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Variability in Cognitive Behavioral Phenotypes in Klinefelter Syndrome (KS) and Other Sex Chromosomal Aneuploidies (SCAs)

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Abstract

Sex Chromosomal Aneuploidies (SCAs) are the most frequently occurring chromosomal abnormalities with an incidence of 1 in 450 births. Males with SCAs are known to have variability in their developmental profile. Aim of this paper is to illustrate clinical variability in the different SCAs. The sample was composed by 53 subjects (mean age=21.16 years, range: 13-54) with karyotype 47, XXY (73%), 49, XXXXY (7%), 48, XXYY (9%), mosaicism 47, XXY/48, XXXY (2%), 47, XYY (5%), 48, XXXY (2%), 49, XXXYY (2%). Only 5 subjects have been diagnosed prenatally (4 KS and 1 XXYY). Primary caregivers completed a comprehensive questionnaire detailing birth, medical, developmental and psychological history. Cognitive and behavioral assessment was performed with clinical interviews with DSM IV criteria and psychometric questionnaires (WISC-R, WAIS-R, CPM, Token Test, VABS, SCL90, and SCQ). Twenty-one sex and age matched subjects karyotypically normal were also evaluated from the behavioural point of view. Mean IQ in typical KS was 87.45 ± 2 ds (sd=20.12) range 45-123, VIQ 91.74 (sd=19.55) range 50-130 and PIQ 86.87 (sd=20.87) range 50-126. Mean IQ in other SCAs was 68.71 (sd=20.81) range 45-106, VIQ 69.36 (sd=21.97) range 47-113 and PIQ 74.72 (sd=21.70) range 45-112. In CPM KS subjects scored 27.75 (range 13-36) and 31.50 in the Token Test (range 21-35) while in CPM the other SCAs subjects scored 22.27 (range 10-35) and 22.50 (range 9-31) in the Token Test ($p<0.05$). VABS scores documented more marked impairment on adaptive behavior in atypical SCAs subjects. SCL90 documented an elevation of paranoid scale in the 70% of KS subjects and 50% of other SCAs. Autistic traits were present in 67% of the other SCAs subjects and in the 18% of KS at the SCQ. A precise identification of the cognitive and behavioral phenotype in different SCAs may enhance the clinical treatment, anticipatory guidance, and care throughout the lifespan.

Keywords: Klinefelter; Sex Chromosomal Aneuploidies (SCAs); Cognitive and behavioral phenotype; Klinefelter's Syndrome (KS)

Introduction

Klinefelter's Syndrome (KS), described for the first time in 1942, is a genetic non-inherited pathology which is caused by an alteration of the number of sex chromosomes in male subjects. Patients affected by this syndrome have 47 chromosomes, due to the presence of one supernumerary X chromosome. This genetic anomaly influences sexual development and physical appearance, cognitive functions, motor and language development, and social skills. Cognitive abilities are typically in the average to low average range with weaknesses in verbal skills. Language difficulties are one of the most distinctive traits in cognitive functioning of people with KS. In fact, KS show an increased risk for developmental delays, speech-language disorders and learning disorders. Limitations in communication and behavioral aspects markedly affect social adaptation and the development of personality.

This prominent effect of the extra X chromosome on cognition, particularly in the language domain [1], has been documented also by fMRI studies. Measuring the patterns of brain activity during language processing in KS men, it was shown that language activity in the brain was less lateralized in the experimental group as compared to controls. It revealed an increased activity in the right hemisphere rather than reduced activity in the left hemisphere that causes a loss of asymmetric processing of language. The regions mostly involved were the Superior Temporal Gyrus (STG) and the supramarginal gyrus region, which is close to the posterior section of the STG and part of Wernicke's area. Reduced language laterality in the STG was highly correlated with the degree of disorganization of thought and language. Decreased functional asymmetry of language areas in the brain in XXY men may be secondary to abnormal X chromosomal inactivation [2].

Moreover, subjects with KS are predisposed to psychopathological risk. Behavior can include hyperactivity, attention problems, impulsivity, aggression, mood instability and autistic traits. In particular, Books [3] observed the presence of a great variability of symptoms in a group of KS boys: learning disorders (65%), ADHD (63%), depressive disorders (24%), psychotic disorders (8%) and schizophrenia (2%). The risk of hospitalization for psychosis in adults KS is greater than in control subjects [4].

