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REVIEW ARTICLE

Neuropsychiatric Aspects in Men with Klinefelter Syndrome

Vito Angelo Giagulli[a,*], Beatrice Campone[b], Marco Castellana[c], Ciro Salzano[d], Alessandra Daphne Fisher[e], Cristina de Angelis[d], Rosario Pivonello[d], Annamaria Colao[d], Daniela Pasquali[f], Mario Maggi[e] and Vincenzo Triggiani[a] on behalf of the Klinefelter ItaliaN Group (KING)

[a]*Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, Interdisciplinary Department of Medicine, University of Bari, School of Medicine, Policlinico, Bari, Italy;* [b]*Psychiatric Unit Department of Health Science, University of Florence, Italy;* [c]*via Turi 44 Rutigliano, Bari, Italy;* [d]*Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università "Federico II" di Napoli, Naples, Italy;* [e]*Sexual Medicine and Andrology Unit, Department of Experimental Clinical and Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy;* [f]*Department of Medical, Surgical, Neurological, Metabolic Sciences and Aging, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy*

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Abstract: ***Background and objective:*** Klinefelter Syndrome (KS) is the most common sex chromosome aneuploidy (47, XXY) and cause of male hypergonadotropic hypogonadism. It is characterized by an extreme clinical heterogeneity in presentation, including infertility, hypogonadism, language delay, metabolic comorbidities, and neurocognitive and psychiatric disorders. Since testosterone is known to have organizational, neurotrophic and neuroprotective effects on brain, the condition of primary hypogonadism could play a role. Moreover, given that KS subjects have an additional X, genes on the extra-chromosome could also exert a significant impact. The aim of this narrative review is to analyze the available literature on the relationship between KS and neuropsychiatric disorders.

Methods: To extend to the best of published literature on the topic, appropriate keywords and MeSH terms were identified and searched in Pubmed. Finally, references of original articles and reviews were examined.

Results: Both morphological and functional studies focusing on the brain showed that there were important differences in brain structure of KS subjects. Different psychiatric disorders such as Schizophrenia, autism, attention deficit hyperactivity disorder, depression and anxiety were frequently reported in KS patients according to a broad spectrum of phenotypes. T supplementation (TRT) was not able to improve the psychotic disorders in KS men with or without overt hypogonadism.

Conclusion: Although the risk of psychosis, depression and autism is increased in subjects with KS, no definitive evidence has been found in studies aiming at identifying the relationship between aneuploidy, T deficit and the risk of psychiatric and cognitive disorders in subjects affected by KS.

Keywords: Klinefelter Syndrome, Hypergonadotropic hypogonadism, testosterone, autism, schizophrenia, attention deficit, hyperactivity disorder, depression; anxiety.

1. INTRODUCTION

Sex differences, their characterization in psychosis and their interaction with laterality are placed within the context of the XY gene hypothesis [1]. Besides differences in clinical manifestations, age of onset and response to therapy, there is a sex-specific cerebral anatomical asymmetry known as "cerebral torque": this is represented by a bias (diagonal) from the right frontal to the left occipital owing to the lateralization of functions, in particular, the language. This asymmetry is more evident in males, whereas the brain seems to develop faster in females [2, 3]. Human "experiments of nature" are useful in analyzing the potential impact of anomalous sex-chromosome gene expression on cerebral dimorphism; among aneuploidies, Turner syndrome (45,X) and Klinefelter syndrome (47,XXY) (KS) are classified. KS provides the opportunity to study the possible role of the extra X chromosome on psychosis development.

On the long arm of X chromosome (Xq11.2-12), the androgen receptor (AR) is mapped. Several studies suggested a relationship between the polymorphism in the number of CAG repeats on exon-1 at the N-terminal domain and clinical signs (including height, arms span, body) composition

*Address correspondence to this author at the Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases, Interdisciplinary Department of Medicine, University of Bari, School of Medicine, Policlinico, Piazza Giulio Cesare, 70124 Bari, Italy; Tel: ++39-080-409-1368; Fax: ++39-080-409-1368; E-mail: vitogiagulli58@gmail.com

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and bone mineral density), as well as social behavior or preference for specific jobs [4, 5]. Testosterone (T) is known to have an organizational, neurotrophic and neuroprotective effect on the brain; since KS subjects may often show low levels of T, it can be hypothesized that hypogonadism could play a role in the characterization of neurocognitive functions and in psychiatric morbidity [6].

This review aims to sum up the latest and advanced researches on the relationship between aneuploidy, hypogonadism and neurological and neuropsychiatric disorders in KS.

