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ORIGINAL CONTRIBUTION

P. Jha
D. Sheth
M. Ghaziuddin

# Autism spectrum disorder and Klinefelter syndrome

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P. Jha · D. Sheth · M. Ghaziuddin (✉)
Division of Child Psychiatry
University of Michigan Hospital
200 East Hospital Drive
Ann Arbor, MI 48109-0277, USA
E-Mail: mghaziud@umich.edu

**Abstract** *Background* Autism is a severe handicapping disorder of early childhood characterized by a distinct pattern of social and communication impairment with rigid ritualistic interests. In about 10–25% of cases, it is associated with known medical conditions. Population-based studies of autism have found that Klinefelter's syndrome (KS), a common chromosome abnormality, is sometimes associated with autism. However, few detailed case descriptions of patients with KS and autism have not been published. *Case Report* In this paper, we describe the occurrence of autistic features in two cases of Klinefelter syndrome, one with the typical XXY karyotype and the other with the XXYY variant. *Conclusion* Autistic features may be more common in persons with Klinefelter syndrome than generally believed. We propose that all patients with KS should be screened for the presence of autism.

**Key words** autism – chromosomes – klinefelter syndrome

## Introduction

Autism, a handicapping disorder of early childhood characterized by a distinct pattern of social and communication deficits, is associated with known medical conditions in about 10–25% of cases. One such condition is Klinefelter syndrome (KS), a chromosomal abnormality characterized by an additional X chromosome [10]. A relatively common condition with a prevalence of one in 600 live male births, its symptoms consist of infertility; hypogonadism; and an increased secretion of the follicle-stimulating hormone [13]. While 47 XXY is the most common type, variants of the condition with differing numbers of X or Y chromosomes have also been described [17]. Generally, the higher the number of chromosomes present, the more severe the phenotype.

Studies of KS have shown high rates of psychiatric symptoms and learning disabilities [12]. Geschwind et al. [8] found that boys with KS performed poorly in school, and as adults, attained lower occupational status compared with matched controls. This, however, was not due to low IQ because most had a variable range of cognitive abilities. A consistent finding was a significant difference between performance IQ and verbal IQ, with a lag in the verbal IQ. A variety of major psychiatric disorders have also been described including schizophrenia and bipolar disorder [2, 18].

While most research on KS has focused on the typical XXY genotype, a few reports have also described its variants. For example, Harkulich and colleagues [11] described an 8-year-old child with the XXYY syndrome and gross language and motor impairment. He was passive, shy, and introverted. On

the WISC test, his verbal IQ was 58; performance IQ was 67 and full scale IQ was 59 [9]. Borghgraef and colleagues [4] described four patients with the XXYY syndrome, ranging in age from 4 to 25 years. All had severe speech problems, including a history of language delay. In addition, they were shy and aloof with poor eye contact; and an IQ in the moderate to mildly retarded range.

Epidemiological studies of autism have commented on the association between autism and KS [see 11]. However, few detailed case-descriptions have been published. Merhar and Manning-Courtney [16] described two boys with XXY syndrome, autism, and suspected seizures. In this report, we extend the literature on the behavioral aspects of KS by describing two cases, one with the typical XXY karyotype and the other with the XXYY variant.

## Case 1

Patient SR, a 16-year-old Caucasian youngster, presented with depressive symptoms. He gave a six-month history of depressed mood, increased tearfulness, social withdrawal, disturbance of sleep and appetite, impaired concentration, and disruptive behavior at school. He had no previous psychiatric history. His medical history was unremarkable.

Developmental history revealed an uncomplicated pregnancy and delivery. He reached his milestones at the expected time. Due to falling grades, he was tested in his ninth grade and was found to be delayed in his reading skills. He had a long history of social deficits. He was shy and aloof; and somewhat immature for his age. He did not like to be away from his parents. He had an excessive interest in Leggos and puzzles, and would spend hours playing with them. He had a huge collection of these objects, which he insisted on displaying in a certain way. He was also fond of collecting souvenir pens. These, too, had to be displayed in a certain manner, and placed in certain positions. He would get upset and anxious if these were misaligned. There was no history of stereotypic behaviors or abnormal movements. His father, too collected souvenir pens and was described as rather rigid. His mother had a history of depression and his brother of ADHD. Examination revealed a thin adolescent male of average height with prominent facial acne. There was no gynecomastia. Genital examination was normal. His facial expression was limited and his eye contact inconsistent. His speech was decreased in tone and volume; with a slight delay in initiating responses. He admitted to feeling depressed and had a poor view of himself and of his future.

