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ARTICLE

Psychiatric Characteristics in a Self-Selected Sample of Boys With Klinefelter Syndrome

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What's Known on This Subject

KS has been frequently associated with LDs, learning problems, and cognitive dysfunctions in both children and adults. Psychiatric screenings in adults with KS indicate a risk for psychotic and affective disease.

What This Study Adds

This study is the first psychiatric survey among minors with KS. Health care professionals should be aware of an increased a priori possibility of psychiatric problems, including ADHD and autism spectrum disorder, when confronted with a child with KS.

ABSTRACT

BACKGROUND. Klinefelter syndrome is the most frequent chromosomal aneuploidy with a prevalence of 1 in 700. Klinefelter syndrome has been widely associated with cognitive impairment and language problems. No previous studies have systematically investigated the association of Klinefelter syndrome with psychiatric disorders in children and adolescents. To our knowledge, the only data available are from psychiatric inventories of adults with Klinefelter syndrome.

OBJECTIVE. To explore the extent of psychiatric morbidity in children with Klinefelter syndrome.

METHOD. Fifty-one subjects with Klinefelter syndrome aged 6 to 19 years were included through the Dutch Klinefelter association and 2 university medical centers. The sample was screened by using structured and standardized assessment procedures covering the full range of psychiatric problems and disorders. In addition, all boys were formally evaluated for the presence of a language disorder.

RESULTS. A wide range of classifications could be applied, with language disorder (65% [33 of 51]) as the most prevalent disorder, followed by attention-deficit disorders (63% [32 of 51]) and autism spectrum disorder (27% [14 of 51]). Behavioral impairment was most evident among cases classified as autism spectrum disorder and psychotic disorder (12% [6 of 51]).

CONCLUSIONS. Children with Klinefelter syndrome seem to be at risk for problems in social and language development, as well as for problems in regulation of emotion and behavior. This is reflected in the broad spectrum of psychiatric classifications applicable in the present selected sample. Health care professionals should be aware of an increased a priori possibility of psychiatric problems when confronted with a child with Klinefelter syndrome. *Pediatrics* 2009;123:e865–e870

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Key Words
Klinefelter, child, language disorder, autism, ADHD

Abbreviations
KS—Klinefelter syndrome
HR—hazard ratio
DSM-IV-TR—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*
ADHD—attention-deficit/hyperactivity disorder
LD—language disorder
K-SADS-PL—Kiddie-Sads-Present and Lifetime Version
ASD—autism spectrum disorder
ADI-R—Autism Diagnostic Interview, Revised
TIQ—average total IQ
NOS—not otherwise specified

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In previous decades, there has been ongoing concern about the cognitive and behavioral phenotype of Klinefelter syndrome (KS).[1] KS is caused by 1 or more supernumerary X chromosomes in males.

A recent study suggested that the prevalence of KS has increased over previous decades from 1.09 to 1.72 per 1000 male births based on newborn surveys.[2] Many cases remain undiagnosed because of substantial variation in clinical presentation.[1] Only 10% of subjects with KS are diagnosed prenatally, with another 25% diagnosed during childhood or adulthood, leaving 65% undiagnosed.[3,4]

In adults, the cognitive defects in KS seem specific and are not caused by a global decline in intellectual functioning.[5] Most men with KS perform normally on nonverbal abilities and overall intelligence but are specifically impaired on measures of language skills.[6,7] The majority of males with KS (up to 70%–80%) suffer from a language disorder (LD) of some form at all ages. Significant impairments are frequently observed in higher order aspects of expressive language, especially in deficits with word retrieval, expressive grammar, verbal processing speed, and executive abilities.[5,8] Furthermore, social cognition in adult KS is often marked by inadequate emotional arousal.[9]

A recent study expanded on the description of the cognitive phenotype of KS in a sample of 50 children.[10] Specific

language, academic, attention, and motor abilities were impaired in this sample. Vocabulary and meaningful language understanding were unaffected, although higher linguistic competence was impaired. Younger children displayed deficits in sustained attention without impulsivity.

