofacial syndrome. Of the more than 200 subjects and affected family members so far recruited in this genetic study, only 4 comply with a possible clinical diagnosis of velocardiofacial syndrome. This case study is presented here because the clinical features are typical of a velocardiofacial syndrome.

Case study:

Mr J is a 21-year-old unmarried student who is living with his parents. He was referred to the genetic study by a private psychiatrist.

Birth to 6 years of age:

He is the oldest of 4 siblings. His mother was healthy during pregnancy. There was an induction of labour and he was born by forceps delivery. At birth he had a ventricular septal heart defect. This defect was corrected with cardio thoracic surgery at 13 months of age. (His second brother and youngest sister were born with craniostenosis defects). He had chronic urinary problems, orthodontic problems (two permanent incisor teeth instead of four) and a umbilical hernia that was surgically corrected. His early neuro-development was within normal limits but according to his mother he experienced feeding problems (regurgitated his food).

He attended a pre-school playgroup where he experienced socialization and learning problems. The socialization problems started at 2 years of age. He was not capable of socializing with friends and he is still experiencing this problem. He was very sensitive to loud noise e.g. vacuum cleaner, from one year of age and this continued to 6 years of age. He was afraid of the dark and experienced concentration and day-dreaming problems from a pre-school age and this continued into high-school years. The playgroup teacher said that he was not school ready because of an emotional and motoric delay in his development. He could not speak clearly.

Primary school (7 - 13 years of age)

He did not make good academic progress. He needed his mother's support to cope with his schoolwork. According to his mother he had a low self-image and lacked confidence. A neurologist evaluated him at the age of 7 years. A diagnosis of attention deficit disorder without perceptual disturbance was made. Methylphenidate was prescribed and he attended occupational therapy classes. He attended these classes for one year and received methylphenidate for four years. From grade one he experienced periods of extreme sadness. His mother says she had the impression that this sadness got worse after methylphenidate was prescribed and it improved mildly after the Ritalin was discontinued. At the age of 12 years the mathematics teacher reported that he was behaving inappropriately in class and pupils were laughing at him. According to Mr J he could not control this inappropriate behaviour. During his grade 7 year (13 years of age) he could not think clearly. He says it felt as if a curtain was covering his eyes and he also experienced a metal taste in his mouth. He was evaluated for epilepsy but an EEG was within normal limits. At the end of his primary school years he became very suspicious and anxious towards fellow pupils. He consulted a psychiatrist who diagnosed an anxiety disorder and an anxiolytic and antidepressant were prescribed.

Primary School Reports:

Two school reports at the age of 6 years and 10 years were obtained.

Grade 1 (first term - 6 years of age):

General observations

- Self confidence/independence:
  - He behaves in a insecure manner.
  - Is in constant need of support.
  - His self image can improve.
- Participation in school life:
  - Kind towards teachers.
  - Very obedient but in need of support.
- Fine motoric development:
  - Not on par.
- Major motoric development
  - Has problems with most of these performances.
  - He has no self confidence.
- Attention and concentration:
  - He is starting to listen with attention.
- Speech and language use:
  - Average vocabulary.
  - Speech is unclear to a mild degree.
  - Lack of confidence.
- General remarks
  - There is an improvement in his self-confidence and self-image. We must continue to work on this.

- He is anxious and wants to please his teacher.
- Very loveable and obedient.

Grade 4 (10 years of age):
General remarks:
At times he does not participate in classroom conversations. I must talk to him directly to get his attention. He only mixes with the pupil who sits directly next to him.

High school (13 years - 19 years):
He did not have friends and he struggled on academically. He travelled by bicycle to school but had the fear that he would die on his way to school. He says it was as if he could not judge his environment e.g. deciding when to cross a busy street. From grade 10 (15 years) he attended a private school where his mother was teaching. This environment was more supportive and good for him e.g. he was not forced to do oral examination that caused him to become extremely anxious. During the second half of his grade 10 year he told a teacher that demons were causing him problems and he experienced auditory hallucinations. These hallucinations did not continue for long periods. He repeated his grade 11 year because his results were not on a university entrance level. During his grade 12 year (18 - 19 years) he became very depressed. This started after the breaking up of a relationship with a girlfriend. At this stage obsessional thoughts that he had experienced from 13 years of age became worse. He consulted a psychiatrist who prescribed bensodiazepines and hypnotherapy. His grade 12-year results did not allow him to study further at university. His mother says that at this stage he was more than just depressed; he was staring at people and could not think for himself.

Post school (20 years to present state):
He did in service training for 2 months in view of obtaining work on a farm. After his training he worked on several farms for a few months at a time. He left these jobs because of interpersonal problems. He was forgetful and did not progress in his work. During this period he also tried to study for higher grades in order to obtain university entrance. He was not able to get university entrance exemption.

He then enrolled at a private academy for training as a teacher. For the first few months he coped well as this was a small and protective student environment. Then he experienced the following symptoms:

- Derealization.
- Vague somatic complaints.
- Auditory hallucinations.
- Somatic and paranoid delusions.
- Thought process disturbance.
- Bizarre behaviour and rituals.
- Obsessional thoughts (controlled these thoughts better).

The above group of symptoms were present for less than 6 months, but he has been experiencing psychotic symptoms from 16 years of age, not always to the same extent. He was admitted to a private psychiatric hospital and treated with an atypical antipsychotic and mood stabilizer. He could no longer function as a student. When the antipsychotic was reduced his psychotic symptoms got worse.

Physical examination:

Length	182.3 cm
Mass	79 kg
Skull circumference	59 cm

He shows facial dysmorphic features which include a prominent nose, without the broad base typical of velocardiofacial syndrome (VCF), as well as maxillary hypoplasia and a maxillary excess causing a long face. This facial profile fits the classical VCF features. Additionally synophyris (eyebrows meeting in the midline), prominent supraorbital ridges, small ears with prominent helixes, a prominent filtrum and a high palate are seen. His neck and shoulders are broad and he has a minor pectus excavatum. His hands are normal. A thoracic surgical scar is present and his heart is normal on auscultation.

DISCUSSION:

Three contemporary prospective cohort studies specify the types of non-psychotic deficits that can occur in pre-schizophrenic patients from infancy onwards.

In the British 1946 birth cohort study early motor development was delayed and speech problems were more frequent among the pre-schizophrenic group. Preference for solitary play at 4 and 6 years was more frequent among pre-schizophrenic children and cognitive performance including verbal, non-verbal and mathematic skills, measured at ages 8, 11 and 15, were impaired. Furthermore, indicators of deviance increased with age and suggested a progressively worsening developmental trend.[20]

In a similar study, teacher ratings of social development by age 7 of children who later developed schizophrenia, were more behaviourally maladjusted than children in any of the other control groups.[21]

In the other cohort study including 9236 participants, school performance ratings between the ages of 7 and 11 of 338 pre-schizophrenic children were compared to those 338 randomly selected as control. Poor classroom conduct, absenteeism and poor performance in sports and handicrafts (activities dependent upon motor coordination) predicted later schizophrenia.[22]

Retrospective studies of childhood behaviour among schizophrenic patients yielded similar findings. Investigators using home movies made during the first 8 years of life found that abnormal social behaviours and reactions, as well as odd movements and postures, reliably cued clinicians as to which children would go on to develop schizophrenia in later years.

In another study, early social and academic deficits were more frequent among 45 schizophrenic patients as compared to psychiatric control with affective disorder with psychotic features.[24]

Other work investigated the association between schizophrenia onset and early deviant behaviours. Among 61 clinic referrals with schizophrenia onset between ages 7 and 17, and their age- and gender - matched non-psychotic controls, early pre-schizophrenic social impairment, motor deficits and language disturbance occurred in a larger proportion of the juvenile onset schizophrenic patients.[25]

An early study had reported similar findings namely that non-psychotic deviance before age 10 predicted an earlier age of first clinical contact among adult schizophrenic patients.[26]

Early deviant behaviour as reported in Mr J's case report include:

- Socialization difficulties (onset 2 years) and learning problems (onset pre-school playgroup).
- Concentration and daydreaming problems.
- Emotional and motoric delay (pre school).
- Speech not clear.
- Low self-image and lack of confidence.
- Inappropriate behaviour (causing children to laugh at him).

School reports confirmed some of the above behaviour as follows:

- 6 years (Gr. 1):
  - Fine and major motoric behaviour problems.
  - Speech unclear.
  - Attention problems.
  - Lacks self confidence and is anxious.
- 10 years (Gr. 4):
  - Attention problems.
  - Only mixes with pupil seated next to him.

Whether these behaviours indicate syndrome onset in some patients has yet to be determined.

The researchers in the present genetic study mostly choose to question patients rather than parents on early childhood behaviour by using a simple semi-structured interview format that precedes the DIGS interview (Diagnostic Interview for Genetic Studies).[27] Brief initial interviews with parents suggested a number of different biases:

- No memory of childhood behaviours.
- Reporting a global impression that the ill adult was impaired in every way - but unable to provide behaviour samples.
- Did not want to provide information that would reflect badly on the child.

In this case report the mother's information on childhood behaviour was objective and more reliable than the information obtained from the patient. The school reports were objective and added value to the existing information. The reporting of learning disabilities/ attention impairment is likely attributable to the increased awareness and detection of learning disabilities over the past 20 years.

The early deviant behaviour became more severe over time in Mr J's case report, as DSM IV-defined schizophrenia approaches. Early non-psychotic deviance does not occur in 100% of schizophrenic patients, however, summarized results from eight independent investigators concluded that 60% of schizophrenic patients functioned normally until the onset of cardinal symptoms.[28]

The onset of Mr J's psychotic symptoms was earlier than the full-blown psychotic breakdown he had at 20 years of age. During his grade 10 school year (16 years old), he experienced auditory hallucinations, delusions, mood symptoms, and strange behaviour with a definite decline in his overall functioning. This sets the onset of Mr J's illness at 16 years and perhaps even earlier (± 13 years).

Age of onset of illness has been an avenue to the understanding of disease across all of medicine, with earlier onset cases often having more striking genetic and environmental influence and/or differing pathophysiologies.[25]

In some cases, the early onset disorder may be physiologically and etiologically different from the later onset illness. For example, the study of early onset disease led to a description of different and important mechanisms of illness. Insulin-dependent diabetes mellitus[30] have been tied to an earlier age of onset of illness, attesting to the importance of the topic. While most cases of schizophrenia have their onset in later adolescence and early adulthood,[33] the disorder has been identified in children since early in the 20th century.

The predominant clinical signs of velocardiofacial syndrome include cleft palate or velopharyngeal insufficiency, cardiac abnormalities, a specific set of facial features, and learning disabilities[34].

Mr J has most of these clinical signs.

Obsessions and compulsions and schizophrenic symptoms may assume various relationships. In some cases the symptoms remain distinct; insight into the irrationality of the obsessions and compulsions is preserved, and they are experienced as ego-alien. In other cases, the obsessions and compulsions become the subject of delusional elaboration during periods of active psychosis. In still other cases, the OCD symptoms are inseparable from delusional beliefs[35].

Some patients with OCD lose insight into the irrationality of their obsessions and compulsions in the course of their illness and become delusional. They can be distinguished from schizophrenic patients with comorbid OCD by the absence of the other signs and symptoms of schizophrenia[35].

The presence of obsessive-compulsive symptoms in patients with schizophrenia is associated with a much poorer long-term outcome[36].

In Mr J's case the obsessions remained distinct initially during the course of the illness. As the active psychosis became more prominent, the obsessions became the subject of delusional elaboration. As the psychotic illness progressed, the obsessions became less distinct.

Initially this family was not keen on becoming involved in the genetic study. After the psychiatrist's diagnosis of schizophrenia was discussed with the patient and the family they reconsidered the option of participating in this study. To them the diagnosis of schizophrenia is still far removed from a medical illness and is stigmatised. The fact that a genetic abnormality may be linked to the development of schizophrenia made it more acceptable as a medical illness for this patient and his family.

CONCLUSIONS:

Because velocardiofacial syndrome and the concomitant symptomatology result from a known genetic region (micro deletions on chromosome 22 q 11), the biological and behavioural characteristics of the syndrome provide an optimal framework for conceptualising the associations among genes, brain development and behaviour.

In the near future, with the uncovering of one or more genes that predispose to schizophrenia on the 22 q 11 chromosome, we will start to understand, and possibly manage, this homogeneous genetic subtype of schizophrenia in a better way.

Hopefully these advances will also help to destigmatise "arguably the worst disease affecting mankind".❐

References available on page 28.