



Neuropsychology and socioeconomic aspects of Klinefelter syndrome: new developments

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Purpose of review

To summarize recent important studies on neuropsychology and epidemiology of Klinefelter syndrome. PubMed was searched for 'Klinefelter', 'Klinefelter's' and 'XXY' in titles and abstracts. Relevant studies were obtained and reviewed, as well as other articles selected by the authors.

Recent findings

Klinefelter syndrome is the most common sex-chromosome disorder in humans, affecting one in 660 men. The key findings in Klinefelter syndrome are small testes, hypergonadotropic hypogonadism and cognitive impairment. Klinefelter syndrome scores significantly below education matched controls on a range of cognitive tests with verbal skills displaying the largest effects. Boys with Klinefelter syndrome are often in the need of speech therapy and many suffer from learning disability and may benefit from special education. New studies are elucidating aspects of cognitive functioning and suggesting that neuropsychological treatment may be of value. The socioeconomic status and educational level of Klinefelter syndrome is severely affected with many struggling to achieve any or only shorter education, resulting in low-income levels and early retirement. In addition, few become fathers and fewer live with a partner compared with controls. Medical treatment is mainly testosterone replacement therapy in order to alleviate acute and long-term consequences of hypogonadism, as well as, treating or preventing the frequent comorbidity.

Summary

The neurocognitive phenotype of Klinefelter syndrome is being unraveled and the need for psychological and cognitive treatment in many cases is evident. The neurocognitive deficits no doubt influence the socioeconomic status of many Klinefelter syndrome patients, which is clearly inferior to age-matched controls.

Keywords

hypogonadism, intelligence quotient, neurocognition, socioeconomic status, testosterone treatment

INTRODUCTION

Klinefelter syndrome, 47,XXY, occurs in about 150 per 100 000 men and is the most frequent chromosomal aberration in men. However, it is also important to keep in mind that Klinefelter syndrome is heavily underdiagnosed, with only a quarter of all expected Klinefelter syndrome ever being diagnosed and 90% only after having reached 15 years of age [1]. It was first described in 1942 [2] with a number of additional conditions, characteristics and abnormalities described in subsequent publications. Klinefelter syndrome has a genetic background, with characteristics involving numerous specialities such as embryology, paediatrics, endocrinology, cardiology, psychology and psychiatry, urology and epidemiology. We have lately expanded our knowledge concerning Klinefelter syndrome, especially concerning the neurocognitive deficits specific to Klinefelter syndrome. In addition, the

socioeconomic status of most Klinefelter syndrome is clearly affected, which together with the cognitive challenges, may lead to quite problematic living conditions.

This review is on aspects of epidemiology, neuropsychology, MRI of the brain and socioeconomic status.

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KEY POINTS

- The neurocognitive profile of males with Klinefelter syndrome is specific, with frequent dyslexia, low verbal intelligence quotient and a host of other characteristics.
- The neuropsychological profile of men with Klinefelter syndrome is specific with higher level of neuroticism and lower levels of extraversion, openness and conscientiousness.
- The neuroanatomy of Klinefelter syndrome is specific, with several brain regions being reduced in size, but without correlation to the neurocognitive measures.
- The socioeconomic profile of men with Klinefelter syndrome is specific, with a poorer outcome on all measures.
- Future studies need to examine the effect of interventional cognitive therapy and testosterone treatment in conjunction. There is a need for viewing Klinefelter syndrome in a holistic manner, stressing that clinicians need to be aware of all aspects of the syndrome in order to improve care.

NEUROCOGNITIVE FUNCTION AND NEUROPSYCHOLOGY

The neurocognitive and neuropsychological phenotype associated with Klinefelter syndrome have been investigated in numerous studies through recent years, leading to a broader and more nuanced description of Klinefelter syndrome today, although we still have much to learn.

