# Violent behaviors and Klinefelter Syndrome: Two forensic cases from the past to the future

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**ABSTRACT**

Klinefelter Syndrome (KS) (XXY) is the most common sex-chromosome aberration among men. The cognitive phenotype includes language learning problems, mental retardation, and psychiatric disorders. Patients can show criminal personality and psychosocial problems. The most common offences reported are sexual abuse, arson, burglary, homicide, drug-related crimes. KS very often goes underdiagnosed. The aim of our study is to verify the hypothesis of correlation between chromosomal abnormalities and criminal behaviors through the analysis of a forensic case of uxoricide/suicide. We report the case of an old man, found dead in his cottage with a gun in the right hand. Judicial inspection demonstrated suicidal single gunshot injuries. Data analysis highlighted a personal story of uxoricide. Autopsy investigation showed the typical KS phenotype. The post-mortem clinical diagnosis was confirmed through the genetic analysis of the karyotype. The retrospective analysis of literature with this case showed a possible correlation between KS and psychiatric traits, with criminal personality and sexual disorders.

**RIASSUNTO**

La Sindrome di Klinefelter (KS) (XXY) è l'aberrazione cromosomica più comune tra gli uomini. Il fenotipo cognitivo include problemi di apprendimento linguistico, ritardo mentale e disturbi psichiatrici. I pazienti possono mostrare personalità criminale e problemi psicosociali. I reati più comuni riportati sono abusi sessuali, incendio doloso, furto con scasso, omicidio, reati connessi alla droga. KS molto spesso va sotto-diagnosticato. Lo scopo del nostro studio è verificare l'ipotesi di correlazione tra anomalie cromosomiche e comportamenti criminali attraverso l'analisi di un caso forense di uxoricide / suicidio. Riportiamo il caso di un vecchio, trovato morto nella sua casetta con una pistola nella mano destra. Ispezioni giudiziarie hanno dimostrato lesioni suicide con singolo colpo d'arma da fuoco. L'analisi dei dati ha evidenziato una storia personale di uxoricide. L'indagine dell'autopsia ha mostrato il tipico fenotipo KS. La diagnosi clinica post-mortem è stata confermata attraverso l'analisi genetica del cariotipo. L'analisi retrospettiva della letteratura con questo caso ha mostrato una possibile correlazione tra KS e tratti psichiatrici, con personalità criminale e disturbi sessuali.

**RESUMEN**

El síndrome de Klinefelter (KS) (XXY) es la aberración de cromosomas sexuales más común entre los hombres. El fenotipo cognitivo incluye problemas de aprendizaje del lenguaje, retraso mental y trastornos psiquiátricos. Los pacientes pueden mostrar personalidad criminal y problemas psicosociales. Los delitos más comunes reportados son abuso sexual, incendio premeditado, robo, homicidio, delitos relacionados con drogas. KS muy a menudo va bajo diagnosticado. El objetivo de nuestro estudio es verificar la hipótesis de correlación entre las anomalías cromosómicas y las conductas delictivas mediante el análisis de un caso forense de uxoricida / suicidio. Informamos el caso de un anciano, encontrado muerto en su casa con un arma en la mano derecha. La inspección judicial demostró lesiones suicidas con un solo disparo. El análisis de datos resaltó una historia personal de uxoricidio. La investigación autopsia mostró el fenotipo típico de KS. El diagnóstico clínico post mortem se confirmó mediante el análisis genético del cariotipo. El análisis retrospectivo de la literatura con este caso mostró una posible correlación entre el SK y los rasgos psiquiátricos, con personalidad criminal y trastornos sexuales.

## Introduction

### History and general characteristics of the syndrome

The most common abnormality of sex chromosomes in humans is the 47, XXY aneuploidy, Klinefelter's Syndrome (KS). KS has an incidence of 1/500 male live births but it is diagnosed in only one-third of the affected. Many individuals with KS have no medical issues and are thus underdiagnosed, whereas others have been diagnosed *post-mortem*.[1-2]

Klinefelter, Reinfenstein and Albrigh were the first to describe in nine subjects a syndrome characterized by gynecomastia, azoospermia, hyalinized and small testes, elevated levels of follicle-stimulating hormone (FSH) and hypogonadism.[3] Recent brain imaging studies suggest a reduction in the brain volume including both white and gray matter tissue.[4-5] In 1957, Pasqualini and colleagues were the first to propose a genetic origin for Klinefelter's syndrome in an important review of the literature. In fact, they observed in a significant proportion of KS cases the presence of chromatin bodies in the cell nuclei of bioptic samples taken from skin, mucosal scrapings, and Leydig cells.[6-10] The authors proposed that these chromatin bodies were likely to be indicative of

the presence of the female Chromosome pair XX. That means, some patients with Klinefelter's syndrome might be genetically females. Apart from these findings, Pasqualini *et al.* also analyzed KS patient's behavior, which since childhood appeared to be characterized by apathy, timidity, hypokinesia, scarce intelligence, lack of initiative. In relation to sexual behavior, in the 70% of cases patients had heterosexual relations, but two of the affected had homosexual experience, occasionally. Some of those patients were characterized by eunuchoidism and had suffered from a severe decreased in libido and potency. Three patients were married, but referred sexual drive reduction.[7,10-13] Different associations between KS and congenital malformations, changes in testicular development, infertility, diabetes, metabolic syndrome, cardiovascular disorders, cancer and osteoporosis were studied. An issue of particular interest is the evaluation of cognitive impairment, psychiatric and criminal personality in KS.