Some problems appear after the onset of puberty, when physical differences in KS become more evident and might result in body image disorders, sense of isolation and shame. Low self-esteem, anxiety, problems of socialization and mood disorders occur in boys with KS during adolescence [5]. The presence of learning difficulties at school, mild cognitive impairment, problems in achieving good academic results often cause feelings of distrust even in childhood. The lack of integration within the peer group is the major source of anxiety and mood disorders. Many of the KS subjects seem to be more sensitive, anxious and insecure, and show a higher incidence of anxious-depressive disorders than the general population and an increased propensity to the use of drugs [5]. Some studies have emphasize that

people with KS are friendly and open to interactions, do not usually have major problems with social interaction and adaptation, although they may be shy, sensitive and unassertive [6,7]. Other studies have showed that males with KS have difficulties in the construction of satisfying social relationships, with antisocial behavior in adolescence and a more unstable occupational history, but a minority of them meets criteria for antisocial behavior disorder in adult hood [8].

KS is characterized by a constellation of physical symptoms: Inadequate virilization, hypogonadism, azoospermia, infertility, gynecomastia, elevated average height (179.2 ± 6.2 cm) and increased plasma gonadotrophins [9,10]. These problems are progressive and they begin to appear with more evidence during adolescence, in correspondence of sexual development.

Aneuploidy 47, XXY is the most common abnormality of sex chromosomes in humans; with an incidence equal to 1/450 male live births. About 80% of the KS patients show an XYY karyotype, but the 20% have other numeric sex chromosomes abnormalities (48, XXXY, 48, XXYY, 49, XXXXY, 46, XY/47, XXY mosaicism) or structurally abnormal sex chromosomes [11]. As the number of X chromosomes increases, the phenotypic severity increases as well and it is estimated that cognitive abilities decrease by 10–15 IQ points for each additional X chromosome [12].

The presence of one or more additional X chromosome(s) above the typical 46, XY in males leads to testicular dysgenesis and hypergonadotropic hypogonadism, and thus, 48, XXYY, 48, XXXY and 49, XXXXY are considered 'variants' of KS (47, XXY) because of these shared features. However, the increased risks for congenital malformations, additional medical problems and more complex psychological involvement in these other Sex Chromosomal Aneuploidies (SCAs) make distinction from 47, XXY important for these patients [12].

47, XXY (KS) is associated with tall stature, with studies reporting a mean adult height ranging from 179 to 188 cm. This characteristic is also of 48, XXXY and 48, XXXY males, in contrast, stature in males with 49, XXXXY syndrome is usually below average. A hypothesis is that the influence of extreme over dosage of sex chromosome genes in the pentasomy condition, affects multiple organ sites and growth pathways. Considering again the body habitus, other SCAs vary from being underweight to obese, and only approximately 30% have gynaecomastia which is usually mild.

The degree of facial dysmorphism in all three syndromes is variable and often subtle, although dysmorphic features are typically more distinct in 49, XXXXY compared with 48, XXYY and 48, XXXY. Across all three conditions, common findings include hypertelorism, epicanthal folds, up-slanting palpebral fissures, hooded eyelids, significant dental problems. All of the findings above have also been described in 47, XXY, but they occur more frequently in other SCAs.

Developmental delays are common in infancy and early childhood, with speech delays, especially in expressive language, and motor delay associated with hypotonia, in almost all patients.

Visootsak et al. [7], using an adaptive functioning assessment (Vineland Adaptive Behavior Scales) in SCAs subjects, found that the mean standardized scores for adaptive functioning were in the disability range.

Other neurodevelopmental and psychological disorders are significant components of the phenotype of other SCAs and are typically more severe and/or complex when compared with typical KS. Developmental dyspraxia contributes to the early language and motor deficits. Attention Deficit Hyperactivity Disorder (ADHD) is present in over 70% of them, significantly higher than typical KS.

At the end, some emotional symptoms, as emotional immaturity, anxiety symptoms, obsessive-compulsive behaviours, impulsivity, behavioural dysregulation and tic disorders, are more commonly seen in these conditions compared with typical KS.

There is still little of knowledge about the cognitive behavioral phenotype of other SCAs. It's sure, anyway, that these patients are considered as a heterogeneous group with different and distinctive characteristics from typical KS. The focus of interest in the study of SCA was the genetics and the neurodevelopmental risk. Accumulating evidence that such genetic conditions not only impact physical development, but also psychological development, increased the awareness of the importance to study also psychological, emotional and behavioral problems [2]. The aim of this research is to compare a group of KS subjects and one with different SCAs, considering cognitive behavioral phenotype. In fact, some studies found that the number of supernumerary X negatively correlated with intellectual development and an increase of symptoms [13]. Moreover, we considered the history of epilepsy, autistic traits and psychosis as important variable of distinction between the two groups. We hypothesize that the other SCAs show more cognitive impairment and more developmental problems than typical KS.