Patient SR was diagnosed with a depressive illness. In addition, he had social deficits with intense interests, and mild communication deficits. Due to this reason, his parents were administered the Autism Diagnostic Interview, revised version (ADI-R), by one of the investigators (MG). While he did not meet the full cut-off for autism on the ADI, he fell within the spectrum of pervasive developmental disorders, and was, therefore, given a diagnosis of pervasive developmental disorder not otherwise specified (PDDNOS) [1]. In view of this diagnosis, a chromosome analysis was performed which revealed an XXY karyotype.

## Case 2

JW, a 9-year-old Caucasian male, was referred with a history of aggressive outbursts. He had recently tried to cut himself and threatened to hurt his mother and his younger brother. Although he had never been hospitalized for behavioral problems, he had received outpatient treatment since the age of five years. His aggressive symptoms started at the age of four years, coinciding with the birth of his younger brother. He reportedly became irritable and anxious, afraid of being separated from his parents. Apart from a diagnosis of separation anxiety disorder, he carried a diagnosis of attention deficit hyperactivity disorder.

His father suffered from depression. JW's paternal cousin had a chromosomal abnormality (deletion 1) and mental retardation; another paternal cousin had a seizure disorder. Other details about the paternal cousins were not available. JW's 4-year-old brother was born with transposition of the great arteries, which was surgically corrected.

He was born by Cesarian section after a full term delivery. His speech was mildly delayed. He had always been 'clumsy and uncoordinated.' At three years of age, he was noted to be anxious, aloof, and clinging in his behavior. When he started kindergarten at the age of four years, his teachers commented that instead of interacting with the other children, he preferred to stand apart and watch them. He had no close friends and had difficulty with transitions. He was also sensitive to certain textures, such as the feel of his underwear, and did not like gritty foods. He had to repeat his first grade and received remedial help. As he grew older, his deficits in reading and mathematics became more apparent. At the age of eight years, he showed a verbal IQ of 82, performance IQ of 78 and full scale of IQ of 78. At the age of 6–7 years, he developed facial acne and axillary hair. A diagnosis of precocious puberty was made. However, a comprehensive assessment performed by the endocrinologist was negative. His testosterone level was normal. His MRI showed T2 flare hyperintensities within the periventricular and deep subcortical white matter, which were read as normal variants by the neuroradiologist.

On examination, he had poor eye contact. Although he denied feeling depressed, his facial expression was flat, and his affect restricted. He was slow in his verbal responses. While he had no abnormal movements, such as, rocking or hand-flapping, he had a tendency to repeatedly pull his hair. He was in the 95th percentile for his height and weight. His hands showed bilateral 5th finger clinodactyly. Apart from prominent facial acne, his skin showed two small café au lait spots, one on his left axilla and another on his back. His neurological examination was normal. Based on the above findings, a diagnosis of pervasive developmental disorder was considered. The points in favor of this diagnosis were: a history of reciprocal social deficits; problems with nonverbal communication; difficulty with transitions and a desire for sameness; a history of increased sensitivity to certain textures etc. Since the 'onset' was not clear and since the symptoms were not marked, a diagnosis of PDDNOS was given. A cytogenetic examination revealed 48 chromosomes with the XXYY karyotype, a variant of KS. A DNA analysis for fragile X syndrome was negative.

