Triple-X Syndrome (47,XXX)

First description and alternative names

In 1959 Jacobs (Jacobs *et al.* 1959) first described triple-X syndrome in an infertile patient. The term “super female” is considered to be controversial and the term triplo-X syndrome is old fashioned. The terms triple-X syndrome, trisomy-X syndrome and 47,XXX syndrome are generally preferred.

After the first description there was a period of research in biased populations, e.g. in institutes for mentally retarded, asylums and forensic psychiatric hospitals (Olanders 1975). In 1974 it was decided to screen 200,000 newborns for chromosomal disorders in several hospitals. The triple-X cases in this study have been evaluated several times for at least 20 years. These newborn-screening studies yielded unbiased data (Robinson *et al.* 1990). After 1990, two of these hospitals (Denver en Edinburgh) published follow-up data in young adults (Otter et al. 2010). The most recent studies, from other research groups, published data from more or less biased groups of cases (Wilson et al. 2019).

Genetics and molecular biology

In triple-X syndrome there is an extra X chromosome in all cells or, in mosaic cases, in almost all cells. Most of the cases are diagnosed through prenatal diagnostic examinations.

In 46,XX females the extra X chromosome is silenced through lionization. The extra X chromosome in triple-X women is also silenced. In 46,XX females one-third of the genes on the X chromosome escape silencing (Migeon 2007). The so-called ‘late-replicating’ X chromosome is the second X chromosome. In cases of an extra X chromosome there is another late-replicating chromosome, so replication time increases during each cell division (Barlow 1973). The extra X chromosome might also have some influence on the nuclear architecture and on epigenetic processes (Kelkar and Deobagkar 2010, Jowhar *et al.* 2018).

Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division and/or epigenetic phenomena are relevant during development in 47,XXX, requires further research (Katsir & Linial 2019) .

Incidence/prevalence

1/1000 females have an extra X chromosome (Otter *et al.* 2010)

Physical features and natural history

Tartaglia et al. (Tartaglia *et al.* 2010) reviewed the physical findings in triple-X syndrome. Since most of these findings (such as clinodactyly, epicanthal folds or hypertelorism) are minor physical features, the majority of cases remain undiagnosed. Tall stature is common, and

especially the underarms and legs are longer. The girls may have their growth spurt earlier than controls. Clinically speaking, decreased head circumference is probably the most important common feature; there seems to be a relationship between head circumference and the level of cognitive functioning (Ratcliffe *et al.* 1994). Motor and coordination abilities seem to be somewhat retarded, and the girls are sometimes described as being clumsy. Neuroimaging studies revealed a smaller head circumference and a lower brain volume (Patwardhan *et al.* 2002).

Since 1959 many physical disorders associated with a triple-X finding have been reported, most of which do not exceeding the population prevalence numbers. But there are some disorders that seem to be more common in triple-X cases: urogenital anomalies, (partial) epilepsy and Premature Ovarian Failure (POF) and infertility (Tartaglia et al. 2010, Stochholm *et al.* 2010).

Behavioural and psychiatric characteristics

Low self-esteem seems to be the most common feature (Otter *et al*. 2010, Freilinger *et al.* 2018). Social anxiety/shyness and executive dysfunction are common in triple X girls (van Rijn *et al.* 2013, van Rijn and Swaab 2015, Lenroot *et al.* 2014). Social cognitive problems are common in triple X girls, probably due to language disorders (Bishop *et al.* 2011, Wilson *et al.* 2019). Another study in triple X girls showed a developmental pattern that resembled the development of girls with autism with mild or late presenting autism symptoms (van Rijn *et al.* 2014). Challenging behaviour may be the result of any of these developmental difficulties. Triple X girls living in a stable family function better than triple-X girls in an unstable family (Netley 1986). The triple X girls seem to be less able to cope in a stressful environment. After leaving school, most of the girls will find a job that reflects their non-verbal abilities (Robinson et al. 1990).