To date, no systematic studies have investigated whether such cognitive and learning problems are associated with psychiatric disorders in children and adolescents with KS. Systematic psychiatric surveys were explicitly advocated in a National Institutes of Health 2003 report on "The expansion of the Klinefelter phenotype and the identification of new research directions."[11]

Data on psychiatric screenings in adult KS emphasize the need for such screenings in minors with KS. A psychiatric screening among 31 adult subjects with KS showed a high prevalence of psychosis (6.4%) and depression (19.4%).[12] A survey of hospital admissions among adults with KS in Denmark ($N = 832$) showed that the hazard ratio (HR) for admission for psychiatric disorders was second highest of all diagnosis groups (HR: 3.65), in particular for psychoses (HR: 4.97).[13]

With this present study we aimed to provide insight into what psychiatric problems might occur during development once the diagnosis of KS has been made. A screening in 51 self-selected school-aged children with KS was performed by using structured assessment procedures to encompass a wide range of psychiatric problems and disorders. To confirm the earlier established association of KS with language problems, all boys were evaluated for the presence of a LD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria. Furthermore, the relationship of IQ with psychiatric problems was evaluated.

METHOD

Patients

The sample consisted of 51 boys (mean age: 12.2 years [range: 6–19 years]; 27 subjects aged <12 years, 17 subjects aged 12–16 years, and 7 subjects aged 16–19 years). The inclusion criteria for the current study demanded an age between 6 and 20 years, no history of closed head injury or neurologic illness, sufficient comprehension of the Dutch language, and a diagnosis of KS confirmed by standard karyotyping. Mosaic forms of the syndrome were allowed ($n = 4$), whereas higher aneuploidies than 47,XXY were excluded because of their association with profound mental retardation.[14]

The Dutch Klinefelter association and 2 centers for clinical genetics and pediatrics situated in the center of the Netherlands were involved in recruiting the children for this study. A newsletter presented on the Internet or in writing informed parents and children of the aim and methods of the study. Parents and children had to apply actively for participation in the study by contacting the research team.

Subsequently, they were sent written information about the selection criteria and the implications of participation in the study. The newsletter encouraged parents and children to participate regardless of any problems present. They were invited for assessment if they met the inclusion criteria. The Dutch Central Committee on Research Involving Human Subjects approved the research protocol. Written informed consent was obtained from participants (if >12 years of age) and their parents or guardians.

Half of the boys (26 of 51) were diagnosed with KS through prenatal amniotic fluid investigation. The boys diagnosed with KS after birth (25 of 51) had different combinations of symptoms that had led to cytogenetic testing. The majority of the group diagnosed after birth suffered from marked hypogonadism (22 of 51) in combination with learning problems (9 of 25) and/or unspecified behavioral problems (9 of 25). Other reasons for suspicion on KS were tall stature with severe allergies or asthma. At the time of the assessments, 14 boys were treated with testosterone and 4 received other medication (atypical antipsychotics [$n = 1$], antiepileptics [$n = 1$], and stimulating compounds [$n = 2$]).

Procedure and Measures

Assessments were conducted at the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht. One investigator (Dr Bruining) performed all psychiatric interviews and observations of the subjects. He is a senior resident in child and adolescent psychiatry. Fully trained child psychologists conducted the psychological examinations (eg, IQ tests).

Initially, a comprehensive medical and behavioral history was obtained from the children. All interviews were videotaped.

The classification for LD was applied on the basis of the DSM-IV-TR criteria with the exception that we allowed a concurrent pervasive developmental disorder. Individual measures of language development and academic achievement were obtained from preexisting records. Language disorders were not subtyped (eg, mixed receptive-expressive and expressive LDs). One combined category of LDs is listed in the Results.

The Kiddie-Sads-Present and Lifetime Version (K-SADS-PL)[15] interview was administered to assess diagnoses in the domains of affective, psychotic, anxiety, and behavioral disorders. The interview is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* and the DSM-IV-TR criteria. Probes and objective criteria are provided to rate individual symptoms.

