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NEW RESEARCH HORIZON ***Review***

Klinefelter's syndrome and psychoneurologic function

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ABSTRACT: Klinefelter's syndrome (KS) is due to the presence of one or more supernumerary X chromosomes. Aneuploidy 47,XXY is the most common abnormality of sex chromosomes in humans, with an incidence of 1/500 male live births. Only one-third of subjects with KS is, however, diagnosed. The aim of this work is to present a review of current literature about neurogenetic functions in KS, referring to both clinical and therapeutics aspects. If it is well known that the majority of subjects with 47,XXY karyotype have a normal intellectual level, the identification of strengths and weaknesses of their intellectual functioning is important for the purpose of planning early psycho-educational interventions. Language difficulties are one of the more distinctive traits in cognitive functioning of people with KS. It has also been suggested that the limitations in communication markedly affect social adaptation and behavioral aspects, as well as the development of personality. Moreover, difficulties in learning language appear to be related to an altered functional lateralization; therefore, KS subjects are a suitable model for studying genetic abnormalities of lateralization. In this, perspective psychopathological risk is analyzed. Early recognition of this aspect is needed to address the educational and therapeutic perspectives for KS subjects.

Key words: Klinefelter / cognition / behavior

Introduction

Klinefelter's syndrome (KS) is due to the presence of one or more supernumerary X chromosomes. Aneuploidy 47,XXY is the most common abnormality of sex chromosomes in humans, with an incidence equal to 1/500 male live births. Only one-third of subjects with KS is, however, diagnosed (10% of cases in the prenatal period through amniocentesis and 26% of cases post-natally for developmental delay, hypogonadism and gynecomastia in the first 18 years and later for infertility, others for behavioral or psychiatric disorders; Abramsky and Chappel, 1997). Many individuals with KS have no medical problems and are thus not diagnosed, whereas others have been diagnosed post-mortem (Hayashi *et al.*, 2000; Matsuoka *et al.*, 2000). Despite wide variability, KS is characterized by a constellation of symptoms that may include: inadequate virilization, hypogonadism, azoospermia, infertility, gynecomastia, elevated average height (179.2 ± 6.2 cm) and increased plasma gonadotrophins (Rovet *et al.*, 1996; Sørensen, 1987).

Chromosomal abnormalities are the most common cause of intellectual disability, and are present in 4–28% of cases. However, the aneuploidy of the sex chromosomes is not usually associated with intellectual disabilities, but is characterized by the presence of specific cognitive profiles (Fig. 1).

Intelligence

The cognitive profile of KS classic type is characterized by some specific features common in most of the subjects and described over the past 20 years, even in a developmental perspective (Geschwind *et al.*, 2000). Heterogeneity of the intellectual profiles and wide individual variability (also in relation to family background Tarani, 2008) is also reported (Sørensen, 1992).

If it is well known that the majority of subjects with 47,XXY karyotype have a normal intellectual level, on the other hand, the identification of strengths and weaknesses of their intellectual functioning is of core importance, for the purpose of planning early psycho-educational interventions.

In this perspective, a useful starting point is the administration of standardized measures of intelligence, the most common of which is the international battery of Wechsler Intelligence Scales, which provide a broad assessment of general intellectual skills and, at the same time, describes the typical functioning in specific areas.

Although it was found that KS subjects have a general cognitive level around the normal range, this is about 10 points lower compared with siblings or peers (Ratcliffe *et al.*, 1990).

Many studies have then emphasized that people with KS occupy work roles often less prestigious than other family members or

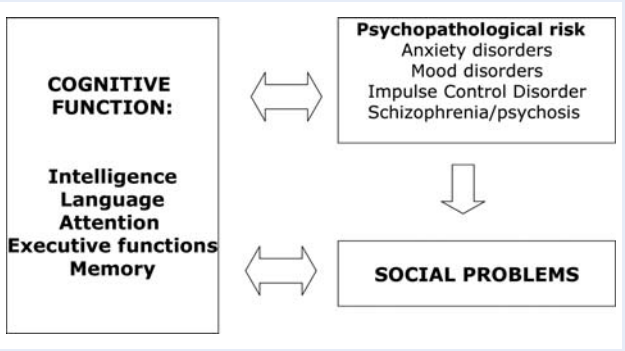

Figure 1 Psychoneurologic function in KS.

control subjects (Ross *et al.*, 2007). Recently, an incidence of 1.2% of XXY subjects in pre-pubertal age has been found in a group of people with intellectual disabilities of unknown cause (Khalifa and Struthers, 2002): therefore, there is a further indication to karyotype in males with intellectual disabilities of unknown cause.