## Discussion

This case report describes the presence of autistic features in two subjects with KS. One patient had the typical XXY karyotype while the other had its variant, the XXYY syndrome. Although the cases differed in the number of X chromosomes, their presentation was remarkably similar. Both had subtle problems with social skills that escaped detection in their early childhood. Both were shy and socially awkward, with a history of immature behavior, including problems separating from their significant care-givers. They were often teased and picked on by their peers. Although they fell within the autistic spectrum, neither met the full criteria for autistic disorder based on the onset; severity; and the range of symptoms. This is consistent with the suggestion that patients with chromosomal abnormalities are more likely to show autistic-like behaviors than the full-blown syndrome of autism [19].

Several studies have speculated on the role of the X chromosome on social development. Patients with Turner syndrome, who have the XO karyotype, show social deficits and problems with reading facial and emotional cues [21]. Evidence also comes from animal studies. For example, in a study of adult XXY mice, Lue and colleagues [14] showed that the mice had deficits in learning and memory similar to those seen in males with Klinefelter syndrome [14]. They evaluated the acquisition of a Pavlovian tone-food association and demonstrated that XXY mice were slower compared with their XXY littermates. The authors speculated that the cause of the behavioral impairment of XXY mice could be due to several factors, such as, low plasma testosterone levels; defect of androgen receptors; or overdose X-linked gene expression in specific brain regions, such as the medial temporal lobes [14]. Van Rijn and colleagues (2006) examined 32 XXY men and 26 controls from the general population. Compared to the controls, XXY men showed a variety of social and cognitive deficits. The authors proposed that these deficits increased the risk of autism and schizophrenia [24]. Imaging studies have shown reduced brain volumes and enlargement of the ventricles; localized volume reduction has also been found in the insula; temporal gyri; and the amygdale [20]. These localized brain changes are consistent with the language-based learning deficits found in patients with the XXY syndrome [9]. The high male-to-female ratio in autism spectrum disorders suggests the involvement of the X-chromosomes. Variants in the genes located on the X-chromosome, such as the neuroligin genes which help in synaptogenesis, have also been investigated in the etiology of autism. However, molecular genetic studies have generally yielded negative results [10, 22, 25].

It is not clear how many subjects with KS or its variants develop autistic features. However, they often show a range of deficits, which may increase the risk for autism. For example, language deficits in KS are first seen as a delay in early expressive language and speech milestones [6]. In the primary school years, difficulties in articulation, word-finding, and phonemic processing become apparent. The disparity between individuals with KS and controls with regards to their language-based tasks increases with age so that by 18–20 years, they are several grade levels below their peers [13–15].

Deficits in social skills also form an integral part of KS. Patients are generally described as introverted, quiet, non-assertive, anxious, and socially withdrawn [8, 12]. Some show marked impulsivity and socially inappropriate and intrusive behaviors, which may be linked to their problems with attention and executive functioning. Based on the performance on tests of executive functioning, Temple and Sanflippo [23] suggested that the addition of an X chromosome had a selective effect on the cognitive phenotype of the patients. Geschwind and colleagues [7, 8] reported a distinct impairment in both executive problem-solving skills and information processing speed. Other deficits include a tendency to low verbal and high performance IQ on tests of intelligence, problems in verbal processing, and deficits in motor dexterity [3].

While patients with KS often show problems with language and social skills, they do not seem to have

restricted interests, one of the core features of the autistic triad. Merhar and Manning-Courtney [16] recently described two boys with XXY syndrome and suspected seizures. Although both met the DSM-IV criteria of autistic disorder, it is not clear if they had a range of restricted interests. However, it is possible that these symptoms are often missed. It is conceivable that some of the odd and, sometimes antisocial, behaviors shown by persons with KS may be due to their restricted interests. For instance, Eytan and colleagues [5] described a 47-year-old male with the XXY syndrome who had a history of fire-setting in the context of social deficits and speech abnormalities. Although a diagnosis of schizophrenia was considered, the childhood-onset history of social and communication problems made the diagnosis of a pervasive developmental disorder more likely [5].

To conclude, patients with KS syndrome may be at an increased risk of developing autistic features. Population-based studies of large numbers of subjects with KS and its variants are necessary to examine the association of autism and KS. From a clinical standpoint, patients with KS—and its variants—should be carefully examined for the presence of autism.

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