There seems to be a higher prevalence of psychiatric illness in general, especially in (mildly) mentally retarded cases, although we should be careful for there is still a paucity of data on development in adults. More specifically, it concerns a higher prevalence of psychotic disorders and adjustment disorders (Olanders 1975). The newborn-screening studies were stopped before the age that psychotic disorders could have become noticeable. Further psychiatric research with standardised psychiatric diagnostic tools is warranted in these females. Adults seem to face physical, social and occupational problems (Otter *et al.* 2012, Stochholm et al. 2010, Stochholm *et al.* 2013).

A study from Germany demonstrated that the extra X chromosome may influence mental health and well being into adulthood. This study made clear, again, that many women with an extra X chromosome do not experience major problems (Freilinger *et al.* 2018)

Scientific progress through neuroimaging findings

Neuroimaging findings in girls with an extra X chromosome demonstrated affected brain regions and related phenotypic characteristics such as language delay (thinner cortex was found in the lateral temporal lobes related to language functions), poor executive function and heightened anxiety (increased thickness in the medial temporal lobe in the vicinity of the amygdala, a region important for social cognition and linked to anxiety) through differences in cortical thickness (Lenroot et al. 2014). Poor executive function and frontal lobe abnormalities have been suggested to be related (van Rijn and Swaab 2015).

A group from National Institute of Mental Health (A. Raznahan) published several papers on neuroimaging in sex chromosomal disorders. These studies revealed changes in cortical thickness and surface areas of the brain (Warling *et al.* 2020.) These studies are of scientific importance, but until now, there is no clinical progress to be expected from neuroiamaging in individual cases.

Neuropsychological characteristics

Data on intelligence in girls and adolescents are consistent, indicating that the full-scale IQ's are almost 20 points lower than what would be expected in the family (Robinson et al. 1990). Whether the girls show problems in reading or arithmetic is not uniformly reported in the case reports. Clinical experience suggests that some difficulties during arithmetic lessons result from language disorders. Mild or serious academic problems/special educational needs are quite common (Robinson et al. 1990, Bishop et al. 2011). Further research is needed to confirm the findings on increased prevalence of attention problems and to explain these attention problems: are they due to receptive language disorder, auditory processing disorders or attention deficit disorder (ADD)(Lenroot et al. 2014)? Clinical experience in treating ADD with medication suggests that the treatment is less effective than in 46,XX cases; however, controlled treatment studies are lacking (Leggett *et al.* 2010).

Available guidelines for behavioural assessment/treatment/management

There is no evidence-based management guideline, although Otter et al. have proposed a guideline of medical and behavioural/psychiatric assessment (Otter *et al*. 2010). It is our sincere advice to use a broad set of tools during this assessment, since recent studies indicate language imparments (Bishop *et al.* 2018, van Elst *et al.* 2020), social behavioural problems (Wilson *et al.* 2019) and neurocognitive problems, executive dysfunction among others (Urbanus *et al.* 2020).

Further reading: Skuse D, Printzlau F, Wolstencroft J. Sex chromosome aneuploidies. Handbook Clinical Neurology 147, 355-76.

Useful websites/associations for more information

- The Dutch parents' support website: http://triple-x-syndroom.nl/. This website shows many links to scientific papers and useful links, e.g. links to international chat pages for parents and triple-X girls/women. Scientific papers and syndrome sheets are available in several languages: English, French, Spanish, German and Dutch.
- Unique, a parents support group from the United Kingdom provides a syndrome sheet with information on physical and behavioural developmental issues: https://www.rarechromo.org/media/information/Chromosome_X/Triple_X_syndrome%20Trisomy_X%20FTNW.pdf

  and

  https://www.rarechromo.org/media/information/Reports/XXX%20Study%20Day%20Report%20FTNW.pdf
- The AXYS website provides a lot of information: https://genetic.org/variations/about-trisomy-x/. Especially parents and triple-X girls/women in the United States will find opportunities to meet experts, other parents and triple-X girls/women. KS&A is active in fundraising for the support of scientific research.

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