In general, the mean scores of global IQ vary greatly depending on the study population and on the modality of recruitment of trial subjects. For example, when subjects are selected following a visit to the military service or by the departments of endocrinology, instead of by departments of psychiatry, the scores are higher.

The typical cognitive profile is mainly characterized by the presence of a 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. This discrepancy has been observed previously in both children and adults, although it may change during the life stages.

When there is better performance in tests requiring the use of verbal reasoning ability, it may be linked to alternative strategies for problem solving learned through experience to compensate for their present difficulties, or may even be linked to the effects of hormonal therapies as reported by Ross *et al.* (2007).

Particularly in view of these aspects, Geschwind *et al.* (2000) emphasized that although measures of general intelligence such as the IQ assessment have a central role to address the educational perspectives, or to test the presence or lack of some cognitive skills, they have less value in the detection of specific neuro-developmental profiles.

Cognitive limitations have been described in cases of comorbidity between KS and seizures, and with increasing number of supernumerary X chromosomes (Ross *et al.*, 2007).

The typical difficulties of KS cognitive profile are increasingly serious and striking in clinical and cytogenetic variations of the syndrome, the most common of which are characterized by XXXY karyotype 48, XXYY 48 and 49 XXXXY. It was, indeed, found that the number of supernumerary X negatively correlated with intellectual development and with height (O'Brien and Yule, 1995). In subjects with atypical aneuploidy compared with those with XXY, the verbal scale is reduced, while the performance IQ is less reduced (Rovet *et al.*, 1995).

Language

Detailed longitudinal studies on particular aspects of cognitive functioning in KS have previously shown a pervasive language-based learning disability (Mandoki *et al.*, 1991; Rovet *et al.*, 1996). Although these prospective studies, which are based on children identified at birth through unbiased consecutive genetic screening, are based on a restricted number of subjects, they consistently reveal fundamental difficulties with language (Geschwind *et al.*, 2000). Language disabilities are documented in 70–80% of XXY males, depending on estimates. However, Geschwind *et al.* (2000) underlines that these prospective longitudinal data are particularly important because individuals with neurobehavioral problems often are selectively referred for evaluation, creating an ascertainment bias (Geschwind *et al.*, 2000). The literature is unanimous in describing language difficulties as one of the more distinctive traits in cognitive functioning of people with KS. It has also been suggested that the limitations in communication markedly affect social adaptation and behavioral aspects, as well as the development of personality (Bancroft *et al.*, 1982).

Graham *et al.* (1988) had shown the presence of specific difficulties in reading in 50% of children with KS, as documented by performance of two standard deviations below the norm in reading tasks associated with the presence of a normal IQ and in the absence of psychiatric comorbidity. Other authors have found in KS adults the presence of such difficulties in 75% of cases (Bender *et al.*, 1993, 1995).

Language difficulties include delay in onset of first words and in acquisition of the main stages of language development, and also problems in some more specific aspects. For example, difficulties in the articulation of sounds or syllables in lexical retrieval and processing phonemes are common. These difficulties result in limitations—from moderate to severe—in reading, expression, writing and reasoning abilities in arithmetic. Often during the developmental age, these problems are framed in learning disabilities (like dyslexia–dysorthography). Consequently, a percentage of between 60 and 86 of students with KS receive special education (Mazzocco and Ross, 2007).

The difficulties described persist during the adolescence, causing a substantial difference in the academic performance of individuals with KS in respect of controls, and gradually extend to other areas, such as arithmetic, problem solving and integration of knowledge. The comparison with unaffected peers documented that patients with KS, therefore, shows greater difficulties in all tasks requiring the use of language skills, especially of verbal comprehension and expressive skills. Rovet *et al.* (1996) have suggested that the extent of language difficulties in other areas of cognitive functioning reflects their dependence on the use of instruction based on language (Rovet *et al.*, 1996).

Individuals with KS have limitations in material processing speed and memory of auditory verbal material, which are associated with problems in decoding words. These problems are associated with a lower speed, accuracy and verbal comprehension, especially when the reading is done aloud. These difficulties are similar and comparable to those found in children with dyslexia.