The neurocognitive phenotype is well described in Klinefelter syndrome associated with several neurocognitive deficits, although the phenotype displays great variability. The general intellectual ability of Klinefelter syndrome varies from average to below average [3–13,14[■]], with verbal abilities being most severely affected, whereas performance intelligence is comparable with education-matched controls, although the two measures are correlated. Furthermore, there is a significant tendency for newer studies to report intelligence quotient (IQ) scores that are lower than older studies (Table 1 and Fig. 1).

This may be due to the fact that some newer studies are larger, and therefore presumably include a more varied and representative phenotypic composition of Klinefelter syndrome. The majority of Klinefelter syndrome patients suffer from some degree of verbal disabilities. These include delayed early language development [22–25], general learning disabilities in reading and spelling [7,26,27], impairments with production of syntax [7], phonemic processing [7], word retrieval [7], comprehension,

encoding verbal information and decreased processing speed [7,20[■],28] and verbal fluency [20[■],29]. As a consequence of these impairments in verbal cognitive domains, a high percentage of Klinefelter syndrome patients receive and benefit from special education [23,29–31]. The majority of Klinefelter syndrome patients also display impairments in executive function related to attention, response inhibition, flexibility and planning [4,17,20[■],28,32]. Contrary to these deficits, visiospatial function and performance IQ seems to be unaffected in Klinefelter syndrome (see Table 1). Together with data from our Danish Klinefelter syndrome cohort (data submitted), these findings elucidate the overall pattern of cognitive dysfunction in Klinefelter syndrome and suggest that neuropsychological treatment such as, for example, social competence intervention may be of value to the patients as a means to improving their executive functions.

Apart from cognitive deficits, Klinefelter syndrome is also associated with a characteristic personality profile. Recently, we published data regarding personality traits in Klinefelter syndrome using the most prominent personality constructs, that is the ‘Big Five’: neuroticism, extraversion, openness to experience, agreeableness and conscientiousness [33[■]]. Our data showed that Klinefelter syndrome is associated with a personality profile characterized by a higher level of neuroticism and lower levels of extraversion, openness and conscientiousness (Fig. 2).

These data are consistent with previous anecdotal descriptions of Klinefelter syndrome patients as anxious [36], experiencing increased emotional arousal [37], as having serious emotional difficulties [3], being unassertive [38], quiet [38] and passive with a withdrawn behaviour [39], and as having difficulties in approaching new events [39].

Klinefelter syndrome is not only associated with cognitive impairments. Psychiatric disorders have also been reported to be relatively common in Klinefelter syndrome. A Danish register study showed that patients with Klinefelter syndrome have a 3.65 times higher risk of being hospitalized with a psychiatric disorder [40]. Depression [32,41,42], anxiety [32], schizophrenia [32,41], autism spectrum disorders [13,32] and attention-deficit/hyperactivity disorders [9,12,32] have been reported to occur with an increased prevalence among Klinefelter syndrome. Autism spectrum disorders in the normal population have a prevalence of approximately 1% (2–3% in boys) [43], whereas for Klinefelter syndrome it has been reported to be 11–27% [44[■]]; for Attention deficit hyperactivity disorder the prevalence is reported to be 63% [32] relative to 5% in the normal population [45] and a

Table 1. Intelligence quotient from studies examining boys and adults with Klinefelter syndrome in a total of 559 individuals