Methods

The sample was composed by 53 adolescents and adults (mean age=21.16 years, range: 13-54) with karyotype 47, XXY (73%), 49, XXXXY (7%), 48, XXYY (9%), mosaicism 47, XXY/48, XXXY (2%), 47, XYY (5%), 48, XXXY (2%), 49, XXXYY (2%) (Figure 1 and Table 1). These subjects were referred to the Laboratory of Cognitive Behavioral Psychology of the National Neurological Institute "C. Mondino" Foundation of Pavia, Italy.

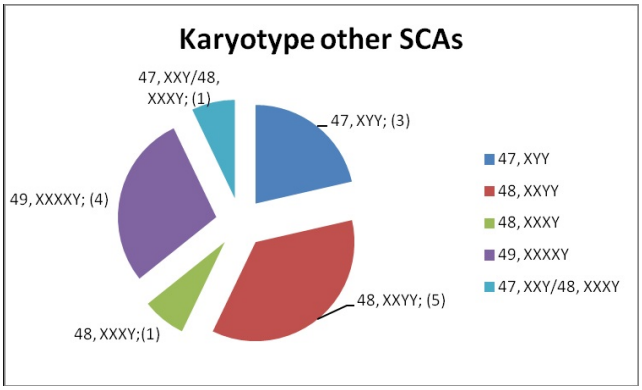

Figure 1: The graphic highlights different genotypes in other SCAs. Five subjects showed 48, XXYY karyotype, four 49, XXXXY, three 47, XYY and one 48, XXXY. One subject showed mosaicism (47, XXY/48, XXXY).

Population		
Karyotype	**n**	**Mean age at first evaluation**
47, XXY	39	24.43
Other SCAs	14	19.66
47, XYY	3	27
48, XXYY	5	20.8
48, XXXY	1	12
49, XXXXY	4	15.5
47, XXY/48, XXXY	1	23
Total	53	21.16

Table 1: The table highlights mean age of the patients at first evaluation, grouped according to the karyotype.

The inclusion criteria were first of all the genetic diagnosis of Sex Chromosomal Aneuploidies (SCAs); moreover, the age: From all the Klinefelter subjects evaluated we chose patients from 13 years old and older. All the patients have been karyotyped using standard techniques, except two of them, who were diagnosed during a screening for intellectual disability, using the Array-Comparative Genomic Hybridation (CGH) molecular cytogenetic method. Only 5 subjects have been diagnosed prenatally (4 KS and 1 XXYY) (Tables 2 and 3). Primary caregivers completed a comprehensive questionnaire detailing birth, medical, developmental and psychological history [14].

KS: *Age at diagnosis	
Age at diagnosis	Percentage (n=39)
Prenatal diagnosis	8.89% (4)
1-10 years	17.78% (8)
10- 18 years	35.56 % (16)
18+ years	20% (9)
*2 patients have no data	

Table 2: Mean age of diagnosis across the entire group KS was 12.89 years. The most frequent diagnosis was in the range of 10-18 years; prenatal diagnosis was the less frequent.

Other SCAs: Age at diagnosis	
Age at diagnosis	Percentage (n=14)
Prenatal diagnosis	7.14% (1)
1-10 years	35.71% (6)
10-18 years	42.86 % (5)
18+ years	14.29% (2)

Table 3: Mean age of diagnosis across the entire group other SCAs was 11.57 years. The most frequent diagnosis was in the range of 10-18 years; prenatal diagnosis was the less frequent.

Cognitive and behavioral assessment was performed through a clinical interview made with the DSM-IV criteria and psychometric questionnaires. For the assessment of global cognitive functioning, Wechsler Scales (WISC-R-Wechsler Intelligence Scale for Children-Revised [15], WAIS-R–Wechsler Adult Intelligence Scale–Revised [16], and Coloured Progressive Matrices (CPM) [17] were used. The Token Test [18] was used to evaluate the ability of oral comprehension. The adaptive behaviour, the ability of personal and social self-sufficiency in real-life situations and the way in which cognitive abilities translate into management of self-autonomy in daily-life, were evaluated with

The Vineland Adaptive Behaviour Scales (VABS) [19]. The Symptom Checklist (SCL-90-R) [20] is considered a valid instrument of general psychological distress in patients with experiencing a range of mental health and medical conditions. The Social Communication Questionnaire (SCQ) [21] offers a quick way to screen for Autism Spectrum Disorder. It was used to evaluate communicative, social and relational skills, and it was administered to parents. At last, Bem Sex Role Inventory (BSRI) [22] measured different aspects of psychological gender traits. A group of control, composed by twenty-one sex and age matched subjects, karyotypically normal, completed behavioral questionnaires (CPM, SCL90, and BSRI). The statistical evaluation was carried out using the T-test and then we used the effect size Hedges' g to have a quantitative measure of the strength of the phenomenon, considering the different sizes of the groups.