Few studies conducted on population of non-institutionalized individuals with KS showed that problems detected early in the language persist during adulthood. Individuals with KS have difficulties, especially in the more complex aspects of expressive language, conditioned by the verbal memory, the recovery of words and verbal fluency.

Recent studies in psycholinguistics are aimed to understand the specific limitations imposed on individual aspects of production and comprehension of language, such as those reported by Geschwind *et al*. (2000). These studies concern the understanding of grammar, the syntactic expression of opinions and the use of complex grammatical structures. These functions are deficient in patients with KS.

Attention and executive function

Executive skills are those involved in concept formation, problem solving, switching tasks, inhibiting inappropriate responses, initiating rapid and fluent responses, planning and sustained attention. Different patterns of disorder among these skills have been found in several developmental abnormalities, including autism, attention deficit hyperactivity disorder (ADHD) and Turner's syndrome (Temple and Sanfilippo, 2003).

Executive skills represent a crucial aspect of cognitive functioning individual, but the literature highlights that executive functions have not received much attention in the studies conducted on patients with KS. The low interest in this aspect could be related, according to Geschwind *et al*. (2000), to the belief that attentional difficulties, which are already present in the age of development in the subject with KS, are related to learning disabilities, often diagnosed as early as a preschool period.

It is easily observable from a clinical point of view that children with KS are hyperactive; moreover, they show difficulties in concentration and short-term memory. These aspects, however, are discussed in the literature: some studies emphasize that children with KS have a docile temperament and lower activity levels compared with unaffected peers, but without any scientific evidence of their effective quantification and distractibility (Sørensen, 1987).

In contrast, studies conducted on small groups of KS show adequate performance in Wisconsin Card Sorting Test, while the administration of Trial Making B and of the Digit Span (a specific measure of short-term and working memory) documented lower performance than normal (Robinson *et al*., 1986). Bender *et al*. (1993) have suggested that the lower scores obtained by the administration of these tests could be related to an artifact of the processing time of the material presented rather than the actual presence of difficulties in attention, since the task required in the Trial Making Test provides a time limit.

In a population of KS aged between 16 and 61, younger subjects have lower performance in tasks that require executive functions, problem-solving skills and speed in processing the information, whereas adults show adequate performance. This finding provided further evidence that the performances of subjects with KS in cognitive tasks may in time change as a result of experience (Geschwind *et al*., 1998).

No significant correlation has been found between the difficulties in executive functions and learning disorders in a subject with KS, thus suggesting a substantial independence between the disturbances (Boone *et al*., 1991).

Temple and Sanfilippo (2003) documented an executive impairment in subjects affected by KS, within which inhibitory executive functions are impaired; however, other executive functions addressing planning, concept formation, problem solving, task switching and speeded responding are intact, although within speeded responding the pattern of responses also indicates inhibitory difficulties (Temple and Sanfilippo, 2003). The consistency of the impairment in this executive domain across the three reported cases suggests a specific cognitive phenotype to the syndrome, with a selective effect upon executive function (Temple and Sanfilippo, 2003). The results also suggest that an inhibitory abnormality may be expressed in differing directions as a failure to inhibit or as an exaggerated inhibition with rigid focus on a subset of stimulus inputs. The results reflect a single dissociation, which indicates that intact inhibitory executive skills are not required for the development of other executive functions constraining potential models of the development of executive skill and consistent with models, in which there are separate developmental paths for executive planning skills and executive inhibitory functions. However, to argue conclusively for selective components within executive skills, which develop relatively independently, a double dissociation would be required. Previous studies have suggested that the reverse single dissociation is found in autism with pervasive impairment in executive skills, including planning but intact inhibitory executive skills (Ozonoff and Jensen, 1999). However, the specificity of this impairment has been questioned more recently, and the issue remains unsolved (Liss *et al*., 2001).

Academic performance

Learning difficulties associated with KS are usually verbal and begin to appear in early school age. From the age of seven, children have problems in reading, language expression and writing ranging from moderate to severe, while the arithmetic skills are less affected (Ross *et al*., 2007). With the transition from primary to middle school, the problems that pupils have in reaching appropriate school target became more and more clear. The difficulties in achieving good results, together with relational difficulties, cause feeling of distrust and contempt.