The presence of an autism spectrum disorder (ASD) was assessed using the Autism Diagnostic Interview, Revised (ADI-R).[16] No subtypes of ASDs (eg, pervasive developmental disorder-not otherwise specified [NOS], Asperger syndrome, autism) were allocated subordinate to a general ASD diagnosis, because no replicable measures exist for such phenotypic refinements. The interviewer (Dr Bruining) was certified for the assessment of the ADI-R. The ADI-R focuses on the 3 core or so-called content domains of autism (ie, social interaction, communication, and stereotyped behaviors).[17] ADI-R items

TABLE 1 Psychiatric Classifications According to the DSM-IV-TR

DSM-IV-TR Diagnosis	Prevalence in Present Study, % (*n*)	Prevalence in General Population, %[a]	TIQ	VIQ	PIQ
LD	65 (33)	2–19[23]	78	77	85
ADHD	63 (32)	5.3[24]	80	79	85
ADHD-IS	43 (22)				
ADHD-CS	20 (10)				
ASD	27 (14)	0.6–1.6[25]	77	75	82
Depressive disorder	24 (12)	9.5[26]	85	84	90
Generalized anxiety disorder	18 (9)		83	82	89
Separation anxiety disorder	14 (7)		84	79	92
Psychotic disorder NOS	8 (4)		85	83	91
Schizophrenia	2 (1)	0.14–0.46[27]	73	79	72
Schizoaffective disorder	2 (1)		101	101	103
Whole cohort	100 (51)		80	78	86

VIQ indicates average verbal IQ; PIQ, average performance IQ; ADHD-IS, inattentive subtype; ADHD-CS, combined subtype.

[a] Prevalence in general population (eg, percentages for underaged populations).

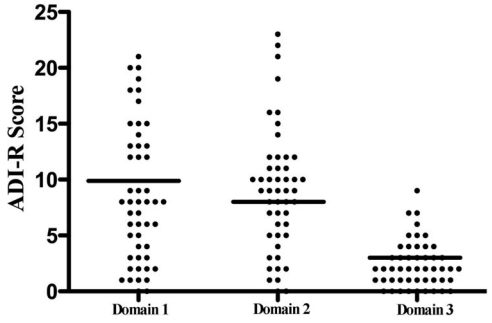

FIGURE 1

ADI-R scores in the sample for all 3 core domains. Horizontal lines depict ADI-R autism cutoff values for each domain. Domain 1: qualitive abnormalities in social reciprocity (cutoff = 10); domain 2: qualitive abnormalities in communication (cutoff = 8); domain 3: restricted, repetitive, and stereotyped patterns of behavior (cutoff = 3).

are coded and converted to numerical scores for these domains and also for an "age-of-onset" domain. A classification of an ASD is applied when scores in all domains are met or when scores are met in 2 core domains and meet criteria on the age-of-onset domain, but are 1 point away from meeting autism criteria in the remaining core domain. Reliability of the ADI-R in a population with mild to moderate mental retardation has been established.[18] Furthermore, the ADI-R proved valuable in studies with populations with genetic syndromes such as the 22q11 deletion and Angelman and Prader Willi syndromes.[19–21]

IQ was assessed by using the Dutch adaptation of the Wechsler Intelligence Scale for Children and in some cases the Wechsler Adult Intelligence Scale, resulting in average total IQ (TIQ) scores with verbal and performance scale scores.[22]

After the completion of all the tests and interviews, the videotapes of all subjects and the outcomes were discussed in a consensus meeting headed by the head of the department (Dr van Engeland). The consensus meeting served to control for procedural mistakes and to verify whether the classifications through the K-SADS-PL interview and ADI-R were in agreement with our clinical judgment.

No classifications were applied for any disorder without threshold scores in the ADI-R or K-SADS-PL interviews. Current DSM-IV-TR guidelines prescribe not to apply particular diagnoses next to an ASD (eg, attention-deficit/hyperactivity disorder [ADHD], LD, schizophrenia, and schizoaffective disorder). However, we assessed all classifications separately regardless of comorbidity rules to provide a complete representation of psychopathology and psychiatric symptoms within the selected group. The concurrence of the most prevalent classifications in the cohort is described in "Results."

RESULTS

Table 1 summarizes the psychiatric classifications for the sample with subsequent intelligence scores.

The DSM-IV-TR criteria for the combined group of expressive or mixed receptive-expressive LDs were met in 65% (33 of 51) of the participants.

The application of the K-SADS-PL interview yielded the following results: 63% (32 of 51) of the subjects were classified as having ADHD, of which 43% (22 of 51) could be classified as having the predominantly inattentive subtype, and 20% (10 of 51) were classified as having the combined subtype.