## Genetics of the syndrome

Jacobs and Strong studied the genetic cause of this syndrome, characterized by the presence of one Y chromosome and two or more X chromosomes in a phenotypic male.[14,15] The most prevalent type of karyotype is 47, XXY, but it is not uncommon to have supra-numerous X chromosomes or mosaicism with a mixture of normal and 47, XXY cells.[15] The genetic etiology of Klinefelter Syndrome is caused by paternal meiotic non-disjunction that generates haploid gametes.[15] This generates trisomies and monosomies. The maternal and paternal non-disjunction happens approximately in 50% of cases of Klinefelter Syndrome. Mother's age can also influence the risk to generate a child with KS. The genotype is characterized by partial inactivation of X-chromosomes, with an over-expression of X linked genes, that in common meiosis is avoided. The AR, localized on the X chromosome, encryption the receptor of androgen. It contains tri-nucleotide polymorphic sequence CAG, extremely repeat in exon 1. The androgen receptor function is inversely related with the length of this CAG repeat. Consequently, a short sequence of CAG is related to specific effect of androgens. The X chromosomes with shortest AR CAG repeat has been proved to be inactivated, during the process nominated "skewed or non-random X chromosome inactivation". In patients with short AR CAG there is a better response to androgen therapy. In patient with Klinefelter Syndrome the hypogonadal phenotype is the effect of non-random X chromosome inactivation that clarify the physical aspect of the affected.[15]

In the last few years, it has been demonstrated that the upstream genetic effects of sex chromosomes act on brain development independently of downstream hormonal factors and, furthermore, they depend on the quantity of sexual chromosomes. This dose-dependent effect can be explained on the basis of gene expression of pseudo-autosomal regions (PARs). Contrary to what happen for other genes on the X chromosome that can be inactivated, genes of PARs have homologous ones on the Y and the other X chromosome. So, these genes are over-expressed in Klinefelter syndrome. This hypothesis is supported by the evidence that the increase in the number of SHOX gene copies on PAR1 is related with body height. Indeed, affected males, which have three SHOX copies, are taller than unaffected ones. Furthermore, some studies show that dysregulation in the expression of some genes in PAR1 may impact on cognition and neuroanatomy.[16]

## Brain development and neuroanatomical correlations

Neurogenetics has an important role in the explanation of the correlation between KS and psychiatric and cognitive deficits. Neuroanatomical changes demonstrated by neuroimaging studies have been associated with KS. The affected individuals present a reduction of total grey and white matter volume. In particular, several studies have shown increased sensorimotor and parietal grey matter volume and reduced amygdalar, hippocampal, insular, temporal, and inferior frontal grey matter volume, that means left parietal white matter volume against frontal and temporal white matter volume. The affected subject has a larger grey matter distribution in bilateral pre and post central gyri and in bilateral parietal-occipital regions, expanding towards the occipital pole. Patients are also characterized by substantial differences in verbal and non-verbal ability. White matter reductions are associated with language abnormalities. In particular, the reduction of superior temporal gyrus and hippocampal volumes is associated with modifications in verbal memory and auditory processing.[16]

The grey matter enhancement in sensorimotor regions in Klinefelter Syndrome could be generated from low synaptic maturation or trimming, leading to increase volume of neuropil, decreased efficiency of synapses, and correlated deficits of sensorimotor system. This, in association with the grey matter regional reduction in hippocampus, parahippocampal cortices and amygdale, suggests the presence of a neuroanatomical substrate for memory deficit and mood alterations, correlated with the incidence of psychiatric disorders.[17] The amygdale volume reduction may also be related with atypical temperament, passivity, and decreased sex drive, typical characteristics of the individuals affected by Klinefelter Syndrome.[18]

## Psychiatric characteristics and behavior in KS

Several studies have demonstrated so far the presence of a high frequency of correlation between KS and neuropsychiatric anomalies. Yet in 1942, Klinefelter and colleagues suggested that patients affected by Klinefelter Syndrome showed a psychiatric syndrome characterized by hysteria, low intelligence and narcolepsy. Also, Heller and Nelson in 1945 observed in six KS patients nervousness, irritability, depression, loss of potency, worrying.[10,13] The main psychiatric comorbidities for KS are mood disorders, cognitive deficits and personality disorders. This contributes to difficulty in social adaptation and onset of behavioral problems. In a study a KS affected male group obtained weaker results than controls in the recognition of facial emotions and, in particular, of disgust and contempt. Similar results have been obtained for feelings of fear and anger. Disgust and contempt are less frequently felt during the day and this can explain the difficulties to identify these feelings. A wrong perception of emotions and troubles to attribute a state of mind to the others may alter the attributional process. Less attentional and executive abilities could have a negative role on the social cognition ability. Indeed, even if the KS group has good capability in visual attention, in this study it has been noted that this ability is not effectual when it is not focused on the right place. Visual attention must be brought to the face to be effective. The authors conclude that alterations in various components of the social cognition can be taken into account as KS phenotypic trait marker.[19] Regarding mood disorders, in a study on a population of 243 participants, it was found that 69% of people were at risk for depression and had relevant levels of depressive symptoms. An important factor in determining depressive symptoms in KS patients is infertility, for the important emotional distress it causes.[20] Moreover, many studies emphasize that people with KS occupy work roles often less prestigious and this can result in the onset of depressive symptoms.[2] Regarding cognitive functioning in KS patients, it has been shown that the most of subjects have a normal intellectual level, but a heterogeneity of intellectual profiles is reported.[21] An incidence of 1.2% of XXY subjects in pre-pubertal age was detected in a cluster of subjects with intellectual disabilities