In terms of education, difficulties emerge even in arithmetic reasoning at the age of 10, so that the educational background of these pupils is characterized by failures. Roughly 50–75% of pupils with KS sooner or later received a diagnosis of specific reading disorder (Bender *et al*., 1993), and 60–86% of them require an individualized educational program (Robinson *et al*., 1986).

As far as the next school grades are concerned, it has been noticed that students with KS often repeat the final year of the high school and in any case few of them finish high school (Leonard *et al*., 1982, Leonard and Sparrow, 1986).

Grace (2004) has recently suggested that the high school dropout rate observed in children suffering from KS is strongly conditioned by the lack of integration within the peer group. With regard to the socialization of individuals with KS, the studies conducted so far have provided rather contradictory results. Some papers have described the children with KS as shy, immature, and intimate, with significant problems in the construction of deep and satisfying social relationships; other studies have instead shown how people with KS appear polite, friendly and open to exchanges and interactions. The literature is quite unanimous on some characteristics of temperament, such as calmness, sensitivity and lack of assertiveness (Visootsak *et al*., 2006). Most of them 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 (Bender et al., 1995).

Developmental profile

Prenatal diagnosis of KS allows clinicians to follow the developmental milestones of the KS children since the first month of age.

Few studies have been conducted so far to describe the motor skills of the KS subjects, but the few data in the literature have revealed the presence of a general low level of motor abilities of KS. Approximately two-thirds of boys with 47,XXY are slightly delayed in the age at which they begin walking (mean age of first steps 18 months) (Robinson et al., 1986). Delayed language development can be observed in half of the boys with KS (mean age of first words 24 months) (Robinson et al., 1986).

Samango-Sprouse and Law (2001) have studied a cohort of prenatally ascertained cases of KS ($n = 73$) from 2 months throughout 7 years of age. Psychomotor development was very delayed compared with healthy controls. The following conclusions have been derived (Simpson et al., 2003):

(i) truncal hypotonia was present in 68% of the KS boys at 3 months of age; 15–20% had flattened occipital region and presented diminished controlateral range of motion in the neck. Deficit in organization and planning were noted in infants and toddlers having truncal hypotonia.
(ii) Mean IQ was 110 in this sample.
(iii) Speech delay was evident by 12 months. Reduction in phoneme development and difficulties with coordinating oral facial musculature, specifically lip and tongue movement, have been evidenced. Speech delay was further defined by limited vocabularies skills and limited expressive processing (Tables I and II).

Speech delay and decreased verbal IQ are more pronounced in XXXY than in XXY. IQ is decreased ~15 points per additional X chromosomes. In 48,XXYY, IQ is usually 60–80 (Simpson et al., 2003).

Difficulties in motor development in the KS subjects have been described by Salbenblatt et al. (1987) and Robinson et al. (1986). Coordination difficulties, balance problems, difficulties in jumping and hopping are evident throughout childhood (Ross et al., 2007). Later slow fine motor movements, together with reduced manual ability, reduced strength and running speed have been observed (Ross et al., 2007). These difficulties may be associated with mirror movements and postural tremor (Ross et al., 2007).

As the complexity of the motor action increases, difficulties in motor action planning become more evident. The association of poor coordination and motor slowness, together with a reduced muscle mass and elongation of the limbs, results in a poor athletic ability, more evident during adolescence. Visual motor function is also impaired (Ross et al., 2008). The motor performance may become better with the replacement therapy (Ross et al., 2007).

Most male with KS demonstrate difficulties with language-based learning from an early age (Ross et al., 2008). From early, childhood difficulties in suck/swallow coordination, particularly with breastfeeding, have been described (Samango-Sprouse and Rogol, 2002). In rare cases, these difficulties are to be connected to a congenital hypoplasia or agenesis of the depressor muscle of the angle of the mouth. Orobuccal musculature is hypotonic, with difficulties transitioning to textured foods and a preference for soft ones (Samango-Sprouse and Rogol, 2002).

Table I Characteristics of developmental profile of subjects with KS (modified from Samango-Sprouse and Rogol, 2002).

Infancy and early childhood	Delay of the first stages of language Dyspraxia
School-age period	Auditory-verbal memory deficits Moderate to severe difficulty in reading skills, writing, spelling and arithmetic

Table II Developmental characteristics in Klinefelter subjects diagnosed with prenatal diagnosis (modified from Samango-Sprouse and Rogol, 2002).