Twenty-four percent (12 of 51) of the subjects had suffered from a depressive episode. Eighteen percent (9 of 51) fulfilled the criteria for generalized anxiety disorder in the present or the past, and 14% (7 of 51) had suffered from separation anxiety disorder at a younger age.

Psychotic disorder NOS was found in 8% (4 of 51) of the subjects. These boys showed psychotic symptoms, accompanied by a circumscribed period of clear distress in which an obvious change of behavior was observed. Another 2 subjects (4% [2 of 51]) suffered from multiple psychotic episodes with chronic distress and decline in functioning, despite intensive inpatient and outpatient treatment. One of these 2 boys fulfilled the criteria of a schizoaffective disorder. The other boy met the criteria for schizophrenia, disorganized subtype.

Psychotic symptoms were reported in 45% (23 of 51) of the subjects. These were predominantly auditory hallucinations and paranoid delusions. The psychotic symptoms by themselves did not cause obvious distress or decline in general functioning, except in subjects with a full psychotic disorder (ie, psychotic disorder NOS, schizophrenia, and schizoaffective disorder).

The ADI-R revealed that 27% (14 of 51) of the boys met the threshold for an ASD. In all of these cases, the diagnosis of an ASD was confirmed in the consensus meeting.

Fig 1 gives an overview of the symptom scores in the 3 core domains measured in the ADI-R. Ten subjects had scores above the cutoff values in all 3 core domains of the ADI-R, 11 had scores above the cutoff values in 2 domains, and 13 subjects in 1 of 3 ADI-R core domains, leaving 17 individuals with no autistic threshold scores in any of the domains. The autism threshold for the

TABLE 2 Clustering of LD, ADHD, and ASD

	Language Disorder		No Language Disorder		Total
	ASD	No ASD	ASD	No ASD	
ADHD	7	11	5	9	32
No ADHD	2	13	0	4	19
Total	9	24	5	13	51

ADHD: subtypes combined to 1 group.

communication domain was most frequently exceeded, in 61% (31 of 51) of the cases, when assessing the domains separately.

All 6 boys with KS who were diagnosed with a psychotic disorder (eg, psychotic disorder NOS, schizophrenia, schizoaffective disorder) also met the criteria for ASD.

All subjects with ASD displayed noticeable behavioral impairment before the age of 5 years. Psychotic disorders did not manifest before the age of 12 years. The onset of the other classifications was not related to age and was evenly distributed in the sample (6–19 years).

In all subjects with an ASD classification, the parents had sought professional guidance for behavioral and/or social problems. The parents generally perceived individual LDs and ADHD as mild impairment, and only a minority had requested psychiatric consultation. However, the majority of subjects, 69% (35 of 51), were attending special education facilities at the time of assessment.

Mean TIQ score was 80 (range: 59–121), mean performance IQ score was 86 (range: 61–125), and mean verbal IQ score was 78 (range: 55–112). Of the 25 individuals with TIQ scores of <80, 72% (18 of 25) had at least one psychiatric classification according to the DSM-IV-TR, in comparison to 21 of the 26 participants (21 of 26 [81%]) with TIQ scores of >80. IQ measures did not correlate with specific types of psychiatric classifications (multivariate analysis of variance).

Table 2 shows the co-occurrence of the 3 most prevalent classifications found (ie, ADHD, LD, and ASD). Twelve of the 14 boys with an ASD also met the criteria for ADHD, and 9 of 14 boys with ASD also suffered from a LD. Furthermore, 7 boys met the criteria for all 3 disorders (ASD, ADHD, and LD). Twenty-two individuals were comorbid for LD and ADHD without a diagnosis of ASD.

The 4 subjects with a mosaic karyotype also met the criteria for ≥1 psychiatric classification, including ASD and depressive disorder.

DISCUSSION

Several psychiatric classifications could be applied in this sample of 51 boys with KS. In concordance with the literature, a high prevalence of LDs (65%) was found. Further prevalent psychiatric classifications were ADHD (63%) and ASD (27%), with markedly higher prevalences than described for the normal population. Intelligence of the subjects did not affect the prevalence of classifications within the sample, with average IQ scores in the sample slightly lower than described in other studies.