for unknown cause.[2,22] Comorbidity has been described between cognitive limitations, KS, seizures, and with increasing number of supernumerary X chromosomes.[2,23] It has been shown that the number of supernumerary X chromosome is negatively correlated with intellectual development and with the height.[1,2,24] In subjects with atypical aneuploidy compared with those with XXY, the verbal scale is reduced, while the performance IQ is less reduced.[2] Language disabilities are also reported in KS patients and they are documented in 70–80% of XXY males, depending on estimates.[2,17,25] Language deficits are one of the more distinctive features in cognitive functioning of people with KS. These deficits cause delay in acquisition of the main stages of language development, and more specific difficulties, such as in the articulation of sounds or syllables in lexical retrieval and processing phonemes. Therefore, these difficulties result in limitations in reading, expression, writing and reasoning abilities in arithmetic. Even children with Klinefelter Syndrome have specific difficulties in reading in 50% of cases.[2,26] Language difficulties are associated with a dysfunctional lateralization.[1] Patients with KS shows difficulties in all tasks requiring the use of language skills, especially in the more complex aspects of expressive language, conditioned by the verbal memory, the recovery of words and verbal fluency. Functions, like understanding of grammar, syntactic expression of opinions, use of complex grammatical structures, are deficient in these patients. Further, they have limitations in storage of auditory verbal material, which are associated with problems in decoding words, especially when the reading is done aloud.[2] This aspect is very important because it generates limitations in social adjustment, communications, personality and behavioral aspects. Learning difficulties usually appear in early school age and the difficulties in achieving good results, together with relational difficulties, cause feeling of distrust and contempt. Most of the sufferers 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.[2] For what concern personality, increased schizotypal and autistic traits were observed in individuals with Klinefelter Syndrome. There is evidence of common structural and functional abnormalities in the brains of subjects with KS and schizophrenic patients.[2] The affected subject reports emotional stimulation in every event that induce emotion, and is influenced in every decision.[27] Studies suggest that X chromosomal abnormalities enhance for KS patients the risk to be hospitalized for psychoses.[15,28,29] As mentioned before, school-age children and adolescents with XXY often show low self-esteem, anxiety, mood disorders and problems of socialization, but during the late adolescence and adulthood, behavioral problems related to poor impulse control become manifest.[2] Steadily high fatal/circulating testosterone is correlate with antisocial behavior. In fact, male gonadal hormones such as testosterone have a critic role in the determinism of chronic antisocial behavior.[30-32] Testosterone is the uppermost male gonadal hormone that influences the brain activity depending on the time of exposure.[33] Greater levels of fetal exposure to testosterone is able to awareness and is masculinizing behavioral responses still life.[33,34] In particular, in childhood the claimed disorder and in adulthood the antisocial personality disorder or psychopathy are correlated to higher testosterone levels.[35-40] Children characterized by traits of callous-unemotional, are at risk of callous violence and antisocial behavior.[41-43] In adulthood, two personality disorders, APD (Auditory Processing Disorder) and BPD (Borderline Personality Disorder), are associated and predictive of antisocial behavior.[44-46] Recent studies and meta-analyses have already confirmed the relation between fetal/circulating testosterone and aggression in humans.[47-51] These studies have demonstrated that high fetal or circulating testosterone has an important influence on the maturation and functionality of mesolimbic dopaminergic circuitry, right orbitofrontal cortex and cortical-subcortical connectivity, consequently cause alteration of motivation, low social sensitivity and influence motivational/emotional processes. Therefore, in conclusion, testosterone induces endophenotypes that could induce a major risk of a chronic antisocial lifestyle.[46] Furthermore, a study conducted on a sample of 46 KS individuals and 43 healthy male controls reported a higher risk in patients with Klinefelter syndrome to develop hypersexuality, paraphilic behaviors and gender dysphoria, which were mediated by obsessive-compulsive and autistic traits. So it is important to evaluate and eventually treat obsessional thoughts and symptoms when hypersexuality and gender dysphoria are suspected in KS.[52]

## Case Report

Here we report the case of a 78-year-old man. The corpse was found in his apartment in December 2011 in Southern Italy. The corpse was lying on the bed with a gunshot wound injury on the left and right temporal regions (Figure 1). The external examination showed a clear gynecomastia with spars body hair. The retrospective analysis of the case with investigators showed an uxoricide made by the same man in the past.