2. METHODS FOR NARRATIVE REVIEW OF LITERATURE

To extend to the best of the published literature on the topic, a three-step search strategy was planned. First, we identified keywords and MeSH terms in Pubmed. Secondly, the terms above were searched in Pubmed. Thirdly, references of included original articles and reviews were searched for additional papers. The last search was performed on December 2017.

3. KLINEFELTER SYNDROME: CLINICAL FEATURES AND GENERAL ASPECTS

KS is the most common sex chromosome aneuploidy (47, XXY), occurring in 1:600 males, and represents the most frequent cause of hypergonadotropic hypogonadism in men [7, 8]. The 80-85% of KS patients are characterized by a 47, XXY karyotype. Other anomalies in the number of sex chromosomes have also been reported, including the presence of a further supernumerary X chromosome 48, XXXY, a 48, XXYY karyotype or mosaicisms such as 46, XY/47, XXY. The fifty percent of the supernumerary X chromosomes is of maternal origin, while the role of maternal or paternal age at the time of conception is still unclear. Even if it has gone by more than 70 years since Dr. Harry Fitch Klinefelter described the first case, the relationship between clinical phenotypes and genetic background has not been fully understood; in general, phenotype correlates with the number of extra X chromosomes, with mosaicism patients exhibiting less severe signs and symptoms [9].

KS is characterized by an extreme heterogeneity in clinical presentation. In 1960s-1970s, KS has been reported to be prevalent among men institutionalized because of mental disability or guilty of sexual crimes. The studies above had been extensively criticized, although their results were partially confirmed in subsequent observations [10]. At the time of writing of the present review, no well-defined guideline on KS diagnosis has been published; this is a confirmation that, despite improvements in understanding, the rise of a clinical suspicion is still challenging.

Only a minority of KS subjects are diagnosed before puberty (about 10%). Most KS subjects show normal pubertal development: T secretion is still preserved, as well as testicular development; following this, development of testes arrests and, in rare cases, even its involution occurs [11]. In line with this, a condition of a relative hypogonadism can be found in the transitional phase, when endogenous T levels appear to be in the lower part of the normal range. In two out of three adults, overt hypogonadism is generally diagnosed. Besides sexual dysfunctions and the fertility aspect (non-obstructive azoospermia) that today seem to be overcome in a satisfactory manner by the means of testicular sperm extraction, KS subjects present a large number of metabolic alterations which may increase their morbidity and mortality [12-14]. These could be influenced by the already stated number of supernumerary X, but also by the duration of diseases, the advancing age and, according to some authors, the delay in TRT [9].

In order to ensure the normal sexual development and to prevent long-term complications of hypogonadism, a preventive T therapy in adolescents with KS has been proposed [15]. However, it should be emphasized that it is not supported by sufficient evidence, since there has been no controlled clinical trial so far. Moreover, studies analyzing the effects of T replacement therapy (TRT) among KS subjects were cross-sectional and in none of them T dosing was standardized. Only two studies showed a partial correction of the fat mass/body mass ratio following TRT, while an improvement in cognitive performance was not demonstrated [16]. A recent review of the literature showed that the benefits of T therapy among KS are still uncertain, especially in those with normal T and high levels of gonadotropins [17].

Nevertheless, highly specific clinical features and laboratory findings include small and firm testicles (<4 cc), hypergonadotropic hypogonadism, gynecomastia, language delay and infertility, which are present in most of the affected subjects. Since KS may also have a clinical phenotype indistinguishable from 46, XY males, the evaluation of the karyotype is requested in order to clinch the diagnosis in difficult cases [9].

4. BRAIN MORPHOLOGICAL AND FUNCTIONAL STUDIES

Clinical studies confirmed that KS patients are characterized by smaller total brain, grey and white matter volume, compared to general population, suggesting that anatomical structures may be implicated in the impairment of cognitive, psychological, social and emotional domains [18-20]. In particular, KS patients displayed decreased grey and white matter volume in the insula, putamen, caudate nucleus, hippocampus, amygdala, right parahippocampal region, cerebellum, temporal lobe and frontal inferior orbita [18, 20-24]. On the other hand, KS patients are characterized by increased grey matter volume in right postcentral gyrus, precuneus, parietal, sensorimotor and occipital regions and enlarged lateral ventricles [18, 20, 21, 23-25]. Little information is available on the possible causes underlying the above-reported differences; nevertheless, the reduced grey matter volume of the amygdala, superior temporal cortex and insula and the increased grey matter volume in the parietal lobe of KS patients have been shown to be linked to sex chromosome number, whereas the increased grey matter volume in the motor cortex to the X chromosome number alone [26].