Study	Year	N	Verbal IQ	Performance IQ	Full scale IQ
Nielsen and Pelsen [10]	1987	34	101.9	103.4	102.8
Graham et al. [15]	1988	12	97	108	103
Geswind et al. [5]	1998	25	99.7	97.2	98.4
Bender et al. [3]	1999	11			90.91
Fales et al. [4]	2003	21	97.9	100.7	98.7
Temple et al. [16]	2003	3	100	111.7	
Itti et al. [8]	2006	18	98.9	101.1	99.5
Stemkens et al. [11]	2006	50	87	92.4	89
Giedd et al. [6]	2007	42			95.2
van Rijn et al. [13]	2008	31	108.6		105.2
Lee et al. [9]	2011	27	98.37	104.56	101.7
Kompus et al. [17]	2011	27			87.9
Bruining et al. [18]	2011	34			84.3
Tartaglia et al. [12]	2012	56	93.02	99.07	97.53
van Rijn et al. [19]	2012	13	96.3	93.7	94.4
Skakkebaek et al. [20 [■]]	2014	65	84.7	96.7	87.8
van Rijn et al. ^a	2014	46			84.15
Brandenburg-Goddard et al. [21]	2014	13			79
Hong et al. [14 [■]]	2014	31	88.3		90.5
Weighted average		559	94.12	98.78	93.25

IQ, intelligence quotient

^aIncludes both men with Klinefelter syndrome ($n=29$) and 47,XXX syndrome ($n=17$).

recent study found that 70% of adolescent patients with Klinefelter syndrome had depressive symptoms (35% in normal adolescents) [42,46]. In a recently published study, we found that Klinefelter syndrome

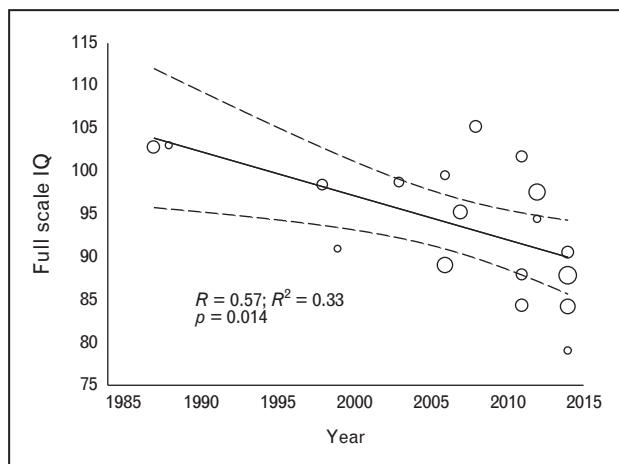


FIGURE 1. Full-scale intelligence quotient from studies examining boys and adults with Klinefelter syndrome in a total of 559 individuals (see also Table 1). The size of each study is illustrated by the size of each circle. A weighted linear regression was performed indicating that newer studies seem to find lower IQ than older studies. IQ, intelligence quotient.

is associated with an increased level of psychological distress, which may predispose Klinefelter syndrome patients to psychiatric disorders such as depression and anxiety [20[■]]. Furthermore, hitherto unpublished data from our Danish Klinefelter syndrome cohort indicate that increased symptoms of depression and anxiety seen in Klinefelter syndrome patients is mediated by their higher level of neuroticism (data submitted).

There has been a growing interest in both anatomical and functional brain imaging as a means for understanding the neurobiological cause of the neurocognitive impairments and psychiatric symptoms seen in Klinefelter syndrome. Several studies have found that Klinefelter syndrome is associated with significant changes in several brain structures, both globally and regionally. In a recently published study, we were able to predict status (i.e. Klinefelter syndrome or control) in 96.9% of cases based on volumetric information alone [20[■]]. Accordingly, in this and other studies, global brain volumes, total brain volume [6,20[■],47–49] and total gray and white matter volumes [6,20[■],48,50] have been found to be significantly smaller in Klinefelter syndrome. Specific regional brain volumes have also been reported to be significantly different from the normal population. The volumes of the temporal lobe,