### Autopsy findings

A gunshot wound injury was analyzed. Ballistics evidences demonstrated the characteristics of entrance and exit wounds respectively on the right and left temporal regions. At autopsy, the reconstruction of intracranial bullet course showed an intracerebral hemorrhage with frontal lobes injuries and debacle of corpus callosum. The terminal ballistics analysis has established a single gunshot injury.[53] Left lung analysis showed histological features of lung cancer. At the liver left lobe it was revealed a pearly white area, probably of metastatic origin. The cryptorchidism with small testicle in abdomen and partially empty scrotum was shown. In this case some clinical data typical of KS were found and are reported below: gynecomastia, hypogonadism, micropenis, tall stature (183 cm), narrow shoulders, wide hips, female hair distribution, spars

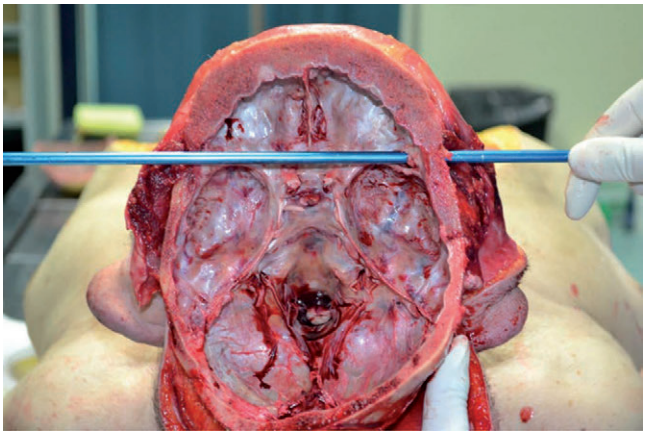

**Figure 1. Gunshot wound injury on the left and right temporal regions.**

body hair, testicular dysgenesis with right cryptorchidism; skeletal abnormalities with pectus excavatum and cranial hyperostosis; eunuchoid habitus, venous insufficiency; disproportion thorax-limbs, hypertelorism, gynoid fat distribution; lung carcinoma (Figure 2,3 and 4).

Data from the circumstantial inspection and judicial autopsy determined the suicidal modality of death.[54] The suicide was confirmed by a small excoriation between the first and second interdigital finger of right hand which took the gun. It was confirmed by the presence of gunshot residue by SEM analysis on samples taken from the right hand and by the presence of victim's fingerprints on the gun.

## Psychiatric analysis of the setting

Also, it was made a survey on the old man family life history by the psychological autopsy method. The investigation demonstrated a medical history of infertility. It was performed an analysis on his criminal pending proceedings which revealed an uxoricide story about 50 years ago (1962). In the court's archives it was conducted a search of the statements made by the man (husband) during interrogation. The examination of court records showed that the 25-year-old woman was killed by her husband with single gunshot injury. She was transported to the near hospital and the doctors showed "internal bleeding from gunshot wound penetrating into the abdominal cavity". In the intervening time her husband vanished and was arrested too later.

## Genetic analysis

The chromosomal aneuploidy typical of the disease can be detected by screening methods based on use of PCR, but diagnostic confirmation requires examination of the karyotype.[15] "Klinefelter's syndrome is diagnosed by karyotype with more than two X- and one Y-chromosome".[1] At present, the most widely used methods for the determination of the genotypic sex using the detection of the Y chromosome in males. The cytogenetic analysis is considered the conventional method for the identification of sex and for the relief of other chromosomal aberrations. It is a rapid, non-invasive and inexpensive method, although not able to detect mosaicism and chromosomal abnormalities.[55,56] Before the advent of genetic diagnosis of disorders related to 'X-linked, with a view to rapid and reliable determination of sex, were used different techniques such as: the non-radioactive *in situ* hybridization, the hybridization with fluorescence in situ hybridization (FISH) and the PRINS, labeling technique triggered *in situ*.[56,57] In addition, for the determination of the sex, the DNA analysis is exploited; the most used techniques are the dot blot hybridization and polymerase chain reaction.[56-58] The diagnosis of sex was attempted through: the cytogenetic study[56,59] ultrasound, biopsy of the gonads and the study of hormonal profiles, in addition to PCR amplification for the detection of SRY and gene loci on chromosomes Y and X. After DNA extraction, we proceeded with PCR amplification. Each 15 µL PCR reaction contains 100 ng DNA, 1.5 µL of 10X buffer II (Perkin Elmer), 1 µL 25 mmol of dNTPs, 1.5 mM MgCl2, 1 pmol of each primer SRY and ATL1, and 0.25 units of Taq DNA polymerase. The reactions were performed in a thermal cycler (Perkin Elmer 480): it begins with cycles of predetermined duration (15 s) at 94°C, followed by cycles of 20 s at 65°C to favor the pairing of primers followed by cycles of 20 s at 72°C to the extension of the primers, with a final extension cycle of 72°C for 10 min. The product obtained after is separated on 2.5% agarose gel, stained in ethidium bromide, and visualized under UV transillumination. Five primer sequences were used to determine the sex.[56,60] A case of Klinefelter Syndrome was suspected during the autopsy, due to the detection of small testes associated with tall stature. In this case, a DNA test was performed in order to confirm the genetic abnormality. By pathological examination were observed sclerotic tubules and hyaline, with the presence of germ cells and sperm.

