# Consensus Document on 22q11 Deletion Syndrome (22q11DS)

## MaxAppeal

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Max Appeal!

Max Appeal! is a UK registered charity supporting families affected by DiGeorge syndrome, VCFS and 22q11.2 deletion


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# Foreword

22q11 deletions affect health and quality of life from birth through infancy and childhood to adult life with over 180 physical, functional and psychological associations having been reported. The phenotype is therefore extremely variable, frequently leading to clinical confusion, diagnostic delay, excess morbidity, early mortality and frustration to both affected individuals and their carers. There is, therefore, a definable need for better awareness and understanding of, and coordination of care in, 22q11 deletion syndrome (22q11DS).

Care of patients affected by 22q11 deletions is ideally multidisciplinary and, for many, this requirement is lifelong. Early recognition and optimised, integrated care can achieve much in the way of improving outcomes and supporting affected individuals and families. This was the context and the impetus for Max Appeal! to commission and task a committee of national experts to develop consensus guidance with the purpose of steering and influencing improvements in day-to-day care and strategic organisation of more informed support at all tiers across the UK.

The aim of this ambitious project was principally to compile a comprehensive and universally agreed lifelong care plan for people with 22q11DS within the framework of the NHS. Any value which the document may also have beyond UK healthcare structures would be seen as a welcome bonus by the authors.

The Consensus Document is a comprehensive but practical and accessible information resource which has had contributions from major centres across the UK, stakeholder organisations, families and over 50 experts (either as authors or advisers) working in the major clinical fields associated with 22q11 deletion. The Committee hopes that the guidance and information supplied will be of significant material benefit to all patients and families and those who provide care and support to them. In particular, given the heterogeneous clinical impact of 22q11DS, it is hoped that the document will be of broad professional interest, relevance and utility. Max Appeal! and the expert group is committed to the dissemination of this information as a basis for identifying and applying minimum care standards, helping to avoid the situation where every family has to forge their own path to access adequate care.

Knowledge of 22q11DS is ever increasing. The Consensus Document is not intended to be static or written inflexibly in stone and will be revisited as necessary to reflect significant new insights, practices, processes and structures.

The Committee wishes to express its gratitude to everyone who has contributed in any way to the development of this document and to Max Appeal! for the opportunity to participate in this project.

**Richard Herriot**
**Chair of the Max Appeal! Consensus Document Development Committee**

# Consensus Document on 22q11 Deletion Syndrome (22q11DS)

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# Executive summary

This report was commissioned by Max Appeal!, a charity for individuals and families affected by 22q11 Deletion Syndrome (22q11DS). It is designed to complement the 'Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome'[1] which are summary guidelines based on a case history and a series of tables indicating the various features of the condition that occur, together with their recommended screening procedures, at different ages; as well as cautions and considerations that need to be borne in mind. These tables are included as Appendices in this report (with permission) and the details have been expanded with particular reference to the UK.

**Methods**

Findings and recommendations are expressed as levels of evidence*. Sections have been compiled by clinicians, therapists and educationalists experienced in the changing needs of 22q11DS throughout the life cycle.

**Genetics, historical trend**

22q11DS is a deletion of 1.5 to 3 Mb on the long (q) arm of chromosome 22. It is the commonest autosomal deletion in humans. Before the deletion was identified it was considered a number of distinct clinical syndromes, principally DiGeorge, Shprintzen or Velocardiofacial and Conotruncal. Diagnosis is often delayed by months or years, in part because specialists may fail to appreciate a genetic link between disparate disabilities.

Deletion occurs spontaneously in 85% or is transmitted by an affected parent. Inheritance is autosomal dominant with a recurrence risk of 50% in offspring. The risk of recurrence from an unaffected parent carrying the deletion in their eggs or sperm (germline mosaicism) is 1%.

The 22q11DS population prevalence is thought to be 1 in 2 to 4000, and at least 1 in 6000 [B]. The number of affected individuals in the UK and Ireland, population 66 million, is approximately 10 to 15,000 with 150 to 200 affected infants born each year.

Diagnosis by Fluorescent In Situ Hybridisation (FISH) of the chromosome deletion identifies 95%. FISH may be superseded by array Comparative Genomic Hybridisation identifying additional variants of the deletion, and Multiplex Ligand-dependent Probe Amplification [B]. Antenatal detection by Chorionic Villus Sampling (CVS) at 10-12 weeks gestation and DNA analysis of fetal cells from 16 weeks is available.