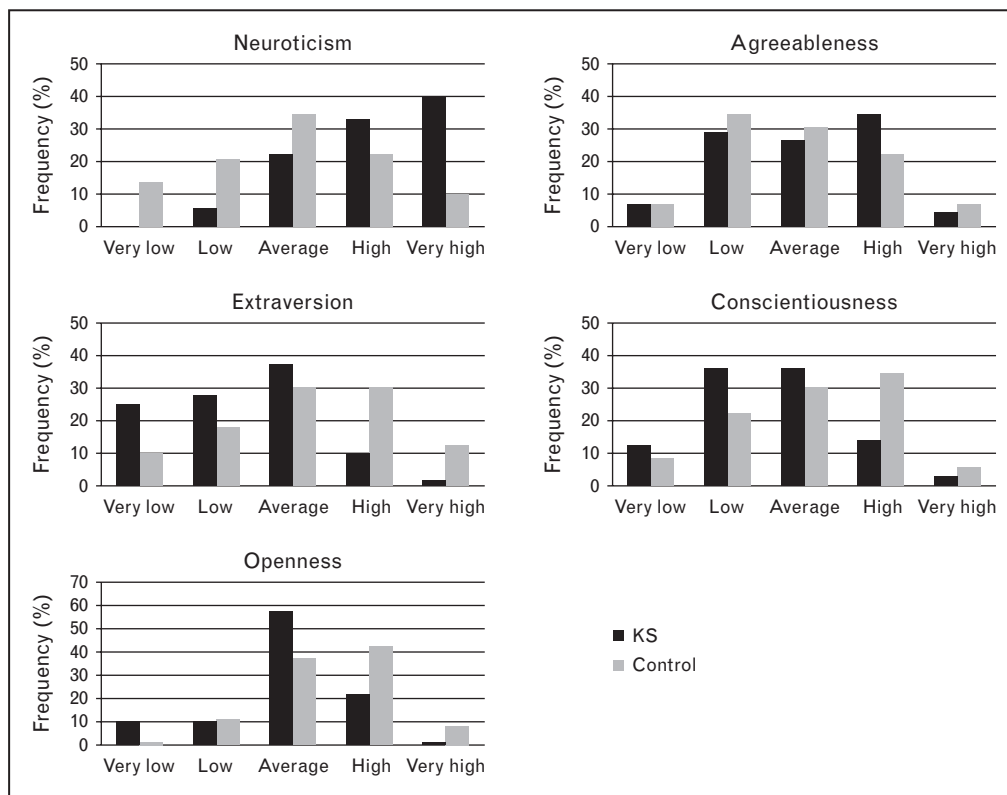


FIGURE 2. Personality profile among men with Klinefelter syndrome in comparison with matched controls [23,34,35]. Data from [20^a].

hippocampus and amygdala have consistently been reported to be smaller [6,8,20^a,47,48,50–53]. Mixed results have been reported for other structures, such as the caudate nucleus [6,20^a], putamen [6,20^a] and insula [20^a,48] with some studies reporting smaller volumes [20^a] and others not [6,48]. Several studies have investigated whether the cognitive deficits in Klinefelter syndrome is associated with the volumetric brain changes seen in Klinefelter syndrome. However, all studies [20^a,47,49–51] except one [8] failed to find any correlation between cognitive performance scores and brain volumes including our recently published study including 65 Klinefelter syndrome patients and 65 male controls. We, therefore, hypothesize that the neurocognitive and neuropsychological phenotype seen in Klinefelter syndrome is related to the microarchitecture of the brain and functional alterations of the neuronal network rather than macrostructural changes. A few functional brain imaging studies in Klinefelter syndrome have emerged over the last decade to further our understanding of the neuronal underpinning of the neurocognitive and neuropsychological phenotype seen in Klinefelter syndrome. van Rijn *et al.* [19] investigated brain activity during social judgement of faces and found that Klinefelter syndrome patients had decreased

activity in specific brain regions related to face processing (inferior temporal regions) and to the limbic system (amygdala, insula). Two other studies, using linguistic stimuli found that Klinefelter syndrome either have a generally decreased language activation compared with controls [54] and/or a decreased language lateralization in the posterior temporal language regions [55].