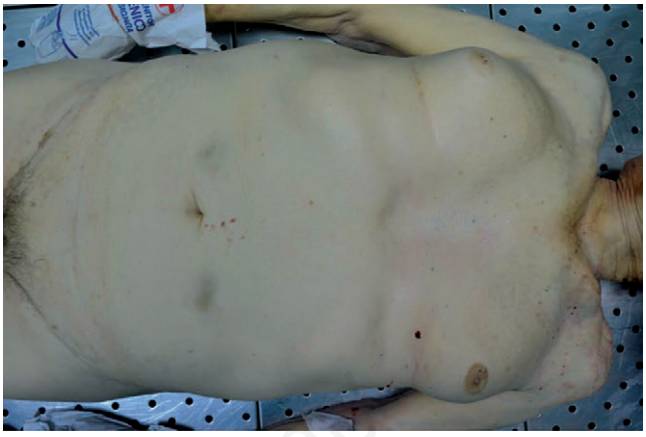

**Figure 2. Gynecomastia of the man.**

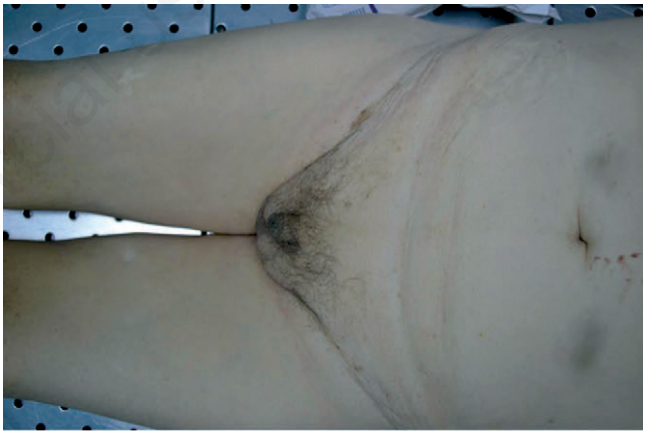

**Figure 3. Hypogonadism and micropenis of the man.**

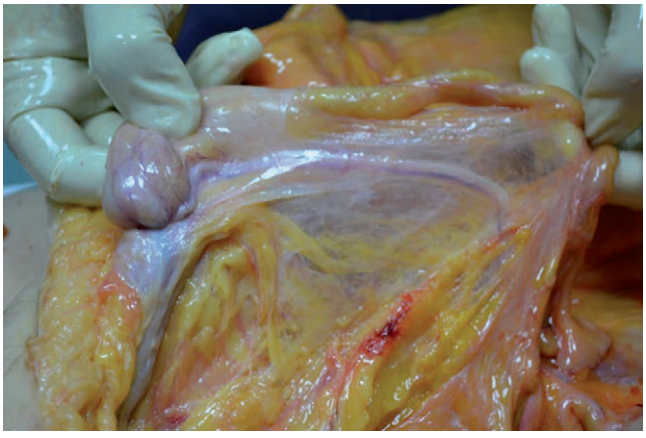

**Figure 4. Testicular dysgenesis with right cryptorchidism.**

## Discussion

At present there is not a clinical definition of Klinefelter's syndrome, however, the correct diagnosis must be based on the presence of some clinical data, combined with an assessment of cytogenetic confirmation. This is confirmed by a meta-analysis in the United Kingdom, where the 26% of adults were diagnosed and a percentage of between 4% and 10% of children, suffering from this syndrome. A possible reason for the difficulty of diagnosing Klinefelter's syndrome, is the great clinical variability that characterizes the syndrome. The few subjects diagnosed in childhood are those suffering from the syndrome associated with a phenotype characterized by particularly severe dyslexia, above average height for age, gynecomastia, while the majority of patients diagnosed in adulthood are characterized by infertility and hypogonadism. Usually, Klinefelter syndrome is diagnosed by karyotype analysis and/or recognition of the sex chromatin. In this case, this method confirmed the diagnosis. Another case reported in the literature is a *post-mortem* diagnosis of KS, found with hypogonadism and a bilateral testicular nodule, during autopsy. The diagnosis was confirmed by FISH technique. Fluorescence in situ hybridization for sex chromosomes, the hormonal profile in serum and histological examination of testicular tissue, with subsequent visualization at light microscopy and electron microscopy. In this case, physical condition and stature of the subject during his life haven't raised suspicion, but the finding of hypogonadism post-mortem has suggested the diagnostic hypothesis. The FISH subsequently carried out on tissue samples, showed a karyotype characterized by mosaicism 46, XY, 47, XXY. Afterwards, post-mortem survey has given the opportunity to demonstrate a Klinefelter Syndrome in cases where the clinical features in life may not be indicative of the disease. The mosaic karyotype may be regarded as consistent with a lesser degree of clinical expression of Klinefelter syndrome, as in this case. The Leydig cell hyperplasia is associated with KS and is based on testicular atrophy.[61-64] A bilateral nodular Leydig cells hyperplasia, as shown here, is a variation on the theme of Leydig cell proliferations, which appear to be common in this syndrome.[61,64] In literature there are not studies that have analyzed the best technique for *post-mortem* diagnosis. Surely death makes it difficult to analyze the karyotype. Although indirect diagnostic signs in addition to those trials are represented by typical histological changes in testicular tissue. Histological indirectly sign in the adult age group may be the hyalinization with interstitial fibrous degeneration of the testis, as confirmed in living. This figure is less susceptible to mistakes the investigation of the karyotype in the corpse, although the most specific technique is the karyotype's investigation. Furthermore, are known molecular biology investigations utilizing specific probes for chromosome X. In the literature these techniques aren't reported as investigations used on the corpse, but only on the living. For this reason, in the treated case was made a histological investigation of the testes. Therefore in this case was confirmed diagnosis of KS. The analysis of human psychiatric data instead showed a behavioral framework characterized by shyness and poor social relationships. These behavioral characteristics, as demonstrated by the literature, are peculiarities of KS. Even our study, in accordance with the literature, showed this correlation. Furthermore, in a study conducted on a sample of 58 patients, the prevalence of these disorders was higher than the general population. More than 40% of the sample showed altered results at four MMPI scales -social responsibility, dominance, Ego Strength and Repression- and their personality pattern was characterized by unreliability, unlikelihood to take on positions of leadership or responsibility within a group, pessimism, and rigidity in their problem-solving approaches. According to some studies, relative deficits in verbal abilities seem more strongly associated with increased autistic traits, whereas relative deficits in visuospatial abilities seem more strongly associated with increased schizotypal traits. Authors found that KS subjects with higher fluid intelligence