**Embryological effects of the deletion**

Within the deletion is the gene *TBX1*, controlling development of the third and fourth pharyngeal arches. Deficiency results in cleft palate, palatal insufficiency, cardiac outflow malformations, parathyroid maldevelopment and absent or underdeveloped thymus. Immune function of T and B cells may be affected, with a life time increased likelihood of immune related disease. Other organs affected include the brain, causing behavioural and cognitive impairment and increased frequency of seizures, schizophrenia, abnormal pituitary development, kidney and genitourinary system formation, and skeletal malformations including scoliosis and club foot.

**Presentations**

These may be considered by body system and characteristic age of initial presentation. Severity, even between affected members of the same family, is highly variable [B].

Fetal anomaly screening may result in identifying that both fetus and mother are affected. Careful multidisciplinary assessment of the pregnancy is required [D].

Facial dysmorphia are subtle especially in infancy. They include long narrow face, almond shaped eyes, a bulbous nose (becoming evident with age), small mouth, overfolded ear helix, asymmetry of facial movement [C], and occasionally skull asymmetry due to cranio-synostosis.

Cardiac malformations affect 50 to 85%. They may appear shortly after birth with cyanosis due to reduced blood flow to the pulmonary circulation by right ventricular outflow obstruction as in Fallot's tetralogy, pulmonary atresia, and multiple aortopulmonary collateral arteries (MACPA), or with cardio-vascular collapse due to systemic outflow obstruction from aortic arch narrowing or interruption. Otherwise, within a few days or weeks heart failure due to large shunts such as VSD and truncus arteriosus may develop. Treatment is individualised according to the underlying lesion.

Hypocalcaemia occurs in 30 to 60%, often by school age [B]. It presents as jitteriness,

seizures, stridor (differentiate from laryngeal web or nerve palsy), or biochemically due to hypoparathyroidism, often uncovered by the stress of birth, cardiac surgery, puberty or pregnancy [C]. Calcium supplements and vitamin D are effective treatment. Tooth enamel is weak and prone to caries.

Immune disorders affect the majority, relatively mildly. In 1% it is severe, requiring thymus transplant [C]. Recurrent upper respiratory infections are increased by concomitant velopharyngeal incompetence (VPI). Pneumonia affects 10%. Antibiotic prophylaxis in winter may be beneficial. Episodes reduce in frequency with age. Autoimmune disease such as juvenile rheumatoid arthritis, cytopaenias, coeliac disease and thyroid disorders are increased in frequency [C].

Early feeding difficulties are common, affecting 40% [C]. Causes to consider include palatal anomalies (14%), gastro-oesophageal reflux, dysphagia (10%) which may be associated with chest aspiration, cardiac failure, and developmental delay. Growth is also frequently affected [B]. Forty percent fall below the 3rd centile in height and weight in the first year. Catch up takes place by late childhood to a little below average by adult life, with a prevalence of overweight [B] similar to the general population. Growth hormone deficiency is increased in frequency [C].

Articulation and communication problems occur in 90%, characterised by hypernasal articulation due to VPI [B/C] and delay in expressive speech and language development [C]. Signing can be a useful adjunct. Surgery for VPI may improve comprehensibility. Deafness is due to otitis media and secretory otitis media in 75% [C]; 15% also have sensorineural deafness.

Most children are mildly educationally impaired, mean IQ in the 70's, and likely to require schoolroom support. By school age verbal ability is similar to or better than performance. Memory, and hence rote learning, are strengths. Ability to grasp abstract concepts, especially mathematics, is weak. Clumsiness and incoordination, with motor hypotonia, are present in the majority, affecting activities of daily living, and the development of gross motor and sometimes handwriting skills.

Troublesome symptoms include constipation and leg pain of unknown cause. Clinically significant scoliosis is relatively common (18%), warranting surgery in 18% of those affected. It may be structural, appearing early, or later at 10 to 12 years, similar to idiopathic juvenile scoliosis.

Behavioural and psychiatric disorders affect up to 93%. In childhood they include autistic spectrum disorders and attention deficit hyperactivity disorder. Mood swings, panic attacks, phobias, passivity and poor social skills are features. Psychotic symptoms may emerge in adolescence. The prevalence of schizophrenia was 24% in one adult study.

Many young adults experience social isolation and employment difficulties and continue to be liable to the emergence of 22q11DS related conditions. The life span may be reduced [C].