Results

Developmental and clinical history

Anamnestic data (Table 4) confirmed the increased prevalence of psycho-motor delay in other SCAs as compared with typical KS. The 70% of other SCAs show language delay, in contrast to only 30% of typical KS. Regarding as motor development, the 57% of other SCAs present a delay, compared with 15% of typical KS.

*Neurodevelopmental and Previous Psychiatric Traits	KS (39) %	"Other SCAs" (14) %
Speech delay	33.33%	64.28%
Motor delay	17.95%	50.01%
Learning disability	35.90%	57.14%
Loneliness	41.02%	64.28%
epilepsy	12.50%	25%
ADHD	17.95%	21.43%
Impulse control disorder	30.77%	35.71%
Psychotic disorder	22.50%	40%
Tic disorder	10.26%	14.28%
Anxiety and Mood disorders		
Generalized anxiety disorder	35.90%	35.71%
Obsessive-compulsive disorder	15.38%	42.86%
Depression	35.90%	21.43%
*Anamnestic data		

Table 4: The table highlights that other SCAs showed a greater developmental impairment Compared to KS, in all neurodevelopmental and psychiatric traits, except for generalized anxiety disorder and Depression that were more evident in KS.

Psychotic disorders emerged for the 40% of other SCAs, compared with 22.5% of typical KS. Epilepsy was diagnosed in the 25% of cases of other SCAs (66% of them were affected by generalized epilepsy, the others by focal) and in the 12.5% of typical KS (75% of them present generalized epilepsy, the others focal).

Interestingly the 57% of subjects with epilepsy show also a psychotic disorder. On a statistic level, correlations with T-test confirmed a significant difference between the groups both for language delay ($t=0.032$; $p<0.05$) and for motor delay ($t=0.013$; $p<0.05$). The effect size for language delay was Hedges' $g=0.114765$, while for motor delay was Hedges' $g=1.247012$. Otherwise, for epilepsy and psychosis, between groups analysis didn't find out any significant difference (E: $t=0.316$; P: $t=0.158$), probably due to a large variability and heterogeneity into a too much small sample.

DSM-IV diagnosis

Considering the axis I disorders, 18% of typical KS and 21% of other SCAs present a diagnosis of ADHD, while the 36% of typical KS and the 58% of other SCAs show a diagnosis of Learning Disabilities. Psychotic Disorder emerged for the 40% of other SCAs, compared to 22.5% of typical KS.

Finally, in the 50% of all patients, adaptive and behavioral problems and depressive or anxious traits were signaled. On axis II, in the typical KS group, the 8% of patients are in the range of moderate-severe intellectual disability and the 17% of mild intellectual disability.

Thirty-eight per cent of them showed an IQ level borderline, 24% were in the normal range and 13% present an IQ level higher than normal. In the other SCAs group, instead, the 31% of patients are in the range of moderate-severe intellectual disability and the 31% of mild intellectual disability.

Twenty-three per cent of them showed an IQ level borderline, 15% were in the normal range and nobody presents an IQ level higher than normal.

IQ and adaptive behavior

Mean IQ in typical KS was 87.45 ± 2 sd (sd=20.12) range 45-123, VIQ 91.74 (sd=19.55) range 50-130 and PIQ 86.87 (sd=20.87) range 50-126. Instead, mean IQ in other SCAs was 68.71 (sd=20.81) range 45-106, VIQ 69.36 (sd=21.97) range 47-113 and PIQ 74.72 (sd=21.70) range 45-112 (Figures 2 and 3).

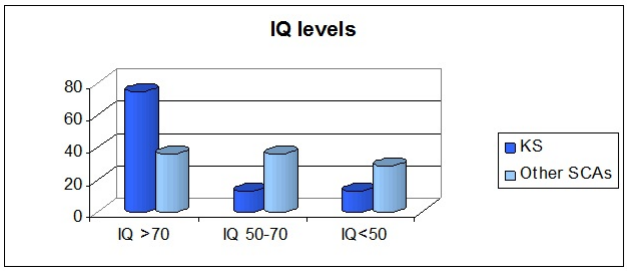

Figure 2: Percentages of IQ levels for KS and for other SCAs. IQ is significantly higher in KS than in other SCAs.

In CPM KS subjects obtained as mean score 27.75 (range 13-36, moda=33) and 31.50 in the Token Test (range 21-35), while in CPM the SCAs subjects mean score was 22.27 (range 10-35, moda=29) and 22.50 (range 9-31) in the Token Test (Figure 4).