and with lower raw scores in five basic MMPI 2 scales (hypochondriasis, depression, psychopathic deviate, psychasthenia, schizophrenia) and in supplementary scales (fear, health concerns, low self-esteem, MacAndrew Alcoholism Scale and Marital Distress Scale) feel healthy, insightful, cheerful and well-identified with social standards and have better impulse control, fewer obsessive-compulsive, schizoid and phobic symptoms, a wide range of interests, lower risk for substance addiction and a better relationship with their partner. This study found that testosterone is not likely to influence cognitive performances in KS adults. The authors did not find any statistically significant difference in personality disorder prevalence and cognitive abilities in treated and untreated patients. However, was observed that testosterone replacement therapy reduced marital distress in KS males, because improves physical symptoms and therefore even relationship abilities and wellbeing and not only frequency/quality of sexual activity. In addition, the literature has shown a correlation between the KS and criminal behavior. Richard-Devantoy *et al.* in their retrospective study analyze the interaction of homicide factors in men diagnosed with Klinefelter syndrome. The factors that lead to homicide in Klinefelter syndrome are complex, heterogeneous, and interactive. Personality features reported in men with the XXY karyotype include passivity, poor concentration, emotional immaturity, shyness, and hypersensitivity and a deficit in inhibitory executive functions. For the authors, the association between Klinefelter syndrome and violence could be linked to a lower verbal IQ. In addition, low IQ and psychiatric symptoms and disorders are more clearly associated with homicide, but the discovery of rare chromosomal abnormalities in cases of homicide should not be the only explanatory or predictive factor for the criminal act. In fact, the overall risk of homicide in men with Klinefelter syndrome was similar to that of controls after adjusting for socioeconomic parameters. Furthermore, homicide has also been related to several nonpsychiatric factors, including the personal history of the perpetrator (as history of violence, juvenile detention, physical abuse and parental arrest record), dispositional (as male gender, younger age and low socioeconomic status) and contextual factors (as recent divorce, unemployment, and victimization). So, to explain the criminal act, the authors propose the hypothesis that numerous comorbid risk factors might be much more clearly involved in homicide than Klinefelter syndrome, even with a multiplicative effect.[65] In the case we examined the analysis of human criminal record showed a history of femicide in the past and subsequent suicide after years. As widely discussed in literature, this association is partly motivated by neurogenetic factors related to neuroanatomical changes. Besides, in the case examined, we found a cranial hyperostosis and a reduction in brain volume.

A study analyzed 296 newspaper articles about 45 homicide-suicide cases in North America. It highlighted that most perpetrators are men and motivations behind these actions are related to idea of "masculinity". Above all the hegemonic masculinity proved to be harmful for the men well-being. Moreover, three main themes are emerged: 1) domestic desperation, 2) workplace justice, 3) school retaliation. Cases in the domestic desperation theme were characterized by the murder of a family member and the basis was men's self-perceptions of failing to provide economic security. Workplace justice cases emerged from men complaints about paid-work, job insecurity, and perceptions of being bullied and/or marginalized by coworkers or supervisors. The school retaliation cases

were linked to the revenge for the hardships suffered by perpetrators. The common reason to three themes was men's loss of control in their lives, hopelessness, and marginalized masculine identities. So, it is important to recognize the link between masculinity and homicide-suicide cases, in order to identify potential Murder-Suicide perpetrators. These individuals could benefit from strategies for prevention of violent behaviors. In this regard, authors identify three key-points for murder-suicide prevention strategies. First point concerns weapons and their availability. In the context of gender, guns have been linked to masculine identities. One challenge is to separate masculinity from the reactive and fatal use of guns and to propose alternative models to state their reason instead to use this type of violence.

