Journal of Psychiatric Research 48 (2014) 128–130

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Klinefelter syndrome and risk of psychosis, autism and ADHD

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ARTICLE INFO

Article history:
Received 12 April 2013
Received in revised form
10 September 2013
Accepted 2 October 2013

Keywords:
Klinefelter syndrome
Schizophrenia
Bipolar disorder
Autism spectrum disorder
ADHD
Epidemiology

ABSTRACT

Background: Schizophrenia, bipolar disorder, autism spectrum disorders and ADHD might be over-represented in Klinefelter syndrome, but previous investigations have yielded inconclusive results.
Methods: We compared a national sample of 860 Klinefelter patients in Sweden with 86 000 matched population controls. To assess the risks of schizophrenia, bipolar disorder, autism spectrum disorder and ADHD in Klinefelter patients, we estimated odds ratios and 95% confidence intervals using conditional logistic regressions.
Results: Klinefelter patients had almost four times higher risks of schizophrenia, odds ratio (OR) = 3.6, 95% confidence interval (CI) 2.0–6.7 and bipolar disorder (OR = 3.8, CI 1.8–7.6) and about six times higher risk of autism spectrum disorder (OR = 6.2, CI 4.0–9.4) and ADHD (OR = 5.6, CI 4.0–7.8).
Conclusions: The risk of psychosis, autism and ADHD is increased in Klinefelter patients. These findings indicate an X chromosome-related factor in the etiology of the studied psychiatric disorders, and may also have implications for treatment of patients with Klinefelter syndrome.

1. Introduction

Klinefelter syndrome is characterized by an extra X chromosome, usually resulting in the 47, XXY karyotype. It is the most common sex chromosome aberration and affects about 1 in 670 men (Bojesen et al., 2003). Previous research suggests that psychiatric disorders might be overrepresented in Klinefelter patients; several case reports describe concurrence with schizophrenia and bipolar disorder (DeLisi et al., 1994). In the same vein, Van Rijn et al. (2006) reported a significantly higher mean level of schizotypal traits among 36 men compared with controls. Further, in 51 boys aged 6–19 years, 12% met diagnostic criteria for a psychotic disorder, 27% had an autism spectrum disorder and 63% had ADHD (Bruining et al., 2009). The risk of psychosis in Klinefelter patients has also been investigated in two studies based on Danish population registers, where the first found no evidence of an increased risk of schizophrenia or bipolar disorder (Mors et al., 2001), whereas the second found a five times higher risk of broadly defined psychosis (Bojesen et al., 2006). Taken together, prior findings suggest that X chromosomal abnormalities may be involved in increased liability to schizophrenia, bipolar disorder, autism spectrum disorders and ADHD, but the status of the associations remain somewhat unclear. We wanted to test the hypothesis that diagnoses of schizophrenia, bipolar disorder, autism spectrum disorders and ADHD are more common among Klinefelter patients in a Swedish population-based setting.

2. Method

We used the National Patient Register (Ludvigsson et al., 2011) to identify 860 Klinefelter patients coded according to the ICD-10 (1997 and onwards, inpatient or out-patient diagnoses of Q98.0-Q98.2, Q98.4). Individuals with schizophrenia (ICD-8: 295.0–295.6, 295.8, 295.9; ICD-9: 295A–295G, 295W, 295X; ICD-10: F20) and bipolar disorder, defined according to a validated algorithm by Sellgren et al. (2011), were also identified through the National Patient Register. Individuals with autism spectrum disorders were identified through the National Patient Register and the Clinical Register for Child and Adolescent Psychiatry in Stockholm County (Lundh et al., 2012), and coded according to ICD-10 (F84) and DSM-IV (299). Individuals with ADHD were also

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http://dx.doi.org/10.1016/j.jpsychires.2013.10.001

identified through the National Patient Register (hyperkinetic disorder, ICD-10: F90), the Prescribed Drug Register, where cases were defined through treatment with stimulant (methylphenidate, amphetamine, dexamphetamine) or non-stimulant (atomoxetine) medication, and the Clinical Register for Child and Adolescent Psychiatry in Stockholm County (ADHD, DSM-IV: 314, hyperkinetic disorder, ICD-10: F90). The Prescribed Drug Register and Clinical Register for Child and Adolescent Psychiatry in Stockholm County were used in order to acquire as good coverage as possible when detecting individuals with autism spectrum disorder and ADHD.

For every Klinefelter patient, 100 control subjects (in total 86 000) matched on sex, birth year and county of residence were randomly selected from the general population. Controls had to be alive and without a diagnosis of Klinefelter syndrome at the time of the first diagnosis of the matched case. To assess the risks of schizophrenia, bipolar disorder, autism spectrum disorder and ADHD in Klinefelter patients, we estimated odds ratios and 95% confidence intervals using conditional logistic regressions. Considering the sampling procedure, odds ratios can be regarded as risk ratios.