There are still many questions concerning the neuropsychological and neurocognitive phenotype, which remains to be answered. For example, our knowledge about genotype–phenotype correlation is still very sparse. Studies addressing genotype–phenotype in Klinefelter syndrome have previously focused on variability attributable to parental origin of the extra X-chromosome, X-chromosome inactivation and androgen receptor CAG repeat length [33^a], however the opportunity to investigate further epigenetic and genetic mechanism, such as DNA methylation and gene expression will hopefully further expand our knowledge and understanding of the neurocognitive and neuropsychological phenotype seen in Klinefelter syndrome patients. The very first studies accessing DNA methylation and gene expression in Klinefelter syndrome patients and mouse models of Klinefelter syndrome have recently been published. Viana *et al.* [56^a] investigated prefrontal

cortex and cerebellum of a postmortem patient with Klinefelter syndrome in relation to DNA methylation and gene expression and found significant differences in DNA methylation and gene expression compared with both female controls and male controls. Ngun *et al.* [57] investigated gene expression in the bed nucleus of the stria terminalis/preoptic area and the striatum of a XXY mouse model and found differences in gene expression compared with XY mouse. However, more comprehensive studies of DNA methylation and gene expression of Klinefelter syndrome, investigating different target tissue (e.g., testis, blood, fat tissue, muscle tissue and brain tissue) is needed to further elucidate the genetic processes underlying the Klinefelter syndrome phenotype.

SOCIOECONOMIC STATUS AND MORTALITY

Although the medical aspects of Klinefelter syndrome are quite well described in many studies through many years and clinical guidelines are available [58], much less is known of the social and economic implications of living with Klinefelter syndrome. Early studies focused on children and followed small groups of Klinefelter syndrome boys until adolescence [23] or into adulthood [10]. These studies documented on an individual level that behavioural problems, learning disorders, poor educational outcome and criminal conduct could be seen, but also emphasized that many led normal lives and even suggested that impact of Klinefelter syndrome subsided with advancing age [10]. Recently, we studied the entire Klinefelter syndrome population in Denmark in an epidemiological setting, merging relevant registries in order to get a more comprehensive picture of life with Klinefelter syndrome. We identified 1040 Klinefelter syndrome and compared these with 100 controls for every Klinefelter syndrome ($n = 100.824$) [59,60], expanding and strengthening our previous epidemiological approach [1,40,61]. The studies have been conducted anonymously and the presented data are, thus, not identifiable on a personal level. Data on the socioeconomic conditions show that Klinefelter syndrome men have significantly fewer partnerships [hazard ratio (HR) 0.66] and that they enter later into such partnerships (median age 27.1 vs. 24.6 years). Not surprisingly, Klinefelter syndrome men achieve fewer fatherhoods (HR 0.24), and for those that succeed they occur later (median age 32.0 vs. 27.0 years). However, the fact that 25% of all Danish Klinefelter syndrome were actually registered as fathers was a surprisingly high number and we speculate that most of these fatherhoods were due to donor semen donation. Data also show