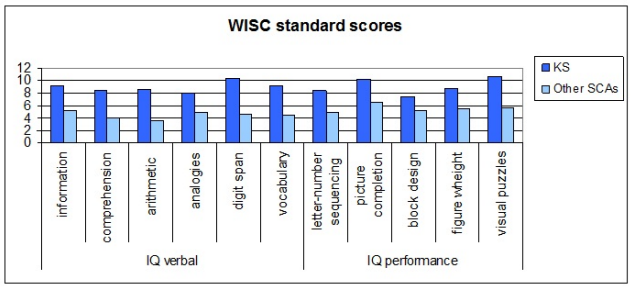

Figure 3: The graphic shows results of the WAIS-R. KS obtained higher scores in all scales. The difference between groups was more evident in the verbal IQ.

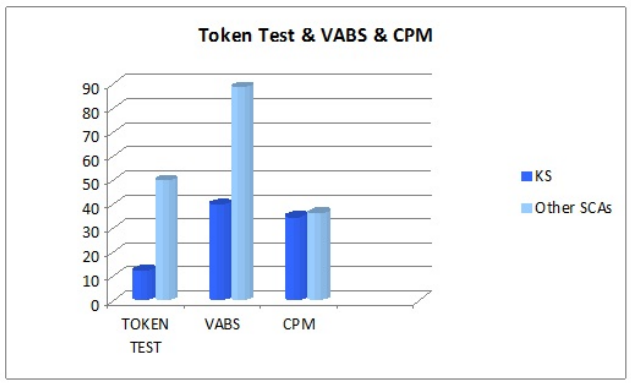

Figure 4: The figure shows results of groups at the Token Test, VABS and CPM. In all tests other SCAs showed worse scores.

Moreover, between groups analysis (t-test) identified significant differences between KS and other SCAs in mean IQ, lower in other SCAs ($p<.05$). The effect size for the mean IQ was Hedges' g=0.923239, that means that the result went in the expected direction. In CPM, we found out a significant difference between KS/control group and other SCAs/control group ($p<0.05$). In Token Test scores, a significant difference between groups was found ($p<0.05$). The effect size was Hedges' g=6.121377. Vineland scale scores documented more marked impairment in other SCAs subjects on adaptive behavior than in KS subjects ($p<0.05$) (Figure 4). In particular, for the other SCAs, communication, socialization and motor abilities resulted as weak points, compared to the average of normative population. Also for the typical KS, communication and motor abilities prove to be weak points, while socialization skills were worse than controls, but less compromised than in other SCAs. At the end, both for other SCAs and for typical KS, the daily-life abilities resulted as strong points.

SCL-90 and psychological problems

SCL90 documented an elevation of psychotic traits in KS/SCAs (about 50%) subjects in comparison with the control group (5%). There was also an elevation in somatization scale in KS subjects (58% KS, 16% other SCAs and 27% control groups), and in paranoid scale (70% for KS; 50% both for other SCAs and control group). However, there wasn't a statistical significant difference between the groups (Figure 5).

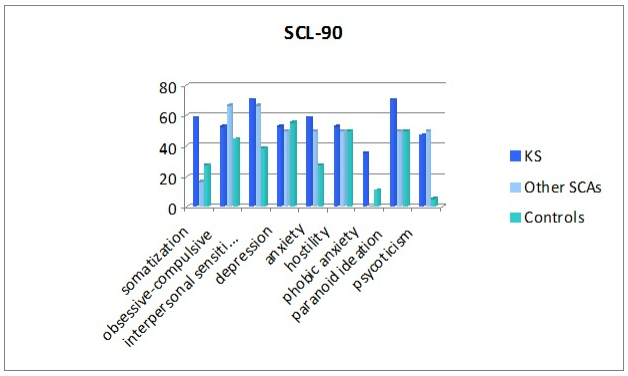

Figure 5: KS at SCL90: higher scores in somatization, interpersonal sensibility, anxiety, hostility, phobic anxiety and paranoid ideation scales, compared to other SCAs and controls. Other SCAs' scores were higher in the obsessive-compulsive scale and in the psycoticism scales. Other SCAs showed a score approximately to the zero in the phobic anxiety. Controls' scores were higher in the depression scale and lower in the psycoticism scale, compared to other SCAs and KS.

SCQ

Considering the comorbidity between KS and ASD, reported by the literature [23], the SCQ was used to verify the presence of mild autistic traits. They were, in fact, present in 67% of the other SCAs subjects and in the 18% of KS. A statistical significant difference was found between the two groups (Figure 6). The effect size was Hedges' g=1.002256.

