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).

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).

Whether incomplete silencing of the extra X chromosome, the prolonged cell cycle during division or epigenetic phenomena are relevant during development in 47,XXX requires further research.

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, the majority of cases remain undiagnosed. Tall stature is common, and especially the underarms and legs are longer. The girls have their growth spurt earlier than do controls. Clinically speaking, decreased head circumference is probably the most important common feature; there seems to be a relationship between head circumference and 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). 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). 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 a 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 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).

Scientific progress through neuroimaging findings

Recent 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).

Neuropsychological characteristics

Data on intelligence 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 assessment (Otter et al. 2010).

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: http://www.rarechromo.org/information/Chromosome X/Triple X syndrome%20Trisomy X%20FTNW.pdf.
- The KS&A (Klinefelter Syndrome and Associates) website provides a brochure and more: http://www.genetic.org/Knowledge/Brochures.aspx . 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.

References

Barlow, P. W. (1973) X-chromosomes and human development. *Developmental Medicine & Child Neurology,* **15,** 205-8.

Bishop, D. V., Jacobs, P. A., Lachlan, K., Wellesley, D., Barnicoat, A., Boyd, P. A., Fryer, A., Middlemiss, P., Smithson, S., Metcalfe, K., Shears, D., Leggett, V., Nation, K. & Scerif, G. (2011) Autism, language and communication in children with sex chromosome trisomies. *Archives of disease in childhood,* **96,** 954-9.

Jacobs, P. A., Baikie, A. G., Court Brown, W. M., MacGregor, T. N., Maclean, N. & Harnden, D. G. (1959) Evidence for the existence of the human "super female". *Lancet,* **274,** 423-5.

Kelkar, A. & Deobagkar, D. (2010) Methylation profile of genes on the human X chromosome. *Epigenetics,* **5**.

Leggett, V., Jacobs, P., Nation, K., Scerif, G. & Bishop, D. V. (2010) Neurocognitive outcomes of individuals with a sex chromosome trisomy: XXX, XYY, or XXY: a systematic review. *Developmental medicine and child neurology,* **52,** 119-29.

Lenroot, R. K., Blumenthal, J. D., Wallace, G. L., Clasen, L. S., Lee, N. R. & Giedd, J. N. (2014) A case-control study of brain structure and behavioral characteristics in 47,XXX syndrome. *Genes Brain Behav,* **13,** 841-9.

Migeon, B. R. (2007) *Females are MOSAICS; X inactivation and sex differences in disease,* (Trans. Oxford University Press, New York.

Netley, C. T. (1986) Summary overview of behavioural development in individuals with neonatally identified X and Y aneuploidy. *Birth defects original article series,* **22,** 293-306.

Olanders, S. (1975) Females with supernumerary X chromosomes; a study of 39 psychiatric cases. In: *St. Jörgen's hospital* (ed H. Forssman). pp. 223. University of Göteborg, Göteborg, Sweden.

Otter, M., Schrander-Stumpel, C. T. & Curfs, L. M. (2010) Triple X syndrome: a review of the literature. *Eur J Hum Genet,* **18,** 265-71.

Otter, M., Schrander-Stumpel, C. T., Didden, R. & Curfs, L. M. (2012) The psychiatric phenotype in triple X syndrome: new hypotheses illustrated in two cases. *Developmental neurorehabilitation,* **15,** 233-8.

Patwardhan, A. J., Brown, W. E., Bender, B. G., Linden, M. G., Eliez, S. & Reiss, A. L. (2002) Reduced size of the amygdala in individuals with 47,XXY and 47,XXX karyotypes. *American Journal of Medical Genetics,* **114,** 93-8.

Ratcliffe, S. G., Masera, N., Pan, H. & McKie, M. (1994) Head circumference and IQ of children with sex chromosome abnormalities. *Developmental Medicine & Child Neurology,* **36,** 533-44.

Robinson, A., Bender, B. G. & Linden, M. G. (1990) Summary of clinical findings in children and young adults with sex chromosome anomalies. *Birth defects original article series,* **26,** 225-8.

Stochholm, K., Juul, S. & Gravholt, C. H. (2010) Mortality and incidence in women with 47,XXX and variants. *American Journal of Medical Genetics. Part A,* **152A,** 367-372.

Stochholm, K., Juul, S. & Gravholt, C. H. (2013) Poor socio-economic status in 47,XXX --an unexpected effect of an extra X chromosome. *Eur J Med Genet,* **56,** 286-91.
Tartaglia, N. R., Howell, S., Sutherland, A., Wilson, R. & Wilson, L. (2010) A review of trisomy X (47,XXX). *Orphanet journal of rare diseases,* **5,** 8.
van Rijn, S., Stockmann, L., Borghgraef, M., Bruining, H., van Ravenswaaij-Arts, C., Govaerts, L., Hansson, K. & Swaab, H. (2013) The Social Behavioral Phenotype in Boys and Girls with an Extra X Chromosome (Klinefelter Syndrome and Trisomy X): A Comparison with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders,* **44,** 310-320.
van Rijn, S., Stockmann, L., van Buggenhout, G., van Ravenswaaij-Arts, C. & Swaab, H. (2014) Social cognition and underlying cognitive mechanisms in children with an extra X chromosome: a comparison with autism spectrum disorder. *Genes Brain Behav,* **13,** 459-467.
van Rijn, S. & Swaab, H. (2015) Executive dysfunction and the relation with behavioral problems in children with 47,XXY and 47,XXX. *Genes Brain Behav,* **14,** 200-8.

Dr. Maarten Otter, Psychiatrist, Spring 2015