**Recommendations for investigation, management and referral**

At diagnosis:

- Full blood count including differential white cell count, lymphocyte phenotyping, immunoglobulins, PHA, post immunisation tetanus and Hib antibodies [B]
- Serum calcium, thyroid function [B]
- Cardiological examination, echo cardiogram [B]
- Parental 22q11 status, and siblings if a parent is affected [B]
- Renal ultrasound looking for single kidney, cysts, dilated collecting system [B]
- Irradiated cytomegalovirus negative blood products if immune status is unknown or severely affected. Urgent specialist referral if T lymphocytes are absent or very low
- Immunisation: no live vaccine if CD4 lymphocytes <400/μL. Fully immunise promptly, including Mumps Measles and Rubella (MMR) [D]. Avoid BCG, and consult an immunologist if circumstances require
- Special senses: hearing and eye examination at diagnosis and as clinically indicated
- Scoliosis examination at diagnosis and in early adolescence
- Monitor height and weight frequently up to 2 years old, annually thereafter. Slowing of growth warrants full assessment, including screening for growth hormone deficiency [D]
- Early recognition of speech difficulties and speech therapy intervention may reduce the appearance of deviant articulation. Adenoidectomy may worsen articulation and

should only be contemplated after expert speech assessment

- Prompt referral to the Paediatric Community Services for assessment and follow up. Involvement of therapists for physiotherapy, occupational and speech therapy according to need
- Child and Adolescent Mental Health Services referral for assessment when ASD, ADHD and behavioural issues in the preschool and school age child cause dysfunction. Early psychotic symptoms need urgent referral
- Local Education Authority for Statement of Educational Needs, usually by school age. Liaison between the school Special Educational Needs Co-ordinator (SENCO) and informed psychologists to initiate teaching programmes supporting learning for the distinctive educational profile many have
- Daily Vitamin D. The dose should be the recommended daily allowance.

Annual:

- Full blood count for cytopaenias, serum calcium and thyroid function
- Height and weight
- Monitor for autoimmune disease; autoantibody testing as clinically indicated
- Regular dental care
- Social work and adult learning difficulty team referral where an affected parent or the family are in need of support and advocacy
- Coordinated care by a key worker to guide the individual's progress
- Limitations of the report: Few 22q11DS studies have high levels of evidence for reports and treatment. Evidence is often extrapolated from studies of unrelated conditions in which the same disability occurs.

**Conclusions**

Advances in cardiac surgery and medical management have resulted in 95% surviving to one year of age. The number of affected individuals in the population is therefore growing. With help to manage their disabilities many more are now reaching adult life. They have the possibility of becoming parents, and adding to the pool of those in need. Careful coordination and a multidisciplinary team approach are required for most individuals, with access to services throughout the life cycle. Fragmented services for adults with 22q11DS need to be brought together to build on the present narrowly focused providers in adult cardiac and mental health services.

*The grades of levels of evidence and recommendations are in descending order A to D, and defined in the main text.

**Alex Habel**

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# 1. Introduction

22q11 Deletion Syndrome (22q11DS) is a chromosomal microdeletion disorder affecting at least 1 in 6000 children. The condition is characterised by impaired communication (especially speech and language delay), subtle facial features, and a typical cognitive and behavioural profile. Between 50-85% of affected individuals have congenital heart disease. Historically a number of different clinical syndromes were described e.g. DiGeorge syndrome (congenital heart disease and T-cell immunodeficiency with absent/small thymus), Shprintzen/velocardiofacial syndrome (palatal insufficiency, congenital heart disease and subtle facial features) and Conotruncal Anomaly Face syndrome (outflow tract defects of the heart with distinctive facial features) before it was realised that they all shared a common pathophysiology[1-3]. Kobrynski and Sullivan provide an excellent comprehensive and contemporary review of the chromosome 22q11.2[4] and there is also an excellent web-accessible GeneReview on the topic[5].

The great majority of patients harbour a submicroscopic deletion of a ~3 Mb interval on chromosome 22q11.2, which encodes more than 35 genes. One of the genes almost invariably affected in 22q11DS is *TBX1* which is a transcription factor involved in the embryogenesis of the third and fourth pharyngeal arches. Hence patients with 22q11DS often have dysfunction in structures derived from these branchial arches e.g. the cardiac outflow tract (Tetralogy of Fallot, Ventricular Septal Defect (VSD), interrupted aortic arch), the thymus (T-cell immunodeficiency), the parathyroid glands (hypocalcaemia) and the palate (cleft palate, palatal insufficiency). Other genes in the interval contribute to the mild cognitive impairment and behavioural aspects of the disorder.

