SSBP Syndrome Sheets

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, conotruncal anomaly face syndrome and cardiac defects, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia (CATCH 22)**.

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 syndrome 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 in 2148 live births and 1 in 992 pregnancies [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, 13]. 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 [13]. It is also likely that the prevalence of the syndrome will rise as mortality decreases and reproductive fitness increases [14, 15]. The syndrome affects individuals of both sexes and of different ethnic background equally [16] although it has been suggested that there are sex differences in the expression of the syndrome [e.g., 17, 18].

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 [19]. The most common features include congenital heart defects (including conotruncal anomalies), thymic hypoplasia/aplasia, palatal anomalies (including submucous cleft palate and/or velopharyngeal incompetence); immunodeficiency; hypocalcaemia; vascular anomalies; feeding difficulties; gastrointestinal issues; scoliosis; sleep disorders; hypotonia and subtle, but characteristic, facial features [9, 13, 20]. Due to the multisystemetic impact of 22q11.2DS, it is important that each individual has an individualised care plan involving a multidisiplinary health care team.

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, 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, theory of mind and social perception [e.g., 25, 26-28]. Problems with understanding maths are common in 22q11.2DS and specific learning disorders including mathematics (dyscalculia) are often diagnosed with significant impact on daily living skills [29].

Behavioural characteristics

Emotion dysregulation is a commonly occuring difficulty for people with the syndrome. There has been reports that children and adults experience both internalising and externalising behaviours with early reports suggestive of extremes of behaviour including temper outbursts as well as shyness and withdrawal [30]. A recent paper found that while some people with 22q11.2DS have not difficulties with emotion regulation, other people may predominantly have either internalising or externalising problems or a combination of the latter [31]. Overall, it was found that externalising problems including aggression is associated with having more difficulties in everyday life. People with 22q11.2DS who also have emotion regulation difficulties are more likely to have diagnoses of autism, attention deficit hyperactivity disorder, anxiety or depression [32, 33]. Adults who also have a diagnosis of schizophrenia are also at an increased risk of aggressive behaviours [34, 35].

Social relationships can be problematic for people with 22q11.2DS, there has been reports of difficulties with social skills and social-cognition that may make it more difficult to initiate and maintain friendships as well as understanding social dynamics [36]. This may be further complicated by emotion dysregulation and more general cognitive difficulties. There has also been reports that many people with the syndrome are victimised or bullied at school with clear impacts on mental health and wellbeing [37].

Mental Health and Wellbeing

Children with 22q11.2DS are at higher risk of being diagnosed with psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, anxiety disorders (generalised anxiety disorder, separation anxiety, and phobias) and autism [38]. It has been proposed that as many as 60-70% of children with 22q11.2 have at least one diagnosed psychiatric disorder. In late teenage years and early adulthood there is an increased risk of depressive disorders and also a high risk of psychotic disorders including schizophrenia. Low full-

scale IQ (FSIQ) in childhood, early cognitive decline, and inattentive symptoms have been found to be risk factors for the development of psychotic symptoms [22, 39]. However, conduct disorder and substance use disorder diagnoses are rare in the syndrome. Most of the psychiatric disorders persist into adulthood [20]. Many people with the syndrome have more than one psychiatric diagnosis, highlighting the complexity of care [38]. 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 [40]. It is also important to note that psychiatric symptoms are likely to be impacted by sleep disorders and fatigue that are common in the syndrome and that has a significant impact on quality of life [41-44]

Family functioning

Parents of children with 22q11.2DS report higher levels of parenting stress and poorer mental health compared to parents of typically developing children [45, 46]. Parents often struggle with managing concerns related to their child's diagnostic journey, interactions with the health care system, education and mental health [47, 48]. The concerns of parents often change over time with an initial focus on the health care needs and speech issues of children in early childhood, changing to a focus on intellectual, learning, social and anxiety related issues in mid-childhood. Around this age there are also increasing concerns about independence and mental health [49]. There has been suggestions that, as in other similar conditions, there is an association between parental stress and mental health and child outcomes [45, 46, 50]. It is important to remember that in order to look after a person with 22q11.2DS well, it is important to consider the whole family system [48].

Available clinical guidelines:

- Updated clinical practice recommendations for managing children with 22q11. 2 deletion syndrome
- Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome

Useful websites/associations for more information

- International 22q11.2 Foundation http://www.22q.org/
- 22q11.2 Society http://www.22qsociety.org/
- 22q Foundation Australia and New Zealand https://www.22q.org.au/

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The information contained in these syndrome sheets is aimed at clinicians, is for guidance only, and does not constitute a diagnostic tool. Many syndromes manifest in varying degrees of severity, and this information is not intended to inform patients of a specific prognosis.

The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation