Chapter 3

Klinefelter's syndrome (karyotype 47,XXY) and schizophrenia-spectrum pathology

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Abstract

Klinefelter syndrome, characterized by a 47,XXY chromosomal pattern, has largely been associated with physical abnormalities. Here, we report high levels of schizophrenia spectrum pathology in 32 Klinefelter men in comparison to 26 healthy controls. Schizophrenia spectrum pathology was measured with the Schizotypal Personality Questionnaire (SPQ) and Positive and Negative Syndrome Scale (PANSS).

Our findings may have important implications for treatment of Klinefelter syndrome. In addition, these results suggest that the X chromosome may be critically involved in the aetiology of schizophrenia.

Introduction

Klinefelter syndrome is the most common sex chromosome disorder, affecting approximately 1 in 400 to 800 males. Individuals with this syndrome are characterized by an additional X chromosome, leading to the 47,XXY karyotype. This sex chromosomal aneuploidy results in a variety of phenotypes including hypogonadism, androgen deficiency and infertility (Lanfranco et al., 2004). Although the primary focus in clinical research has been on physical phenotypes of these men, there is a an awareness of neuro-anatomical, cognitive and behavioral abnormalities (Lanfranco et al., 2004; Shen et al., 2004). Specific impairments on measures of verbal skills, high incidence of dyslexia and social dysfunctioning are among the most consistentlty reported behavioral phenotypes (Geschwind et al., 2000). On the other hand, in a recent review on Klinefelter syndrome the authors conclude that it still remains unclear whether Klinefelter syndrome can be associated with psychiatric disturbances (Lanfranco et al., 2004). Interestingly however, many of the abnormalities in Klinefelter syndrome resemble those found in schizophrenia.

For example, structural MRI studies have reported smaller whole brain volumes, enlarged lateral ventricles and volume reductions of the superior temporal gyrus (STG), amygdala, hippocampus, insula and cingulate in Klinefelter men (Shen et al., 2004). A comparison of these findings to structural MRI studies in schizophrenia shows that all these regions are also affected in schizophrenia. Support for the hypothesis that sex chromosomes may play a role in the development of schizophrenia is derived from studies showing that males are more often affected by the disease than females and have an earlier age of onset (Aleman et al., 2003).

Case studies have been published describing Klinefelter subjects suffering from schizophrenia and higher rates of Klinefelter syndrome among samples of schizophrenia patients (DeLisi et al., 1994). Studies investigating psychiatric pathology in Klinefelter syndrome have been limited in that they described Klinefelter men in psychiatric care and mental hospitals, or recorded mental hospital admissions. However, there have been no systematic reports of levels of schizophrenia psychopathology in a large sample of Klinefelter subjects unselected for psychiatric disorders. In addition, a biological-genetic vulnerability to schizophrenia may not only be investigated using dichotomous, diagnostic outcomes, but also using dimensional measures of schizophrenia spectrum pathology, which are more sensitive measures of vulnerability to schizophrenia. Schizophrenia spectrum phenotypes share common cognitive, neuro-anatomical and genetic characteristics with the severe schizophrenia

phenotype. The present study was designed to test the hypothesis of increased levels of of schizophrenia spectrum pathology in subjects with Klinefelter syndrome.

Methods

32 Klinefelter men (mean age 38.8, SD 8.1) and 26 healthy controls (mean age 35.0, SD 9.0), matched for age, sex, years of education and intellectual ability, were included in the study. Klinefelter subjects were recruited from the Dutch Klinefelter Association and not selected for psychological or behavioral abnormalities. Also, the psychiatry department was not mentioned during the recruitment process. The diagnosis of Klinefelter syndrome (47,XXY karyotype) was confirmed by karyotyping using standard techniques. In all Klinefelter males, all 16 cells that were screened showed a 47,XXY karyotype, indicating non-mosaicism in this group. 80% Of the Klinefelter men received testosterone supplementation. Mean age of onset of treatment was 27.8 years (SD 7.6). Control subjects were recruited by advertisements. None of the controls met criteria for an Axis-I psychiatric disorder, as shown by screening with the MINI-Plus. After complete description of the study to the subjects, written informed consent was obtained.

Schizophrenia spectrum pathology was measured with the Schizotypal Personality Questionnaire (SPQ). The SPQ is regarded as an indicator of the genetic vulnerability to schizophrenia, since there is a gradient increase in schizotypal traits in relatives of schizophrenia patients that is in proportion to the risk for schizophrenia associated with the degree of kinship with the schizophrenic family member (Vollema et al., 2002). Factor analytical studies have revealed three dimensions of schizotypy; *Positive schizotypy* (for example referential thinking and delusional atmosphere), *Negative schizotypy* (for example constricted affect and social anxiety) and *Disorganization* (odd speech and eccentric behavior).

In addition, the Positive and Negative Syndrome Scale (PANSS) was included. This is a widely used structured interview to assess symptom profiles in schizophrenia that are present in the week prior to the interview. The PANSS allows categorization of negative-, positive-, and general symptoms.

Intellectual ability was measured with the National Adult Reading Test and Raven's Advanced Progressive Matrices , an estimator of verbal I.Q. and performance I.Q. respectively.

Group differences were tested using analysis of variance (ANOVA). Effect sizes were presented as Cohen's d.

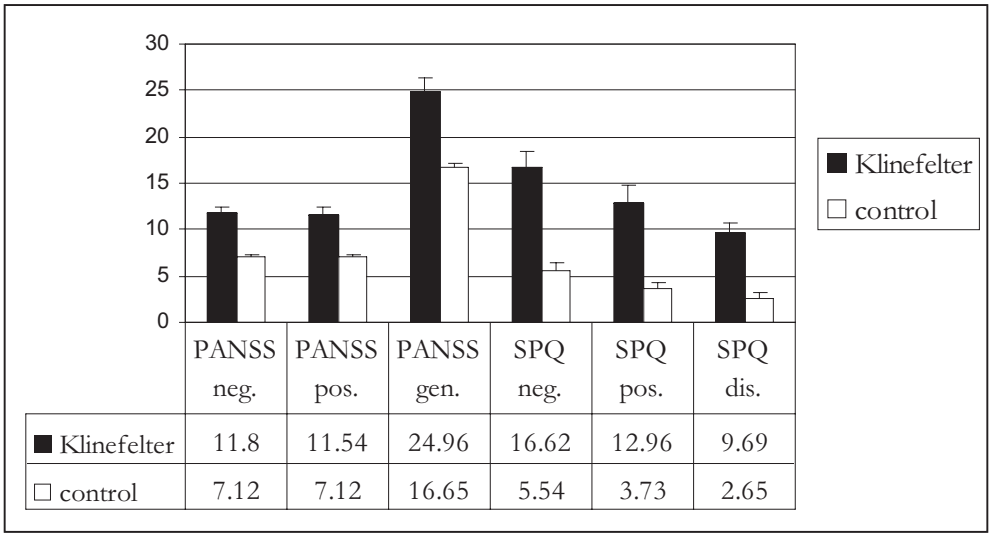
Results

In the Klinefelter group, the mean level of schizotypal traits, measured with the SPQ, was significantly higher than in healthy controls ($F(1,56)=36.67$, $p<0.0001$). Scores on all individual subscales were significantly increased (see table 1, presented as supplementary data at http://bjp.rcpsych.org/). Effect sizes were 1.43 for the negative dimension, 1.31 for the positive dimension and 1.81 for the disorganized dimension. The impact of these findings is illustrated by findings in schizophrenia. A study including 93 schizophrenia patients and 172 healthy controls, also using the SPQ, showed that the effects size (cohen's d) for mean total SPQ score was 1.95, for positive schizotypy 1.86, for negative schizotypy 1.83 and for disorganized schizotypy 1.45 (Rossi & Daneluzzo, 2002).

Similarly, PANSS scores showed increased levels of schizophrenia symptoms in the Klinefelter group ($F(1,56)=48.80$, $p<0.0001$). All symptom categories contributed to this effect. Effect sizes of 1.60 were observed for negative symptoms, 1.45 for positive symptoms and 1.66 for general psychopathology.

Results are presented in Figure 1. No significant group differences were observed for the estimators of verbal- and performance I.Q.

Figure 1
Schizophrenia spectrum pathology scores in Klinefelter syndrome (mean, SE).