Physical features	%	Developmental features	%	Growth features	%
Truncal Hypotonia	68	Developmental dyspraxia	50–80	Height	>75
Joint laxity at hips and elbows	50	Reduced phoneme repertoire	50–75	Mean height 179.2 ± 6.2	
Hand tremors (after 5 years of age)	20–50	Age-appropriate language comprehension	80	Head circumferences	15–25
Clinodactyl or curved fifth finger	26	Delayed auditory memory	50–80	Weight	30
Sternal depression (pectus excavatum)		Enhanced Visual memory	50–80	Mild disproportion with long arms but especially legs	
Delayed pubertal development	50	Normal IQ within 10–15 points of siblings	80		
Flat feet	30–40	Delayed balance skills	50–80		
Cherubic faces as infants		Sensory differences			
Breast enlargement	30	Pseudo-torticollis	20		
Mirror movements	40	Reading differences and/or dyslexia	50		

KS children present an atypical phonemic development, delayed imitation of sounds and delayed babbling to the completion of the first year of life.

Language comprehension is appropriate to the chronological age. There is a delay of expressive language. Fifty-two percent of KS children require logotherapy (Samango-Sprouse and Rogol, 2002).

After the first year of life, delayed onset of first words and difficulty in passing to the word-sentence are present. The combination of delayed language acquisition, difficulties in imitation of simple sounds and words, and oro-motor difficulties in organizing the mouth suggests a deficit of motor planning similar to dyspraxia observed at the level of gross motor skills.

In conclusion, the developmental characteristics of the KS child strongly resemble the profile of the older children with developmental dyspraxia (Samango-Sprouse and Rogol, 2002). KS children require precocious multidisciplinary evaluation to determine appropriate treatments, such as physical therapy, infant stimulation programs and speech therapy (Wattendorf and Muenke, 2005). Poor fine motor performance and diminished gross motor function have been observed in KS adults. This aspect is very important not only for the academic performance, but also for the difficulties coping with athletic efforts, thus limiting the possibility of taking part in sports activities, very important to develop social relationships (Leonard and Sparrow, 1986).

Disorders of lateralization and morphology of the central nervous system

One of the most interesting asymmetries, as regards the human brain, is the lateralization of cerebral hemispheres, which has profound implications for higher cognitive functions and behavior.

Several studies have noted that the consistent presence of behavioral and anatomical asymmetry is reflected in the specific functions of each cerebral hemisphere (Geschwind and Galaburda, 1985). However, little is known about the molecular basis of these asymmetries.

Even in the daily life of every human being, it is possible to observe lateralized behavior, namely the constant use of the right hand by most people. More than 90% of the population is right-handed, while ~8% is left-handed, without any significant differences among geographic regions (Annett, 1982). The importance of this observation is underscored by the association between handedness and lateralization of language in the cerebral cortex. The language is localized in the perisylvian region of the left hemisphere in 97–99% of right-handed subjects. A wide range of methodologies have shown that for left-handers, the areas relating to language are localized in the left hemisphere (50%) or bilaterally (40–45%), and less frequently (5–10%) in the right hemisphere (Geschwind and Galaburda, 1985). This functional asymmetry is correlated with a structural asymmetry of the planum temporale, the back of the superior temporal gyrus (STG), that is up to 10 times larger on the left in the majority of right-handed subjects (Chi *et al*., 1976). The structural asymmetry of the planum temporale of the posterior superior temporale gyrus develops prenatally, after the completion of cortical neurogenesis, and provides therefore the neural substrate on which behaviors, such as handedness and language develop (Geschwind *et al*., 1998). Left-handers often diverge from normal patterns of anatomical and functional asymmetry of language found in the right-handed, so that their condition was described as 'anomalous dominance' (Geschwind and Galaburda, 1985). Pathological conditions involving alterations in the development of language, such as dyslexia and stuttering, are frequently connected to this asymmetry (Geschwind *et al*., 1998). Several studies have shown that there is a bigger proportion of left-handed among stutterers and dyslexics than the general population.

The anatomical post-mortem investigation and the *in vivo* brain imaging of dyslexic subjects have also shown a lack of the typical asymmetry of the planum temporale, similar to what was observed in left-handers (Galaburda, 1993). It is interesting to note that both dyslexia and left-handedness have significant genetic components (Annett, 1985).

People with KS show difficulties in language learning and change in manual dominance and functional lateralization; therefore, they are a suitable model for studying genetic abnormalities of lateralization (Geschwind *et al*., 1998).

