Brain, behavior and life of XXY people: a new study (2015)

The entire title of the paper is "**Neuropsychology and socioeconomic aspects of Klinefelter syndrome: new developments**" by Skakkebaek et al. http://www.ncbi.nlm.nih.gov/pubmed/25899809

I will summarize the most important findings of the paper and will add some points I missed to be discussed.

Behavior, psychiatric conditions and brain differences:

Verbal abilities are most severely affected, **IQ scores** are slightly lower than average.

The majority suffers from …

- delayed early language development
- general **learning disabilities** in reading and spelling
- impairments with production of syntax, phonemic processing, word retrieval, comprehension, encoding verbal information and decreased processing speed, verbal fluency
- **executive dysfunctions** related to attention, response inhibition flexibility and planning

In contrast, visiospatial function and performance IQ seem to be unaffected. **(1)**

There is a charateristic personality profile of XXY people, displaying a higher level of neuroticism (emotional instability) and lower levels of extraversion, openness to experience and conscientiousness.

These data are confirmed by anecdotal descriptions revealing

- anxiety
- increased emotional arousal
- serious emotional difficulties
- being unassertive
- quiet
- passive with withdrawn behaviour
- having difficulties in approaching new events

Psychiatric conditions associated with XXY

- Depression (35 % in general population, 70 % in XXY)
- Anxiety
- Schizophrenia

- Autism (prevalence of 1 % in the general population, 11-27 % in XXY)
- Attention-deficit/hyperactivity syndrome (5 % in general, 63 % in XXY)

XXY is often associated with increased level of psychological distress. Higher levels of emotional instability contribute to increased risk of depression and anxiety.

Brain differences

- Global brain volume, total brain volume, total gray and white matter volumes were found to be significantly smaller in XXY.
- Volumes of temporal lobe, hippocampus and amygdala were also smaller.
- All studies except one didn't find any correlation between cognitive performance scores and brain volumes. It is assumed that microchanges of brain structures are more important.

Van Rijn examined the brain activity during social judgements of faces and found that XXY people had decreased activity in brain regions related to face processing (inferior temporal regions) and to the limbic system (amygdala, insula). Two other studies found that decreased language activation and/or decreased language lateralization in the posterior temporal language regions were present.

There is still uncertainty about the exact mechanisms of parental origin of the extra X chromsoome, X-chromosome inactivation and androgen recepter CAG repeat length.

Education, living, mortality and criminality

Several studies suggest that behavioral problems, learning disorders, poor educational outcome and criminal conduct could be seen.

It is also emphasized that many led normal lives and the impact of syndromal effects subsided with advancing age. **(2)**

XXY men …

- have significantly fewer partnerships
- enter later into such partnerships
- achieve fewer fatherhoods and for those who had luck they occur later

However, at least 25 % of all Danish Klinefelter Syndrome were registered as fathers, probably mostly due to donor semen donation.

Data also show that …

- educational level is low leading to a lower income throughout their lifetime and that many retire early (43,5 vs. 60,3 years)
- mortality is almost doubled, partly influenced by cohabitation and educational status (without them, less prominent)
- criminality is enhanced for sexual abuse, arson, burglary and 'other offenses' but decreased for traffic crimes **(3)**

If the social and economic background is taken into account, the risk is generally reduced.

XXY are relatively seldom diagnosed…. There are long delays and frequent-false negatives. Only about 25 % are diagnosed, and the majority has to wait until adulthood.

Several problems follow:

1. all current XXY studies may have selection bias and the present knowledge may not cover the undiagnosed cases.

2. 90 % of XXY remain undiagnosed until after 15 years of age, missing an important window of opportunity for correcting or alleviating the symptoms

3. we should change our current diagnostic strategy and introduce a new one, diagnosing XXY on blood from neonatal heel prick test (Guthrie test).

