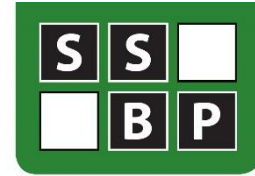


22q11.2 Deletion Syndrome (Velo-Cardio-Facial Syndrome)



First descriptions and alternative names

As is so often the case, chromosome **22q11.2 deletion syndrome (22q11.2DS)** was first described independently by several perceptive clinicians back in the 1950s to 1970s. As these clinicians were experts within different specialties and therefore not focussing on the same medical problems, several constellations of features were described as separate conditions. The first person to describe children who most likely had 22q11.2DS was the otolaryngologist (i.e. ear nose and throat specialist) Eva Sedlačková who already in 1955 described children with hypernasal speech associated with a congenitally shortened soft palate, facial dysmorphology and intellectual impairments [1-4]. She was later to show that many of these children also had cardiac malformations and submucous clefts. Following Sedlačková's observations, other clinicians such as the endocrinologist Angelo DiGeorge (first English publication) described children with presentations of immunodeficiency, hypoparathyroidism and congenital heart disease [5], the physician Kinouchi described children with cardiac abnormalities and a typical face [6] and the speech-language pathologist Robert Shprintzen described children with cleft palate, cardiac anomalies, a typical face and learning problems [7]. To avoid confusion, the syndrome is nowadays typically referred to as 22q11.2 deletion syndrome, a description based on its underlying genetic cause, however **alternative names for the syndrome are velo-cardio-facial syndrome (VCFS), velofacial hypoplasia, Sedlačková syndrome, DiGeorge syndrome, Shprintzen syndrome, Cayler syndrome and conotruncal anomaly face syndrome.**

Genetics/aetiology

Whilst visible cytogenetic deletions were identified in about one quarter of children with DiGeorge syndrome in the mid-1980s, it was not until the early 1990s that the microdeletions of chromosome 22q11.2 was identified as the cause of most cases of DiGeorge and that indeed, children with other groupings of symptoms, including most of those with VCFS, were found to share the genetic aetiology [8, 9]. Whilst the microdeletions vary in size, the deletion typically encompasses 0.7 to 3 million base pairs, a region that contains approximately 50 genes. The majority of people diagnosed with 22q11.2DS have a de novo or spontaneously occurring deletion and a smaller proportion (about 15%) have an inherited deletion. The deletion is inherited in an autosomal dominant manner, meaning that if a person has the deletion there is a 50% chance that the deletion will be passed on to their offspring.

Incidence/prevalence

Generally the prevalence of the syndrome is described to be 1 in 3,000 to 1 in 6,000 live births [e.g., 10, 11]. However, it has been argued that the syndrome is still clinically under-recognised with many older individuals diagnosed when they themselves have children diagnosed with the syndrome [12]. Whilst most people, including many health care

professionals, have not heard of 22q11.2DS it is the most common cause of syndromic palatal anomalies and also one of the most common causes of congenital heart defects and developmental delay [12]. It is also likely that the prevalence of the syndrome will rise as mortality decreases and reproductive fitness increases [13, 14]. The syndrome affects individuals of both sexes and of different ethnic background equally [15] although it has been suggested that there are sex differences in the expression of the syndrome [e.g., 16, 17].

Physical characteristics

22q11.2DS is a multisystem disorder including more than 180 characteristics. However, there is a large variability in the expression of the phenotype even amongst members of the same family and characteristics can range from life threatening to very mild [18]. The most common features include congenital heart defects (including conotruncal anomalies), palatal anomalies (including submucous cleft palate and/or velopharyngeal incompetence); immunodeficiency; hypocalcaemia and subtle facial characteristics [9] .

Behavioural characteristics

High levels of internalising symptoms and poor social skills are common amongst children with the syndrome [19]. Children with 22q11.2DS are also at higher risk of developing psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, anxiety disorders (generalised anxiety disorder, separation anxiety, and phobias) and, arguably autism spectrum disorders [20]. In late teenage years and early adulthood there are an increased risk of depressive disorders and also a high risk of psychotic disorders including schizophrenia. There are indications in the literature that despite the high prevalence of psychiatric disorders, many individuals with 22q11.2DS are not receiving the appropriate psychiatric care (Young et al 2011; Tang et al 2014).

Cognitive characteristics

Whilst there is a large variability within the cognitive profile of individuals with the syndrome, cognitive impairments are very common and are associated with learning problems. Intellectual functioning typically range from low average to mild intellectual disability with the majority of individuals having an intellectual ability in the Borderline range [21]. Typically, verbal intellectual functioning decline slightly with increased age but more so in the presence of psychosis [22]. Specific cognitive impairments in executive functioning, memory, working memory, sustained attention, numeracy, visual-spatial processing are common [e.g., 23, 24]. In addition, individuals with the syndrome have been found to have deficits in social cognition including problems in interpreting facial expressions [e.g., 25, 26, 27]

Available guidelines for behavioural assessment/treatment/management

- Practical guidelines for managing adults with 22q11.2 deletion syndrome [28]
- Practical guidelines for managing patients with 22q11.2 deletion syndrome [12]
- Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times [29]
- Consensus Document on 22q11 Deletion Syndrome (22q11DS), MaxAppeal http://www.maxappeal.org.uk/downloads/Consensus_Document_on_22q11_Deletion_Syndrome.pdf

Useful websites/associations for more information

- International 22q11.2 Foundation <http://www.22q.org/>
- 22q11.2 Society <http://www.22qsociety.org/>