Knowledge in this area comes from studies using magnetic resonance imaging (MRI) of the brain. These studies documented a lobar asymmetry, indicating a reduction in the total volume of the lateral ventricles in adults with KS (Warwick *et al*., 1999). MRI has documented that adult KS subjects show a gray matter volume reduction in the left temporal lobe: this asymmetry is less pronounced in KS subjects treated with testosterone (Patwardhan *et al*., 2000, Patwardhan *et al*., 2002). On the contrary, the subcortical structures like the hippocampal complex and the cerebellar hemispheres appeared more reduced in the right side (Itti *et al*., 2006).

These neuroimaging studies have also suggested that the lateralization of language may be genetically influenced (Itti *et al*., 2006). KS may therefore be a model for future studies in order to understand the genetic mechanisms involving the X chromosome that can cause abnormal brain lateralization of language functions.

Another important line of research has focused on the relationship between abnormal cerebral lateralization and increased vulnerability to psychosis.

Recently, emphasis has been placed on the presence of schizophrenia spectrum disorder in patients XXY (Crow, 2004; DeLisi *et al*., 2005). A possible biological mechanism behind this association would be a reduced hemispheric specialization for language disorder predisposing to ideation disorder.

Functional MRI was used to study the lateralization of language in 15 subjects XXY, compared with a group of controls (van Rijn *et al*., 2006, 2008). A psychiatric interview and a questionnaire were used to explore the relationship between the lateralization of language and mental functioning of these subjects. Compared with controls, the XXY group showed a reduced hemispheric specialization for language, with reduced functional asymmetry in the STG and in the supramarginal gyrus (part of Wernicke's area). The reduced lateralization in the STG was significantly correlated with signs of disorganization of thought. These results suggest that the X chromosome may be involved in hemispheric specialization for language. Moreover, the reduced hemispheric specialization for language processing in the STG may have significant effects on mental functioning, being associated with disorganization of thought, as schizophrenic subjects have showed (van Rijn *et al*., 2008).

Psychopathological risk

Epidemiological studies have reported a higher incidence of psychiatric disorders (anxiety, depression, behavioral disorder and schizophrenia) in people with 47,XXY karyotype, compared with the general population (Bender *et al*., 1995; DeLisi *et al*., 2004), although studies were mostly conducted on limited samples (DeLisi *et al*., 2005).

In general, the sex chromosome aneuploidies are considered a risk factor for psychosis (Crow, 2004; DeLisi *et al*., 2005; van Rijn *et al*., 2008). These data are supported by the evidence of common structural and functional abnormalities in the brains of subjects with KS and schizophrenic patients, and from similar performance in cognitive tasks.

Behavioral problems, such as closure and anxiety, occur in KS childhood. School-age children and adolescents with XXY often show low self-esteem, anxiety and mood disorders and problems of socialization (Bender *et al*., 1995).

Ross *et al*. (2007) pointed out that the presence of school problems, linked to the impossibility of achieving a satisfactory profit together with the poor socialization, often produced by suffering derision by their peers, is the source of anxiety and mood disorders. A great variability of symptoms is, however, observed (Ross *et al*., 2007; Boada *et al*., 2009).

Recently, a study based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; APA, 2000) found in a population of 51 boys with KS (mean age = 12.2 years) the presence of learning disorders (65%), a high incidence of ADHD (63%), depressive disorders (24%), psychotic disorders (8%) and schizophrenia (2%) (Boks *et al*., 2007). During the late adolescence and adulthood, behavioral problems related to poor impulse control become manifest. The risk of hospitalization for psychosis in adults with KS is greater than in control subjects (Bojesen *et al*., 2003).

Genotype/phenotype correlation in KS: animal models

The X chromosome has accumulated a disproportionate number of genes linked to mental functions and is thought to play a crucial general role in intelligence (Lewejohann, *et al.* 2009). X-linked genes are supposedly involved in social-cognition and emotional regulation (for review, see Skuse, 2005). Most X-linked genes are inactivated on one X chromosome in the presence of an additional X chromosome. The Klinefelter phenotype is hypothesized to be due to X chromosomal genes that escape inactivation and thus are expressed in excess (DeLisi *et al*., 2005).

In the male mice carrying a supernumerary X chromosome (Lue *et al*., 2005; Lewejohann *et al*., 2009), cognitive deficits have been confirmed.