(PANSS neg.= negative, pos.= positive, gen.=general;
SPQ neg.=negative, pos.=positive, dis.= disorganised)

Table 1
Scores on each of the individual subscales of the Schizotypal Personality Questionnaire were significantly increased in the Klinefelter group compared to controls (mean, SD).

	Klinefelter	**control**
Ideas of reference	2.7 (1.8)	1.3 (1.5)
Delusional ideas	1.0 (1.2)	0.3 (0.4)
Excessive social anxiety	4.1 (2.7)	1.1 (1.7)
Magical thinking	2.5 (2.2)	0.7 (1.2)
Unusual perceptual experiences	3.1 (3.3)	0.6 (1.7)
Odd or eccentric behavior	2.1 (2.2)	0.7 (1.6)
No close friends	4.5 (3.1)	1.3 (1.7)
Odd speech	7.8 (3.7)	2.0 (2.1)
Constricted affect	2.5 (2.0)	1.0 (1.2)
Suspiciousness	3.0 (2.5)	1.0 (1.0)

Discussion

The present study shows that the 47,XXY karyotype is strongly associated with high levels of schizophrenia spectrum pathology. This was evident in dimensional measures of schizotypal traits (SPQ) as well as actual schizophrenia symptoms (PANSS). Notably, magnitudes of the effect sizes of schizotypy levels approached those from a recent study with schizophrenia patients (Rossi et al., 2002; Vollema et al., 2002). Although healthy first degree relatives of patients with schizophrenia also have increased schizotypy scores when compared to individuals from the general population, schizotypy levels of relatives are substantially lower than those in schizophrenia patients (Vollema et al., 2002). Thus, the liability for schizophrenia might be higher in Klinefelter subjects than in relatives of schizophrenia patients. The presence of schizophrenia spectrum pathology in Klinefelter syndrome might have important implications for treatment. Whereas treatment is currently focused at medical problems, our data suggest it to be important to screen Klinefelter men for mental illnesses, in particular schizophrenia spectrum disorders.

Furthermore, our findings suggest a link between a X-chromosomal abnormality and liability to schizophrenia. This might provide a useful heuristic in the search for the genetic aetiology of schizophrenia. Indeed, a crucial role for X chromosome abnormalities in the aetiology of schizophrenia has been proposed (Lishman, 1998). Specifically, it has been argued that abnormal cerebral lateralisation may contribute to the development of schizophrenia, possibly involving abnormal expression of a gene on the X chromosome directing development of cerebral asymmetry (Crow, 2002). It is interesting in this regard that abnormal cerebral asymmetry has also been reported in Klinefelter syndrome . Additional support for a link between X-chromosomal abnormalities and liability to schizophrenia comes from two studies investigating the presence of 47,XXY karyotypes in a sample male schizophrenia patients. Whereas the prevalence of Klinefelter Syndrome in the general population is 0.1-0.2% (Lanfranco et al., 2004), these studies indicate that the prevalence of Klinefelter Syndrome in the schizophrenia population might be several times higher (DeLisi et al., 1994; Kunugi et al., 1999). Also, the present findings are consistent with a very recent study that reported auditory hallucinations in four out of eleven Klinefelter men (DeLisi et al., 2005).

Research with Klinefelter subjects, who are at increased risk for schizophrenia, may reveal specific genotype-phenotype associations. Endophenotypes in schizophrenia, i.e. expressions of a genetic predisposition at a neural or cognitive level, that are shared by Klinefelter syndrome and

schizophrenia may be the result of a X-chromosomal abnormality.

Finally, we are aware of some limitations of the present study. As many men with Klinefelter syndrome remain undiagnosed, our sample may not be completely representative. In spite of this, we believe that the present effect sizes convincingly indicate a relationship between Klinefelter and schizophrenia spectrum pathology, although the possibility that effect sizes might be attenuated in a representative sample from the general population can not be excluded.

In sum, Klinefelter syndrome can be associated with high levels of schizophrenia spectrum pathology. This suggests that the X chromosome may be critically involved in the aetiology of schizophrenia. Studying the genetics of Klinefelter syndrome may help localizing genes that are involved in the development of schizophrenia.

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