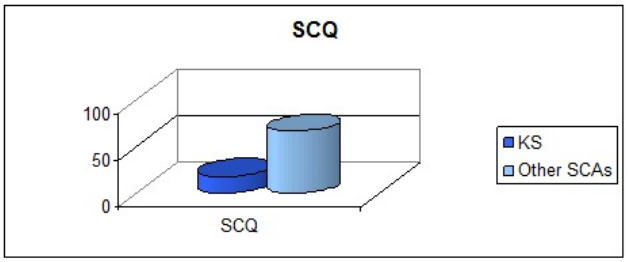

Figure 6: The graphic highlights that other SCAs showed higher occurrence of autistic traits compared to KS.

Bem sex role inventory

In the feminine and masculine scales of BSRI profiles there was a significant difference between KS and other SCAs ($p<0.05$). KS subjects show a low masculine scale in comparison with both SCAs and controls, while feminine scores are similar to controls. In other SCAs subjects the feminine scores were very low, while they showed a very high masculine scale (Figure 7).

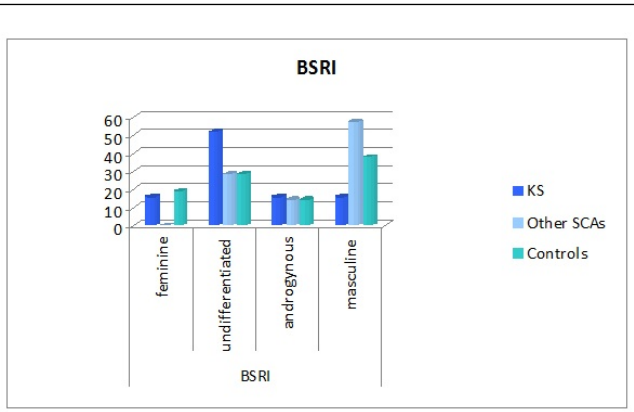

Figure 7: Graphic highlights that other SCAs showed very higher scores in the masculine scale, but in the feminine scale they obtained a score approximately to the zero. In the undifferentiated scale and in the androgynous scale, other SCAs scores were similar to controls. KS scores were quite homogeneous in each scale, except for the undifferentiated scale, where they got a higher score than controls and SCAs. In the androgynous scale, scores were very similar between the three groups.

Discussion

The aneuploidy of the sex chromosomes is not usually associated with intellectual disability, but it is characterized by the presence of specific cognitive profiles. However, the cognitive level in KS proves to be in mean ten points lower than those of their brothers or peers [11]. The typical cognitive profile is mainly characterized by the presence of the discrepancy between scores on performance tasks and those achieved in the verbal subtests, in favor of the former. Some studies have shown that verbal IQ scores are 10 points below the average compared with those of performance IQ [24]. This discrepancy may change during the life stages: differences in verbal conceptual and non-verbal reasoning skills may diminish over time, with the former no longer being such an area of deficit. In our sample, mean IQ in typical KS was 87.45, in a range of normality/low average. Unlike what suggested in literature, mean of VIQ (91.74) was higher than mean of PIQ (86.87). This could be due to the use of alternative strategies for problem solving that require the use of verbal reasoning ability, learned through experience to compensate for their present difficulties, or may even be linked to the effects of hormonal therapies [24]. On the other hand, in our other SCAs subjects, mean IQ was 68.71, VIQ was 69.36 and PIQ was 74.72, in line with previous studies. Moreover this data confirm our hypothesis: the other SCAs show a lower IQ than typical KS. Other SCAs present a highlighted language, motor and social delay during the development, and a greater incidence of seizures and psychotic disorders. These data are consisted with literature. In fact, it was found that the number of supernumerary X negatively correlated with intellectual disability and an increase of symptoms [13]. Through parents' interviews, we found that a motor delay in the acquisition of first steps was more marked for other SCAs (about 19 months) than typical KS (about 14 months) (Table 4).

Adaptive functioning skills were found to be significantly lower than IQ in most cases, with a mean adaptive functioning in the disability range. These findings indicate that overall daily functioning is often more impaired than would be expected based on cognitive (IQ) scores. While the factors involved in the discrepancy between cognitive abilities and adaptive functioning deficits are not fully understood, these deficits contribute to the disability and prevent many individuals from achieving academic and occupational success [12].

A frequent problem reported by the patients was the seizures, documented by clinical history. Epilepsy was diagnosed in the 25% of cases of other SCAs and in the 12.5% of typical KS. The incidence is higher for other SCAs in comparison to typical KS. In fact, it is known that epilepsy is a common health problem among people with Intellectual Disability (ID). The estimated prevalence of epilepsy in people with ID ranges from 15-30%, while the prevalence of epilepsy in the general population is estimated at 0.6–1% [25].