The psychiatric outcome was not influenced by age except with psychotic disorders, which were exclusively observed in subjects aged 12 years or older. This is in accordance with the literature stating that psychoses at a younger age are extremely rare.[28]

Classifications of ADHD, ASD, and LD seemed to cluster in our sample of boys with KS. Language disorders have been frequently associated with ASD without KS.[29] An overlap of ADHD with ASD in samples of other children with psychiatric disorders has been described before.[30,31]

All children and adolescents in the present study with a psychotic disorder NOS (n = 6) were comorbid for ASD. In general, earlier studies have described an overlap of autistic symptoms with early features of schizophrenia or psychotic disorder.[32,33] Specific association between ASD and psychotic risk in adult KS is supported by the findings of van Rijn et al.[34,35] Their cohort of 32 adult men with KS showed high scores on the Autism Spectrum Questionnaire,[36] an instrument that measures autistic traits, as well as elevated scores on the Schizotypical Personality Questionnaire,[37] an indicator of genetic vulnerability to schizophrenia. In addition, van Rijn et al described high levels of social cognitive deficits and subsequent social behavioral dysfunction in the same KS cohort.[9,34] They suggested that the social cognitive deficits could be associated with high risk for autism and schizophrenia in KS. The concurrence of ASD and KS has incidentally been described before in 7 case studies.[38–42] Schizophrenia in adults with KS has been reviewed and studied by DeLisi et al.[43,44] The prevalence of KS with schizophrenia in their review of cytogenetic screenings in adult psychiatric cohorts (numbers ranging from 60–6000) was ~4 to 6 times higher compared with the general population rate. However, Mors et al[45] did not find an association of KS with schizophrenia. Future studies should provide insight into the structure and development (eg, longitudinal studies) of psychiatric problems in children with KS.

Limitations of the present study should be taken into account. The sample consists of self-selected children who were already diagnosed with KS, and the findings cannot be generalized to all children and adolescents with KS. In addition, it must be understood that the classifications in our research sample were primarily derived by the use of standard instruments. The classifications found do not naturally reflect requested help by the parents, notably in the cases of individual LD and ADHD. The advertisements for the current study aimed to invite participants regardless of any problems or illness present. However, it is likely that parents who experienced problems in the upbringing of their children were more willing to participate in the study. The knowledge of parents and teachers of the child's KS karyotype might influence the environmental expectations and attitudes toward these children, possibly resulting in a biased observation from our part. In this sample, however, no clear differences in prevalence of psychiatric problems were found between the group di-

agnosed with KS before birth and the groups diagnosed later in life (results not shown).

Although structured procedures and quantification of symptom scores were used, it would have been preferable if the child psychiatrists had been blind to the genetic make-up of the child. This is practically difficult given obvious somatic features in some cases of KS.

With regard to the specific diagnosis of an ASD, the administration of a standardized observation in addition to the structured interview method of the ADI-R, such as the procedure according to the Autism Diagnostic Observation Schedule,[46] would have strengthened the assessment procedures.

CONCLUSIONS

The present study reveals that normal functioning in children and adolescents with KS might be challenged because of the risk of serious developmental psychopathology. Impairments in the areas of communication, socialization, and disorganized behaviors may be present in boys with KS. This makes them liable to isolation and emotional problems that may require guidance and treatment.

Clinicians should be aware of the possibility of KS in a child with psychiatric problems. Specific behavioral problems might trigger suspicion of KS. A language-based learning disability with physical features of KS should justify karyotyping in a child given the high prevalence of the syndrome, especially if social problems and difficulties with behavior regulation are present. Pediatricians should have a low threshold for obtaining a karyotype in children with autism and/or ADHD, particularly in boys who are tall.

It must be emphasized that only 10% to 25% of the expected diagnoses of KS are made before puberty.[5,6] It is as yet unknown whether the large contingent of subjects with undiagnosed KS is largely unaffected by psychiatric disorders. On the basis of the findings in the present self-selected sample, we recommend that all children with KS be examined by a child psychiatrist, which may prevent delay of treatment and may possibly protect these children from adverse environmental influences. Screening for behavioral and cognitive/learning problems in all children with KS is recommended, preferably before the age of 10 years. Early detection could improve the prognosis of psychiatric problems, some of which may be alleviated by medication or other timely interventions.

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