3. Results

The number of individuals with Klinefelter syndrome, schizophrenia, bipolar disorder, autism spectrum disorder and ADHD identified from the Swedish registers are presented in Table 1.

The results from the conditional logistic regressions are shown in Table 2. Individuals with Klinefelter syndrome had 3.6–3.8 times higher risks of having a diagnosis of schizophrenia or bipolar disorder and 5.6–6.2 times higher risks of having autism spectrum disorder or ADHD, compared with controls.

4. Discussion

We found that Klinefelter patients had a nearly four times higher risk of being diagnosed with schizophrenia and bipolar disorder and an about six times higher risk of autism spectrum disorder and ADHD. These findings are consistent with most prior investigations (DeLisi et al., 1994; Van Rijn et al., 2006; Bojesen et al., 2006; Bruining et al., 2009). Given the relatively high prevalence of Klinefelter syndrome, clinicians should be aware of the possibility of the syndrome in a proportion of children with autism spectrum disorder or ADHD. If Klinefelter syndrome is detected in early ages, ethically considered intervention strategies may reduce the risk of later development of schizophrenia and bipolar disorder. Moreover, our data suggests a causal role of X chromosomal abnormalities in the liability to schizophrenia, bipolar disorder, autism spectrum disorders and ADHD, a role that should be investigated further.

As Klinefelter syndrome often remains undiagnosed (Bojesen et al., 2003), our sample contains only those that received chromosomal testing, which in Sweden is a clinical routine when Klinefelter syndrome is suspected (Stefan Arver, personal communication 2013-08-27). Hence, undiagnosed individuals with Klinefelter syndrome may not suffer from psychiatric disorders to the same extent as the identified patient population (Bojesen et al., 2006). However, although associations could be weaker in a completely representative sample, we believe that the large sample size and the robust associations observed do indicate a relationship between Klinefelter syndrome and the studied psychiatric disorders. Further, it is probable that Klinefelter patients are more likely to receive psychiatric diagnoses because they already suffer from one condition and therefore have more contacts with health care (ascertainment bias). However, in our sample, the first psychiatric diagnosis most often preceded the first Klinefelter diagnosis; thus, we do not believe that ascertainment bias explains the magnitude of the associations more than marginally. On a similar note, since Klinefelter syndrome was a hot topic in Swedish psychiatric research during the 1970s and 1980s, when genotyping of psychiatric inpatients was common, selective screening of psychiatric inpatients might have inflated the associations. However, apart from 21% of the schizophrenia cases (where diagnoses of schizophrenia preceded those of Klinefelter syndrome), none of the psychiatric cases had their first inpatient episode during the 70s or 80s. Therefore, our results are unlikely to reflect a reversed causal relation between Klinefelter syndrome and the studied psychiatric disorders.

Table 1
Number of patients with Klinefelter syndrome, schizophrenia, bipolar disorder, autism and ADHD, and the respective registers used for detection.

	Register used for detection			Overlap between registers	Total
	National Patient Register	Prescribed Drug Register	Register for Child and Adolescent Psychiatry in Stockholm		
Number of patients in each disorder group					
Klinefelter syndrome	860	n/a	n/a	n/a	860
Schizophrenia	58 334	n/a	n/a	n/a	58 334
Bipolar disorder	48 180	n/a	n/a	n/a	48 180
Autism	27 569	n/a	5783	1646	31 706
ADHD	48 024	49 788	7312	39 595	65 529

n/a = Not applicable.

Table 2
Risk of schizophrenia, bipolar disorder, autism and ADHD in a national sample of Klinefelter patients and matched controls. Estimates presented are odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

	Klinefelter syndrome		ORs (CIs)
	Yes (n = 860)	No (n = 86 000)	
Schizophrenia	11 (1.3%)	308 (0.4%)	3.6 (2.0–6.7)
Bipolar disorder	8 (0.9%)	215 (0.3%)	3.8 (1.8–7.6)
Autism	24 (2.8%)	409 (0.5%)	6.2 (4.0–9.4)
ADHD	42 (4.9%)	829 (0.9%)	5.6 (4.0–7.8)

Contributors

MC performed the analyses and wrote the first version of this manuscript. AOG contributed in the write-up of the manuscript. MB wrote the programs that the analyses are based on and HL contributed with issues pertaining to classifications of disorders. ES and NL contributed with valuable comments on the clinical significance of the results and were parts in the write-up of the final version of the manuscript. ML and PL contributed with advices regarding the study design and sampling procedure in the planning face, and were important resources in the interpretation of the results. All authors contributed to the final manuscript and have approved it.

Declaration of interest

None.