Grey matter volume reduction in the hippocampus, parahippocampal cortices and amygdala is associated with memory impairment and mood dysregulation [20, 23]; in particular, the involvement of amygdala may be related to atypical

temperament, passivity and reduced sexual drive [20]. The decreased left inferior frontal area and the motor strip, particularly on the left side, were linked to the muscular weakness in the trunk and shoulders [21, 27]. On the contrary, the increased grey matter volume in the sensorimotor and occipital regions in KS was associated with sensorimotor deficits [20]. Ventricular volume was demonstrated to be inversely correlated with verbal processing speed and verbal executive function [24]. The literature on this topic is conflicting and other authors have found no significant association between changes in grey matter volume and cognitive and psychological factors in KS patients [18].

Few clinical studies concurrently evaluated brain structure and functionality in KS patients. Studies focusing on brain activity by single photon emission computed tomography (SPECT) and measuring regional cerebral blood flow (rCBF) demonstrated that in KS patients, rCBF was significantly increased in the right hemisphere regions, in particular in prefrontal motor, parietal associative and temporal language areas, when compared to controls; moreover, increased rCBF in several right-sided temporal gyri was associated with lower verbal scores [28]. Studies with functional magnetic resonance imaging (MRI) found that the activation of the amygdala and the insula, areas involved in socio-emotional function and in subjective emotional experience, respectively, were reduced in KS. Moreover, the activation of the fusiform gyrus and the superior temporal sulcus, which play a role in the perceptual processing of faces, was also reduced [29]. Lastly, in KS patients, a less lateralized language activity was demonstrated, due to increased activity in the right and reduced activity in the left hemisphere, particularly in the superior temporal gyrus and the supramarginal gyrus regions. These functional changes were associated with impaired thinking and language skills [30].

Few clinical studies focused on the effect of TRT on the brain and neural pathways and brain volume in KS, with conflicting results as well. Studies comparing T-treated and untreated KS patients found no differences in total brain, grey and white matter volume [18, 24]. A study comparing prepuberal KS with controls confirmed that T levels did not influence grey and white matter volume [20]. In contrast with these results, a second study demonstrated that T-untreated KS patients had smaller temporal volume when compared to the general population, whereas no significant difference was found between T-treated KS patients and the general population [31].

In summary, the results of morphological and functional studies focusing on the brain demonstrated that KS patients are characterized by significant differences in brain structure, including reduced total brain, grey and white matter volume, when compared to general population; these differences have been associated with functional impairment, involving in particular language abnormalities, but further research is still warranted.

5. THE XY THEORY FOR PSYCHOSIS: THE ROLE OF X CHROMOSOME

It is well known that the X chromosome carries genes responsible for the neural development as well as cognitive and mental functioning [22]. In general, a greater vulnerability to psychopathology has been reported among KS [32-38]. Considering the schizophrenia spectrum disorders, KS has been found to show higher scores in all domains regarding schizotypal and schizophrenia symptoms [34]. Furthermore, studies using cytogenetic analysis on patients suffering from schizophrenia and other psychotic disorders found a higher prevalence of 47,XXX and 47,XXY karyotypes when compared to general population [32, 33, 36, 39-42].

Among KS, psychiatric symptoms encompass different manifestations, according to a broad spectrum of phenotypes [8]. In particular, an increasing incidence of conduct disorders, anxiety and depression, deficits in attention and impulse control was found [43-45]. A higher risk for autism and attention deficit hyperactivity disorder (ADHD) traits were reported [32-38].

Psychobiological traits (endophenotypes) associated with psychosis have also been described. In psychosis, the most frequent endophenotypes are eye tracking dysfunction, including smooth pursuit eye movement (SPEM) and sensory gating which are both genetically determined. Sensory gating is commonly evaluated through prepulse inhibition (PPI) and P50 suppression. Van Rijn *et al.,* demonstrated significant impairment in SPEM and PPI in KS patients when compared to controls, while no differences were found in P50 [42, 46-56].

From an intelligence quotient (IQ) perspective, even if KS shows normal IQ scores, two specific cognitive patterns can be described: one is characterized by verbal IQ (VIQ) score lower than performance IQ (PIQ) (VIQ < PIQ), the other by PIQ lower than VIQ (PIQ < VIQ) [57, 58]. The former shows the significantly higher level of autism traits; the latter presents higher schizotypal traits, in particular, magical thinking, delusional ideation and eccentric behavior. These associations are independent of age [59-61].

A reduction of the mesial temporal lobe bilaterally has been proposed as the biological mechanism leading to vulnerability to psychosis [62-64]. This is in line with findings among patients at risk or suffering from schizophrenia as confirmed in MRI studies [65-70].