Lue *et al*. (2005) examined behavioral deficits in 41,XXY mice (possessing a full Y chromosome) by testing conditional learning of a Pavlovian association and found the rate of learning to be significantly slower in XXY mice compared with their XY littermates. They concluded that there is an impaired medial temporal lobe function in XXY mice. Several causes might induce this failure: low plasma testosterone levels, defect of the androgen receptor or overdosed X-linked gene expression in specific brain regions responsible for learning (Lue *et al*., 2005).

In a recent study (Lewejohann, 2009), a strong correlation between testosterone and performance in the novel object task in controls but not in XX^{Y*} mice was found. This indicates that higher levels of testosterone in some of the XX^{Y*} mice fail to bring about an increase in memory performance. Therefore, 15 XX^{Y*} males and 15 XY* controls were subjected to a battery of behavioral tests, including a general health check, analysis of spontaneous exploration and locomotor activity, measures for anxiety-related behavior and the 'novel object task' to test memory performance (Lewejohann, 2009). Physiologically, XY* males did not differ from C57Bl/6 wild-type mice carrying a normal Y chromosome, which provided a valid control group. XX^{Y*} mice did not differ from their wild-type littermates with respect to locomotion, exploration and anxiety-related behavior. XX^{Y*} male mice, however, exhibited no significant recognition memory performance in contrast with wild type XY* males that readily fulfilled a given task. These findings support the hypothesis that the presence of a supernumerary X in male mice influences cognitive abilities. The authors suggest that altered endocrine state and/or changes in the dosage of X-linked genes in the XX^{Y*} mouse model affect brain function, in particular those regions responsible for cognition and learning behavior. We conclude that adult XXY mice have testicular failure and learning deficits, similar to its human counterpart, KS (Lue *et al*., 2005).

Therapeutic aspects

Patients with KS should be treated with lifelong testosterone supplementation that begins at puberty, in order to secure proper masculine development of sexual characteristics, muscle bulk and bone structure, and to prevent the long-term deleterious consequences of hypogonadism. However, the optimal testosterone regimen for patients with KS has still to be established (Bojesen and Gravholt, 2007). Improvements with a systematic replacement therapy were reported in various parameters of physical and emotional well-being (Zacharin and Warne, 1997). Also successful fertility treatment for KS has been recently reported by Ramasamy *et al*. (2009).

A significant genotype–phenotype association exists in KS patients: androgen effects on appearance and social characteristics are modulated by the androgen receptor CAGn polymorphism (Zitzmann *et al*., 2004).

Differences in the X-linked androgen receptor AR sequence are characterized mostly by a highly polymorphic trinucleotide repeat (CAGn) in exon 1, the normal length of which is 9–37; expanded numbers are observed in the neurological disorder of X-linked spinobulbar muscular atrophy (X-SBMA). *In vitro*, the T-induced transactivation activity of the AR is inversely associated with the length of CAGn due to reduced binding of AR coactivators, and accordingly, marked features of hypogonadism are noticed in X-SBMA (Zitzmann *et al*., 2004).

In a cohort comprising a broad range of Klinefelter's phenotypes, analysis of the CAGn polymorphism of the AR gene in combination with X chromosome inactivation demonstrated that a modulation of morphological traits as well as social aspects is exerted via this genomically determined entity (Zitzmann *et al*., 2004). The authors describe a marked influence of CAGn length on the social status of KS patients; men with higher androgenic activity (shorter CAGn)

were more likely to live with a partner and present because of fertility problems than because of endocrine disorders. It has to be remarked that profound disturbances of spermatogenesis occur in all KS patients due to meiotic problems. Only those men sufficiently virilized to find a partner will then present with the desire for paternity. Those subjects with short CAGn were also more likely to work in highly skilled professions.

It is important to remember that the diagnosis and therapy of andrological diseases interact with two biological functions—fertility and sexuality—that are more sensitive to psychological, educational, cultural, religious and social factors than any other body function (Jannini *et al*., 2006).

The treatment strategy depends on the age of the patient and the goals of therapy (restoration of fertility and/or production and maintenance of virilization). Moreover, as suggested by Ross *et al.* (2008) (Table III), subjects with KS require appropriate educational interventions that target their pattern of relative deficits in complex language processing and impaired attention as well as motor function (may be related to atypical lateralization) (Ross, 2008). Behavioral interventions and classroom accommodations can help children with KS to be more available for learning, having an increased risk of attention deficit without hyperactivity during school age. Early speech/language therapy is particularly essential in helping the child to develop adequate skills to maximize the comprehension and the production of more complex language (Visootsak and Graham, 2006), with the objective of giving support to the patient and the caregiver to improve communication and avoid social consequences of the speech disability.