that the educational level is low, and that this leads to a lower income throughout their lifetime, and that many retire early (average retirement age: 43.5 vs. 60.3 years). We also found that mortality among Klinefelter syndrome men was almost doubled in comparison with a large control group (HR 1.9), and that this increase to a small degree was influenced by the cohabitation and educational status, because after adjustment for these variables, the increase in mortality was not as prominent (HR 1.5). Lately, we also studied criminality in the same cohort and described an increased absolute risk of receiving a sentence in areas of sexual abuse, arson, burglary and 'other offenses'. Adjusting these data for the socioeconomic variables mentioned above reduced the risk estimates, but they were still significantly elevated for sexual abuse and arson [60]. Interestingly, we found lower risk of receiving a sentence for traffic crimes and we speculated that this was due to socioeconomic factors, leading fewer Klinefelter syndrome to have a car and driving licenses, and thus drive less than other men. These new data corroborate older literature [23,34,35] that had long been criticized for being heavily biased and based on small sample sizes [23,34,35], whereas one other study could not confirm an increased risk of criminality [62]. In other words, it is clear that suffering from Klinefelter syndrome has severe socioeconomic consequences, which may also spur on an increased risk of criminality within certain areas, and it, therefore, seems very relevant to discuss whether clinicians can in any way mitigate these apparently quite severe consequences of the syndrome. Additionally, Klinefelter syndrome is difficult to diagnose, leads to long delays in diagnosis [1] and frequent-false negatives [1,63]. In fact, only about a quarter of the expected numbers of Klinefelter syndrome is currently thought to be diagnosed and the majority has to wait until adulthood in order to get a proper diagnosis [1,63]. This poses several problems. First, all current Klinefelter syndrome studies are subject to selection bias and the present knowledge of Klinefelter syndrome may not extend to the nondiagnosed cases, who may present with a more neutral phenotype. Second, as 90% of all Klinefelter syndrome remain undiagnosed until after 15 years of age, we may miss an important window of opportunity for correcting or alleviating the symptoms, not least the sociocognitive deficits, present among Klinefelter syndrome. Third, the knowledge of the natural history of Klinefelter syndrome should lead us to discuss whether we should change our current diagnostic strategy (or lack thereof) and introduce a new diagnostic paradigm – utilization of the fact that we can actually, at low cost and with modern technology [64,65], diagnose

all Klinefelter syndrome on blood from the neonatal heel prick test, which all newborns in the Western world are subjected to. Although it will be very difficult to provide evidence that early diagnosis is superior to late diagnosis in a research setting, circumstantial evidence suggests that this is the case. Early diagnosis would increase the likelihood that psychosocial and neurocognitive problems [13,66,67] could be alleviated or even abolished, if it turns out that early testosterone supplementation is efficient [68] and that neuropsychological early prepubertal intervention is effective. This has not been proven, but the neuropsychological profile of many adult Klinefelter syndrome suggests that it might prove beneficial with an early and targeted intervention, which would of course both be helpful on the individual level, but not least on a societal level, given all the socioeconomic and criminal repercussions of Klinefelter syndrome mentioned above. Early diagnosis, and thus treatment would probably also beneficially affect the unhealthy body composition, the increased risk of type 2 diabetes and the metabolic syndrome seen in adulthood, as well as the bone structure [69–71].

FUTURE

The breadth of knowledge of Klinefelter syndrome is rapidly expanding and pertinent questions concerning our current approach need to be discussed. Although it is quite clear that the neurocognitive phenotype is being resolved, currently there seems to be no studies focusing on proper treatment or intervention in order to better this phenotype. The link between the neurocognitive phenotype, psychosocial problems and later socioeconomic profile is suggestive, although such a relation has not been formally delineated. In other words, the neurocognitive deficits, linked to dyslexia and other learning-related problems, may well lead to a poor socioeconomic profile, which again is linked to poorer health-related outcome. Thus, in order to deal appropriately with a young adolescent with Klinefelter syndrome in the clinic, one needs to take a holistic approach, and be aware that current actions or the lack thereof, might have very long-term and profound implications. We propose randomized, placebo-controlled studies on children and adults with Klinefelter syndrome, with testosterone preparations that will restore testosterone to normal values, in a population large enough to detect small changes in measured outcomes. Recently, established animal models are exciting in this respect and could be used to generate new data on fertility [72], bone morphology [73] and brain functioning [74]. A discussion of whether or not early diagnosis

will lead to a better outcome is also needed, and to qualify such a discussion we need more scientific data.

CONCLUSION

The neurocognitive phenotype of Klinefelter syndrome is clearly abnormal and the need for psychological and cognitive treatment in many cases is evident. These impairments no doubt influence the socioeconomic status of many Klinefelter syndrome, which is clearly inferior to age-matched controls.

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Conflicts of interest

There are no conflicts of interest.

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