6. PSYCHIATRIC DISORDERS AND PSYCHOPATHOLOGY ASSOCIATED WITH KLINEFELTER SYNDROME

As already stated, a large number of studies reported an increased risk not only for psychotic disorders but also for depression and anxiety in KS [19, 36, 41, 44, 71, 72].

A survey conducted in Denmark among 832 KS patients and 4033 controls showed an increased risk of hospitalization for psychiatric disorders (HR 3.65) [32]. Other studies reported a high prevalence of depression ranging from 19 to 24% [36, 41]. It has been questioned whether depressive symptoms are specifically associated with genotype alterations in KS or are consequences of physical and emotional traits due to the syndrome [73]. Van Rijn *et al.* reported an increasing emotional arousal and difficulty in the identification and verbalization of emotions [34]. The organic basis for this could be probably found in alterations in the amygdala and other limbic structures involved in the

regulation of emotions, as well as in aggressive and impulsive behaviors [74-77]. A role for genetic and hormones in the early stages of development has been hypothesized, as confirmed by the finding of estrogen and androgen receptors in mammalian hippocampus and amygdala and in the temporal area in human [78-81]. Another proposed factor is the cortisol level, increasing during anxiety and depression states [82, 83]. A relationship between hypogonadism and depression has also been proposed. Two population-based studies showed a hazard ratio of 4.2 for depression being hypogonadal and of 1.55–2.71 for hypogonadism being depressed [84, 85]. Indeed, evidences on this topic are conflicting: some studies reported an improvement in depression in KS undergoing TRT, while others did not [86-88]. However, the link between hypogonadism and depression might be considered in the light of the shared symptoms.

For what concerns anxiety, a study of Tartaglia *et al.* screened behavioral features of 57 KS: 25% reported pathological effects or had increased risk scores in the areas of anxiety, depression and somatic complaints; 50% were in the area of social withdrawal [89]. These results were confirmed by Bruining *et al.* in a study on 50 KS: depressive disorder was reported in 24% and anxiety disorders in 32% [36]. Anxiety and depression are the bases for difficult social interactions; in particular, they show social anxiety and withdrawal, problems in peer-relationships, social impulsivity and shyness [30, 58, 71, 90-94].

Psychopathological traits in KS should be considered in the light of cognitive dysfunctions related with chromosome trisomies, such as difficulties in speech and language, motor skills, educational achievement and, hence, in basic psychophysiological mechanisms in the area of visuo-motor control and sensory gating [95].

A significant clinical variability in cognitive functioning and school performance has also been found in KS [57, 96, 97]. When compared with other chromosomal trisomies (trisomy 21, trisomy 18), KS on average does not suffer from global intellectual disability [97]. However, many studies associated KS with mild cognitive impairment; specifically, subjects with XXY-karyotype are reported to be more dysfunctional in the language area, while XXX have mild global intellectual delay [96, 98, 99]. Indeed, according to some epidemiological studies, groups of subjects with mild learning disorders, also have higher rates of psychiatric disorders [100, 101].

CONCLUSION

Given that X chromosome has numerous genes co-regulating neural development, cognitive and mental functioning and given that KS is an aneuploidy characterized by at least an extra X chromosome, it can be considered a human "experiment of nature" to verify the role of those genes in psychosis disorders. Several psychiatric symptoms have been associated with KS according to a broad spectrum of phenotypes. Schizophrenia, autism, attention deficit hyperactivity disorder, depression, anxiety and conduct disorders were those more frequently reported in different surveys.

Although it is generally accepted that the basis of vulnerability to psychosis is a reduction of mesial temporal lobe bilaterally, especially the reduction of gray matter in that area, MRI studies carried out in subjects with KS have been inconclusive so far. Similarly, TRT, even in those KS subjects with a deficit of T, was unsuccessful in enhancing the psychotic disorders.

In conclusion, the risk of psychosis, depression and anxiety is increased in subjects with KS. Additional studies are needed to better define the relationship between aneuploidy, T deficit and the risk of psychiatric and cognitive disorders in subjects with KS.

LIST OF ABBREVIATIONS

AR	=	Androgen Receptor
rCBF	=	Regional Cerebral Blood Flow
KS	=	Klinefelter Syndrome
IQ	=	Intelligence Quotient
MRI	=	Magnetic Resonance Imaging
PIQ	=	Performance Intelligence Quotient
PPI	=	Prepulse Inhibition
SPEM	=	Smooth Pursuit Eye Movement
T	=	Testosterone
TRT	=	Testosterone Replacement Therapy
VIQ	=	Verbal Intelligence Quotient

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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