Physical therapy should be considered for boys who have hypotonia or are delayed in gross motor skills that may impact the muscle tone, balance and coordination (Visootsak and Graham, 2006) to improve positive self-esteem as well as cognitive and sensory processing/integration.

In the case of fine motor dyspraxia, occupational therapy should be recommended (Visootsak and Graham, 2006).

A core component for the management of KS patients is psychological support. Psychologist or psychiatrist consultations can help adjust the patients to their condition, including support on how to inform the patient, over time and in an age-appropriate methodology. Emotional support is required while accepting the communication of diagnosis, especially after the onset of puberty, when physical

Table III Guide for counseling clinicians and parents (modified from Ross, 2008).

Recognize	Consider	Effects of intervention
Delayed early expressive language and speech milestones	Early speech therapy and language evaluation	To restore and improve impaired speech, language, voice, fluency Support of patient and carer to improve communication and avoid social consequences of the speech disability Teaching compensatory strategies to improve intelligibility and general communicative effectiveness
Increased risk for attention deficit without hyperactivity during elementary school	Classroom accommodations, avoid distractions at home when doing homework, medications	Behavioral interventions help children with KS to be more available for learning
Deterioration in school performance in transition from elementary school to middle school	Retesting to discover areas requiring extra attention at or before entrance to middle school	To promote educational continuity in school setting
Difficulty with arithmetic at all ages	Request testing and remediation	To reduce the sense of deficiency that limits their aptitude to acquire knowledge and understanding of fundamental ideas in numeracy
Increased chance of left-handedness	Writing and sports accommodations	To reduce negative associations of left-handedness in language, to enhance fine and gross motor ability
Difficulty with complex language processing: specifically understanding and generating oral language	Language evaluation, communication through written language, acquire written notes from lectures	To modify or enhance communication performance
Decreased running speed, agility, and overall strength in childhood	Physical therapy, occupational therapy Choose sports that emphasize strengths	To improve positive body-self perception, through the exercise of gross and fine motor skills, balance and coordination, strength and endurance as well as cognitive and sensory processing/integration
Communication of diagnosis Problems in accepting the diagnosis	Emotional support	To address the psychological, behavioral and social factors that may influence the adaptive process to the KS condition
Pubertal delay Body image disorders or refuse	Group psychotherapy	To help address their sense of isolation and shame and to experience the support of peers
Increased risk of anxiety, depression, and psychoses. Psychopathology	Psychotherapy	To solve problems concerning dysfunctional emotions, behaviors and cognitions through a goal-oriented, systematic procedure
Pharmacological compliance	Teaching possible strategies to improve compliance with medication	To reduce patient noncompliance by understanding the reasons maintaining the behavior

differences in males with KS (e.g. lack of gonadal development; sparse or absent facial hair; and thin, long-limbed body habitus) often become more evident and might result in body image disorders (Johnson *et al*., 1970).

Group psychotherapy could help KS adolescents to address their sense of isolation and shame and to get the support of peers. Psychological or psychiatric evaluation should be offered to all patients with KS because they may be at increased risk of anxiety, depression and psychoses or behavioral disorders (Smyth and Bremner, 1998). Psychological intervention could also be aimed to teach possible strategies in order to improve KS subjects' pharmacological compliance.

A recent study on quality of life of KS subjects reveals reduced well-being perceptions in patients with KS on androgen replacement therapy (de Ronde *et al*., 2009). The participation into KS Support Groups is suggested to reduce the sense of isolation and to support scientific research aimed at accelerating progress toward effective treatments.

Conclusions

The cognitive profile in KS is characterized by extreme variability. Developmental risk should be considered with specific regard to the language and, subsequently, with possible emotional and behavioral problems. An early diagnosis is useful in order to plan different types of rehabilitation, where the need is documented. KS subjects who have had prenatal diagnosis developed learning and language disabilities in a lower proportion than patients diagnosed by chance (Girardin *et al*., 2009). The potential benefits of testosterone therapy on cognition should be evaluated prospectively.

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