References

1. Sedlackova, E., *Insuficience patrohltanoveho zaveru jako vyvojova porucha*. Cas Lek Cesk, 1955. **94**: p. 1304-1307.
2. Turnpenny, P. and R. Pigott, *Deletion 22q11 syndrome: acknowledging a lost eponym as we say farewell to an acronym*. Journal of Medical Genetics, 2001. **38**(4): p. 271-273.
3. Vrticka, K., *Present-day importance of the velocardiofacial syndrome. To commemorate the late prof. Eva sedlackova, MD, on the 50th anniversary of her original publication*. Folia Phoniatr Logop, 2007. **59**(3): p. 141-6.
4. Sedláčková, E., *The syndrome of the congenitally shortened velum the dual innervation of the soft palate*. Folia Phoniatica et Logopaedica, 1967. **19**(6): p. 441-450.
5. DiGeorge, A., *Discussion on a new concept of the cellular immunology*. J. Pediatr, 1965. **67**: p. 907-908.
6. Kinouchi, A., et al., *Facial appearance of patients with conotruncal anomalies*. Pediatr Jpn, 1976(4): p. 17:8.
7. Shprintzen, R.J., et al., *A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: velo-cardio-facial syndrome*. Cleft Palate J, 1978. **15**(1): p. 56-62.
8. Scambler, P.J., et al., *Microdeletions within 22q11 associated with sporadic and familial DiGeorge syndrome*. Genomics, 1991. **10**(1): p. 201-206.
9. McDonald-McGinn, D.M., et al., *22q11.2 deletion syndrome*. Nat Rev Dis Primers, 2015. **1**: p. 15071.
10. Oskarsdottir, S., M. Vujic, and A. Fasth, *Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden*. Arch Dis Child, 2004. **89**(2): p. 148-51.
11. Tezenas Du Montcel, S., et al., *Prevalence of 22q11 microdeletion*. J Med Genet, 1996. **33**(8): p. 719.
12. Bassett, A.S., et al., *Practical guidelines for managing patients with 22q11.2 deletion syndrome*. J Pediatr, 2011. **159**(2): p. 332-9 e1.
13. Costain, G., et al., *Sex differences in reproductive fitness contribute to preferential maternal transmission of 22q11.2 deletions*. J Med Genet, 2011. **48**(12): p. 819-24.
14. Repetto, G.M., et al., *Case fatality rate and associated factors in patients with 22q11 microdeletion syndrome: a retrospective cohort study*. BMJ Open, 2014. **4**(11): p. e005041.
15. McDonald-McGinn, D.M., et al., *The Philadelphia story: the 22q11.2 deletion: report on 250 patients*. Genet Couns, 1999. **10**(1): p. 11-24.
16. Green, T., et al., *Psychiatric Disorders and Intellectual Functioning Throughout Development in Velocardiofacial (22q11.2 Deletion) Syndrome*. Journal of the American Academy of Child & Adolescent Psychiatry, 2009. **48**(11): p. 1060-1068.
17. Kates, W.R., et al., *A gender-moderated effect of a functional COMT polymorphism on prefrontal brain morphology and function in velo-cardio-facial syndrome (22q11.2 deletion syndrome)*. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 2006. **141B**(3): p. 274-280.

18. Cirillo, E., et al., *Intergenerational and intrafamilial phenotypic variability in 22q11.2 Deletion syndrome subjects*. BMC Medical Genetics, 2014. **15**(1): p. 1-8.
19. Tang, K.L., et al., *Behavioral and Psychiatric Phenotypes in 22q11.2 Deletion Syndrome*. J Dev Behav Pediatr, 2015. **36**(8): p. 639-50.
20. Schneider, M., et al., *Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome*. Am J Psychiatry, 2014. **171**(6): p. 627-39.
21. Swillen, A. and D. McDonald-McGinn, *Developmental trajectories in 22q11.2 deletion*. Am J Med Genet C Semin Med Genet, 2015. **169**(2): p. 172-81.
22. Vorstman, J.A., et al., *Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome*. JAMA Psychiatry, 2015. **72**(4): p. 377-85.
23. Campbell, L.E., et al., *Executive functions and memory abilities in children with 22q11.2 deletion syndrome*. Aust N Z J Psychiatry, 2010. **44**(4): p. 364-71.
24. Simon, T.J., et al., *Visuospatial and numerical cognitive deficits in children with chromosome 22q11.2 deletion syndrome*. Cortex, 2005. **41**(2): p. 145-55.
25. Gur, R.E., et al., *Neurocognitive development in 22q11.2 deletion syndrome: comparison with youth having developmental delay and medical comorbidities*. Mol Psychiatry, 2014. **19**(11): p. 1205-11.
26. Franchini, M., et al., *Visual processing of emotional dynamic faces in 22q11.2 deletion syndrome*. J Intellect Disabil Res, 2016.
27. Campbell, L., et al., *Visual scanning of faces in 22q11.2 deletion syndrome: Attention to the mouth or the eyes?* Psychiatry Res, 2010. **177**(1-2): p. 211-5.
28. Fung, W.L.A., et al., *Practical guidelines for managing adults with 22q11.2 deletion syndrome*. Genetics in medicine : official journal of the American College of Medical Genetics, 2015. **17**(8): p. 599-609.
29. Habel, A., et al., *Towards a safety net for management of 22q11.2 deletion syndrome: guidelines for our times*. European Journal of Pediatrics, 2014. **173**(6): p. 757-765.

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