Second, in the cases there are implicit and explicit references to mental illness when describing the M-S perpetrators. Acute and chronic mental and psychological distress entwined with idealized masculinity, including resistance to seeking professional help, are shown by perpetrators. Equipping and educating service providers to better identify and treat men's mental illnesses may help address some of these issues. Third, while it is affirmed the importance of masculinity in men's illness, less often discussed are men-centered interventions. It would be important to begin to assert less rigid ideals and plural masculinities to reduce the likelihood of action among potential male M-S perpetrators. For example, potentially emasculating issues, financial and family provider failures and being visibly weak and subordinate can catalyze men's M-S actions and violence as masculine ways to contest oppression. Indeed, many men overidentify with popular culture's hypermasculine ideals in attempting to regain their sense of control and male identity. Furthermore, the social context of hegemonic masculinities, including violence to enforce or maintain masculinity plays a central role to understanding the Murder-Suicide dynamics. Authors consider the perpetrator's employment circumstances also. At work, men's mental health can be compromised by the pressures and stresses that come from the long-standing economic volatility and increasing job insecurity. Moreover, it has been argued that, the equalization policy around paid employment in Western society has eroded some men's sense of masculinity particularly in terms of self-worth because of failure role of financial provider for the family. this is a traditionally male role. Authors conclude that the connection between M-S and masculinities are underresearched and their study goes some way toward breaking the silence on an important men's health issue.[66] In our case, we also found, however, in the man's criminal record a history of femicide. Female homicide is the seventh leading cause of premature death for women. During a woman's life, it is estimated that domestic violence prevalence varies between 25-30%. In case of uxoricide the victim is the wife, in 30-55% of cases the guilty is the current partner, in the remaining part is the ex. Generally, uxoricide is preceded by episodes of physical violence. According to some authors, there is an escalation of violence that ends with killing woman. Uxoricide is the most common type of familicide after killing sons. According to statistics, the familicide perpetrators are often married. Furthermore, familicides are almost exclusively committed by men, typically in their 30s or 40s. Compared to men who commit other types of crimes, they have a better level of education and employment. Furthermore, they have less criminal records and seldom suffer from a mental illness, at most they manifest a personality disorder. However must emphasize that loss of a job, continuous unemployment and subsequent inability to support his family are found among perpetrators. These conditions determine a sense of loss of control over their wife as well as over family life, and this provide a motivation to killer. From a psycho-evolutionary perspective, a woman's threat of withdrawal or estrangement constitutes a loss of control over her reproductive capacity and to regain this control, they may respond with violence. In this case, children may be perceived as 'her' children and equally responsible for her betrayal. It must stress that in many cases the motivation behind uxoricide and familicide is the wish to "protect" family when the man is no longer able to provide for the family economic needs. In such cases, the perpetrator perceives that only he can satisfy the needs of his victims. Failing their role as provider, controller and central figure in the lives of their families, these men become desperate, homicidal and suicidal. As regard the psychopathological factors, in most case studies, the role of depression is highlighted, sometimes evolving into a psychosis or in other cases accompanied by morbid jealousy. Liem and Koenraadt,[67] in their study, extract a sample of 536 persons admitted to forensic psychiatric observation hospital in Utrecht, The Netherlands, in the years 1953-2006. The sample was divided into three categories: 23 were accused of familicide,133 of filicide and 380 of uxoricide. The study showed that familicide perpetrators are similar to uxoricide perpetrators: both are almost exclusively male and generally older than filicide perpetrators. With regard to the relationship between victim and accused, according to literature, it was found that the familicide perpetrator typically killed his wife and his biological children. Very few of both familicide and filicide perpetrators had previously been convicted of a violent offence, unlike uxoricide perpetrators.

As regard personality disorders, dependency and narcissistic traits particularly pronounced were found. Narcissism could play a key role in the attribution of guilt in an ended relationship or failure of acquiring custody. The considerable representation of narcissistic elements among these suspects could be related to their lack of suicidal behavior. Unlike persons with narcissistic trait of personality in which there is not suicidal behavior, persons with psychotic depression or schizophrenia would be a more likely suicide candidate. In all three types of family homicide, psychotic motives were common. According to literature, other similarities between the groups can be found in a fear of abandonment by the perpetrator when the intimate partner leaves him or excludes him from contact with the children. Further, these men are unable to manage the anger, jealousy and rage against their wife. The main difference found between filicide and familicide lies in the abuse leading to death because a considerable proportion of filicide cases resulted from physical abuse. Also it was found that in many cases of familicide and filicide, the perpetrator attempted to commit suicide subsequently to the offence; instead this trend was not found in cases of uxoricide. Authors hypothesized that this behavior was due to conviction of perpetrator that, after his suicide, no one will take care of his children. For this he killed them configuring the so-called "extended suicides".