Early diagnosis would improve

- cognitive functions, learning, verbal abilities and behavior, if it turns out that early testosterone supplementation is efficient, and that neuropsychological intervention before puberty is effective.**(4)**
- the unhealthy body composition, with increased risk of type 2 diabetes and metabolic syndrome seen in adulthood, as well as bone structure.

Future:

Studies are currently missing focusing on proper treatment or intervention to better the phenotype.

neurocognitive deficits, linked to dyslexia and other learning-related problems, may well lead to poor socioal and economic outcome.

A holistic approach is needed.

Conclusion:

The neurocognitive phenotype of Klinefelter syndrome is clearly abnormal **(5)** and the need for psychological and cognitive treatment in many cases is evident.

Remarks on statements:

(1) “visiospatial function” seems to be unaffected. Studies by Jay Giedd show that visual and spatial thinking of XXY people are actually a strength of their thinking architecture. So, visiospatial function isn’t only normal but better pronounced. A lot of XXY people have a good visual memory.

(2) The social environment and intervention is very important. In countries and regions with poor density of experienced specialists, therapeutic outcome will be probably less satisfying, and increasing age could strengthen depressive mood and anxiety.

(3) The enhanced risk to commit crimes of sexual abuse [and arson] could probably be related to inappropriate testosterone supplement therapy. Overdosing testosterone might enhance emotional instability and overemphasize masculine behavior of males. It would be interesting to know whether the participants were already taking testosterone supplements and whether on a daily basis (self-medication) or in larger intervals (injections).

(4) It is important to emphasize that testosterone supplement is neither a one-cure-for-everything therapy nor necessarily suited for all children and adolescents. See additional remarks.

(5) The neurocognitive phenotype of Klinefelter syndrome is clearly DIFFERENT.

Additional remarks:

1. Though I know that science in genetics and behavior usually concentrates on deficit thinking in genetic anomalies, it would be helpful for us affected persons to highlight strengths and positive outcome. Anecdotal descriptions reveal enhanced sense of creativity, sensitivity, social justice, honesty, enhanced detail perception, good visual memory/long-term memory, good with animals.

2. In the vast majority of these studies and papers, the term “men or boys with Klinefelter syndrome” is used, neglecting a minority of XXY people who do not identify as men, for different reasons… Either there are born intersex, or born as transgender preferring to transition into female later as a teenager or adult. Some identify as male but don’t feel well with masculinization through testosterone supplement therapy, either. A few XXY are also reported to have androgen insensitivity syndrome and testosterone therapy will probably not work for them.

One of the most difficult and heavily discussed topics in the XXY community is whether early intervention with testosterone therapy is a benefit for all XXY children, as transgender or persons who don’t want to be masculinized may not be suited to receive additional testosterone or even require estrogen therapy instead. In these cases, the term Klinefelter’s syndrome referring to hypogonadism (testosterone deficit) doesn not seem to be appropriate.

I hope we – as XXY community and individuals – are able to convince the scientific community to put more focus on gender identity in XXY before recommending one-size-fit-all-cures for young XXY.

3. I missed some lines about sensory processing disorder. There is only one study about that:

Van Rijn et al, Psychophysiological Markers of Vulnerability to Psychopathology in Men with an Extra X Chromosome (XXY), *PLoS ONE*, **6(5)**: 2011

confirming sensory gating disorder in XXY (in other words, XXY often have difficulties to filter out background noise/distraction)

The existence of a handout about sensory processing disorder on AXYS as well as several reports about motoric difficulties suggest that sensory processing and integration disorder is likely to be common in XXY.

Anecdotal evidence is furthermore given about enhanced sensitivity to sensory stimuli like noise, light, motions, smell/taste and touch suggesting a crucial commonality with autism spectrum conditions. One should probably think of XXY as possible specific subtype of the large autism landscape.

http://factsaboutklinefelter.com/2015/05/01/brain-behavior-and-life-of-xxy-people-a-new-study-2015/