Seizures in KS and in other SCAs are rare. Probably we have found a higher incidence [26-28] because our laboratory is located in an institute for neurology. Cognitive functioning of KS subjects is characterized by the difficulty in expressive language. Language difficulties have been identified in 70-80% of children with KS at an early age [29]. Language difficulties include delay in onset of first words and in acquisition of the main stages of language development, in reading, expression, writing and reasoning abilities in arithmetic. Children with KS show difficulties in expression, inability to communicate their thoughts, ideas and emotions; otherwise the comprehension ability is in the standard. Often, during the developmental age, these problems are framed in learning disabilities as dyslexia and dysorthography [30]. Receptive language deficits have also been noted. Problems with phonemic discrimination, processing speed and comprehension of grammatical and morphological aspects of language have been reported [31-34]. Limitations in material processing speed and memory of auditory verbal material, which are associated with problems in decoding words, have been found in individuals with KS.

In our sample, these data were confirmed already by parents' reports. Both typical KS and other SCAs showed a delay in the acquisition of first words in comparison with typical children (typical KS: 16 months; other SCAs 17 months). Consequently the production of the first sentences results difficult and slow, in fact, in our sample, children of both groups have reached this ability at about 31 months of age. It's obvious that there is a deficit in expressive language already in early development. As reported above in the data of verbal IQ, this delay persists during the life span.

Early language difficulties influence social adaptation and behavior disorder, together with personality development [35].

Moreover, adults with KS displayed relative difficulties in discriminating emotions in tone of voice, and, to a lesser extent, in verbal content [2]. This finding suggests that the XXY chromosomal pattern may not only be associated with difficulties in semantic aspects of language, but with prosodic aspects, as well. This finding may contribute to the development of more comprehensive models addressing the role of the X chromosome in normal and abnormal development of social communication. In fact, the limitation in communication markedly affects social adaptation and behavioral aspects, as well as the development of personality, even if the literature is not unanimous in describing social traits and personality in KS.

The sex chromosome aneuploidies are considered a risk factor for psychosis and psychopathology [36-38]. A higher incidence of psychiatric disorders, as anxiety, depression, behavioral disorder and schizophrenia, has been documented in people with KS compared with general population (5) [39]. A recent study reported that 8% of KS