Cechova-Vayleux *et al.*[68] have carried out a study on 32 cases of uxoricide, 26 cases of intrafamily murder and 97 cases of extra-family murder. Their results are consistent with the literature; indeed uxoricide perpetrators have an average age of 37.8 years, a professional employment, traumatizing events during childhood, psychiatric, judicial and violence against others records; furthermore they have paranoid delusions and premeditation more frequently than other categories of murderers. Firearms and cold weapons are the most commonly used means. In this series, uxoricide perpetrators tend more to commit suicide. Authors underline as often the uxoricide is preceded by a homicidal ideation phase or anxiety or depression. Moreover, the intensity of jealousy and associated feelings influences the choice of mean used, the female murder mode and the intensity of force used. The more intense is the jealousy, the more violent is the death, and the killer get to use their hands as a means to kill. Furthermore, the homicide-suicide can be

linked to male jealousy and obsessive belief of woman unfaithfulness. According to literature, authors underline that homicide-suicide can also take the form of "altruistic" murder when the man suffers from depression. As regard personality traits, uxoricide perpetrators have an addictive or passive-aggressive personality. Narcissism, separation anxiety, loss of control power are essential to understand this type of murder, which, for authors, cannot be considered as a crime of passion. According to some series, the incidence of acts of violence before homicide is not very high. However, it must be emphasized that connections between aggressor and victim are very complex and domestic violence can be established deviously. This brings the woman to be subjected to control and neutralization of her desires. The desire for exclusive possession, "property" and jealousy are common among uxoricide. With this in mind, marital separation, actual or threatened, is a reason for triggering the explosion of murderous violence and uxoricide occurs in the following months the separation, with a three-month peak. It must add that the risk of uxoricide is reduced with advancing age, because female reproductive capacity is reduced. Indeed, a woman of childbearing age elicits greater jealousy. In this regard, Shackelford *et al.*[69] selected and analyzed a sample of 13,670 cases in which a man killed the woman to whom he was legally married. They found that: reproductive age women incur a higher risk of uxoricide, relatively younger men are overrepresented among uxoricide perpetrators and even women married to much older men risk to be victims of uxoricide. The uxoricide rate of reproductive age women were compared with the uxoricide rate of post-reproductive age women across two groups: women married to younger men and women married to older men. Regardless of the age of her husband, the uxoricide rate was higher for women of childbearing age. According to the authors, these results are consistent with the theory that young women elicit more jealousy and male feelings of sexual proprietariness, but even with the theory that the most of the uxoricides are premeditated. Moreover, they point out that in many men, the sense of "ownership" is reason to care and protection towards what they consider their own. With this in mind, the unfaithfulness or the end of the relationship constitute the double-selective effect of one's own loss being an intrasexual rival's gain. Besides, we have to consider that young women marry young men more frequently. Between them, generally there is the largest part of homicide perpetrators and also for this reason this type of women incurs an increased risk to be the victim.[6]

Our results agree with the literature, although in this study is meant to emphasize the role of sexual disorders and fertility in the genesis of behavioral disorders that lead to specific psychiatric conditions and subsequently into criminal behavior. In the reported case, we have shown that the common denominator of KS are sexual disorders that cause an accumulation of frustrations related to the sexual sphere (hypogonadism, reduced libido, infertility). Therefore, the sexual disorder related to hypogonadism, reduction of libido and infertility can result in the generation of abnormal and criminal behavior. No studies have emphasized the importance of the role of sexual disorders in this syndrome in the genesis of criminal behavior. This finding in our case has been confirmed by the "reasons" of uxoricide related to a frenzy of jealousy probably triggered by sexual problems against his wife. Therefore the focus of our study has highlighted that the KS is multifactorial in the genesis of behavioral disorders at the base of criminal behavior because of:

1. Neurogenetic factors;
2. Neuroanatomical abnormalities;
3. Sexual disorders.

Unquestionably, the sexual component plays a crucial role in the genesis of criminal behavior in the affections of KS. Therefore, as a preventive measure in view of the reduction of criminal acts, a clinical and psychiatric outdoor intervention could be significant on the prevention and treatment of sexual problems of patients suffering from the KS.

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Contributions: IA, is the forensic pathologist and the official responsible of the case, performed the autopsy, conceived the idea and managed the whole realization of the paper; MAS, CS, contributed to the writing of the paper; SS, II, analyzed the acts of the process about the uxoricide; PDF, MS, performed a review of literature about the psychiatric aspects of Klinefelter syndrome; PR, co-performed the autopsy and co-managed the realization of the work.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Key words: Klinefelter Syndrome; sexual disorders; criminal behavior; autopsy; uxoricide.
Parole chiave: Sindrome di Klinefelter; disturbi sessuali; comportamento criminale; autopsia; uxoricidi.
Palabras clave: Síndrome de Klinefelter; trastornos sexuales; comportamiento criminal; autopsia; uxoricidas.

Received for publication: 1 May 2019.
Accepted for publication: 14 May 2019.


*Rivista di Psicopatologia Forense, Medicina Legale, Criminologia 2019; 24:43*
*doi:10.4081/psyco.2019.43*