meet criteria for psychotic disorder, 45% have isolated psychotic symptoms and 24 % meet criteria for depressive disorder [40]. In our study, psychosis problems emerged for the 40% of other SCAs, and for the 22.5% of typical KS. The SCL-90 documented psychotic traits in about 50% of KS/SCAs subjects in comparison with 5% of control group. There was also an elevation in somatization and in paranoid scales. A risk for hospitalization for KS adults is higher than the controls [4]. Subjects with both KS and schizophrenia show structural and functional anomalies in the Central Nervous System (4). Sex chromosome aneuploidy is considered a risk factor for the development of psychiatric disorder. Neuroimaging studies have documented anomalies in the brain structures of boys and adults with KS, which correlated with the presence of psychosocial problems [41]. These psychopathological aspects may be partly explained by a psycho-neurological phenotype that includes grey matter deficits in the superior temporal gyrus, the orbitofrontal cortex and the inferior frontal gyrus, white matter anomalies, impaired executive functions with severe deficits in the inhibitory component, abnormal structure of amygdala, caudate and putamen [37-42]. These alterations may be caused by excessive expression of genes that lie in the pseudo-autosomal regions of the X-chromosome [41]. Moreover, total brain volume in typical KS is 7–8% smaller than healthy age-matched controls, whereas a reduction of 20% in males with other SCAs was found [43]. These reductions suggest that the X chromosome influences overall brain volume to a greater extent than the number of sex chromosomes in total [43]. Considering the different aspects of personality, many of the KS people seem to be more sensitive, anxious and insecure, and show a higher incidence of anxious-depressive disorders than the general population and an increased propensity to the use of drugs [5]. Other studies have emphasize that people with KS are friendly and open to interactions, do not usually have major problems with social interaction and adaptation, although they may be shy, sensitive and unassertive (6.44). KS subjects have difficulties in the construction of satisfying social relationships, with antisocial behavior in adolescence and a more unstable occupational history, but a minority of them meets criteria for antisocial behavior disorder in adulthood [8]. Although children with KS are reported by clinicians to be hyperactive and to show difficulties in concentration, some studies have showed that children with KS have a docile temperament and lower activity levels compared with unaffected peers [10]. Gives a measurement of psychological androgyny, or high levels of both masculinity and femininity, considering that gender roles may be defined as "expectations about what is appropriate behavior for each sex" [44,45]. The masculine scale has items as aggressive, ambitious, analytical, competitive, dominant, forceful, individualistic., while the feminine scale's items are for example affectionate, cheerful, compassionate, gentle, tender, sympathetic, understanding. Men with KS exhibit marked variations in phenotype, which may range from males with severe signs of androgen deficiency to normally virilized males. In our sample we found out an interesting statistical significant difference in the scores of BSRI between typical KS and other SCAs. In other SCAs subjects, the feminine scores were very low, quite approximately to the zero, while the masculine scores are high. On the contrary, typical KS presented feminine scores quite similar to those of the controls, but they showed a low masculine scale. Another important aspect in the KS phenotype, considering a neuropsychological perspective, is the impact on the area of social information processing. Men with KS are reported to have inaccurate perception of social-emotional cues and difficulties in expressing their emotions [46]. A study has showed that 27% of the boys with KS met criteria for autism spectrum disorders [40]. In fact, children with KS show significant impairments in social cognition, in particular, they present deficit in ToM (Theory of Mind) when compared with the typically developing children, with performance not different from children with ASD, independent of level of intellectual functioning, receptive and expressive language. Impaired ToM may result in social difficulties. Moreover, both KS and ASD, also show difficulties in facial affect recognition, specifically in identifying angry facial expressions [47]. However, this mentalizing deficit may be related to a different set of cognitive dysfunctions: a recent neuroimaging study, showed frontal deficits in KS group in contrast to amygdala deficits in the ASD group [47]. In our sample, autistic traits were present in 67% of the other SCAs subjects and in the 18% of KS at the SCQ, with a statistical significant difference between groups. Taking in account of the variability of cognitive behavioral phenotype and considering the DSM-IV diagnosis of each patient, the incidence of diagnosis of Intellectual Disability, of ADHD and of Learning Disabilities, is higher for other SCAs than for typical KS. In the same way, also at a diagnostic level, the frame of SCAs subjects appears generally more compromised. Our hypothesis has been confirmed: Other SCAs show more impairment and more developmental problems than typical KS, taking into consideration their cognitive behavioral phenotype. Anyway the cognitive profile in KS is characterized by marched variability and this could be influenced also by an early diagnosis, useful in order to plan different types of rehabilitation, when the developmental disorders are evident from a clinical point of view. A treatment, when begins in early life, could prevents some difficulties and developmental risk, considered with specific regard to the language and subsequently with possible emotional and behavioral problems. In fact, KS subjects, who had prenatal diagnosis, develop learning and language disabilities in a lower proportion than patients diagnosed by chance [48]. A limit of the present study is to have not considered the correlation between the age of diagnosis and the different disabilities of patients. In relation to these medical and psychological different impairments, we did not analyze the influence of the medical complications (cardiological, gastric, bone problems) in the SCA subjects and their consequent cognitive and behavioral phenotype [49]. Moreover, our sample is small and in the future it could be interesting to study more subjects. It could be also intriguing to consider the role of the medical treatment of the patients, when it is applied. In fact, the diagnosis and therapy of andrological diseases interact with fertility and sexuality that are more sensitive to psychological, educational, cultural, religious and social factor than any other body function. In KS patients, androgen effects on appearance and social characteristics are modulated by the androgen receptor CAGn polymorphism [41]. The CAGn length has a marked influence on the social status in Ks patients. Men with shorter CAGn, and so higher androgenic activity, present more fertility problems than endocrine disorders. These men are more likely to live with a partner because they are sufficiently virilized, and so then they could present with the desire for paternity. This frame could influence positively in particular the social and behavioral aspects of men with KS. It could be interesting analyze if also at an andrological level exists a significant difference between typical SCAs and other KS, that could condition their phenotype. At the end, in relation to the assumption of therapy, a limit of the present study could be the lack of consideration of its possible influence in particular on the BSRI scores.

Conclusion

Klinefelter's Syndrome (KS), is a genetic non-inherited pathology which influences sexual development and physical appearance,

cognitive functions, motor and language development, and social skills. A high variability of cognitive and behavior features is a characteristic of different SCAs disorders. The present study confirmed that other SCAs demonstrate more impairment and more developmental problems than typical KS. As the number of X chromosomes increases, the phenotypic severity increases as well. The other SCAs show a lower IQ than typical KS. The same picture emerged for the other ability and problems taken into consideration: other SCAs present a highlighted language, motor and social delay during the development, and a greater possibility to succumb to episodes of seizures and to psychotic disorders. These data are consistent with literature. Taking into consideration the variability of cognitive behavioral phenotype and considering the DSM-IV diagnosis of each patient, the incidence of diagnosis of intellectual disability, of ADHD and of learning disabilities, is higher for other SCAs, as well as for autistic traits. It appears obvious that the variability in cognitive behavioral phenotypes in KS is wide and future studies could continue to investigate the various problems. In fact, it is important to note that an early identification of the cognitive and behavioral phenotypes in all patients with KS, typical and atypical, may enhance the clinical treatment, anticipatory guidance, and care throughout the life span.

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