The 22q11DS has a minimum birth prevalence of 1 in 5950 births[6] [B] and occurs in all major ethnic groups. Approximately 85% of cases arise *de novo* (with no family history); in the remainder the condition is inherited from an affected parent. It is common for the diagnosis in a parent to be recognised for the first time following the birth of an affected child. This may be due in part to the very variable expressivity seen in 22q11DS and also to the greater awareness of the condition amongst paediatricians than amongst adult specialists.

22q11DS is a highly variable disorder. At present, there is little understanding of the factors which contribute to this variability. Speculatively, this may be related to structural and sequence variation elsewhere in the genome and environmental factors which interact in some way with dosage sensitive genes in the 22q11DS. Due to the many different body systems which can be affected, the disorder may present to a fetal medicine specialist, neonatologist, paediatrician, cardiologist/cardio-thoracic surgeon, immunologist, cleft surgeon, speech and language therapist, endocrinologist, clinical geneticist or general practitioner. Diagnosis is often delayed by months or years.

Optimal care of an individual with 22q11DS requires a multidisciplinary team approach. This consensus document seeks to outline best practice for the diagnosis and management of individuals with 22q11DS.

**Helen Firth**

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# 2. Methods

MaxAppeal assembled a steering committee of UK medical experts to develop a consensus document summarising standards of care for the diagnosis and holistic management of individuals with 22q11DS. This guideline is based on evidence as well as on expert opinion and is for use by both clinicians and those caring for patients with 22q11DS. The recommendations are evidence graded. During the development of this consensus document a variety of stakeholders were consulted with responses received from the following:

- American Cleft Palate-Craniofacial Association
- British Cardiovascular Society
- British Congenital Cardiac Association
- British Society for Immunology (Clinical Immunology and Allergy Section)
- Clinical Genetics Society
- Department of Health (Genetics and National Specialised Commissioning Teams and the Human Genomics Strategy Group)
- Addenbrooke's Hospital, Birmingham Children's Hospital and Great Ormond Street Hospital specialist teams
- NHS Scotland (specialty advisers)
- Parent/Carer representative
- Royal College of Paediatrics and Child Health (with input from the British Paediatric Allergy, Immunology and Infection Group, British Paediatric Mental Health Group, British Academy of Childhood Disability, British Society for Paediatric and Adolescent Rheumatology, British Society for Paediatric Endocrinology and Diabetes)
- Royal College of Pathologists
- Royal College of Psychiatrists (Faculty of Child and Adolescent Psychiatry)
- Royal College of Physicians (London)
- United Kingdom Primary Immunodeficiency Network
- Unique (Rare Chromosome Disorder Support Group).

Their comments and suggestions were considered by the steering committee. Where evidence is lacking, consensus was reached by the committee and experts co-opted by the committee.

Evidence for the recommendations was obtained by employing electronic literature searches using the primary key words:

- **Velocardiofacial syndrome**
- **DiGeorge syndrome**
- **the chromosome 22q11DSs**.

Because of the confusing nomenclature of the syndrome, the terms 22q11DS (for the syndrome), 22q11.2del (for the micro-deletion) and 22q11.2 (for the chromosomal location) are used consistently throughout this document.

Each article was reviewed for suitability for inclusion in the guideline. The recommendations were evidence graded at the time of preparation of these guidelines. The grades of recommendation and the levels of evidence are based on the Scottish Intercollegiate Guidelines Network scheme[1]. Categories of recommendations are labelled A, B, C, and D (see below)[2].

## 2.1 Key to evidence statements and grades of recommendations

**Levels of evidence**

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++ High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies, e.g. case reports, case series

4 Expert opinion

## 2.2 Grades of recommendations

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated

as $2^{++}$, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as $1^{++}$ or $1^{+}$

C A body of evidence including studies rated as $2^{+}$, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as $2^{++}$

D Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as $2^{+}$.

The references were downloaded from PubMed to a dedicated file within NCBI on the PubMed website. Details of how to access this file can be obtained from the editor.

**Dinakantha Kumararatne**

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# 3. Genetics

The deletion on chromosome 22q11.2 is below the threshold of light microscopy and so requires molecular cytogenetic techniques such as Genomic Array, Fluorescence In Situ Hybridisation (FISH) or Multiplex Ligand dependent Probe Amplification (MLPA) studies for laboratory confirmation of diagnosis[1] [B].

Flanking the deleted region on chromosome 22q11.2 are two genomic regions with high sequence homology termed LCR22s[2]. There are a number of such regions along the length of chromosome 22. The mechanism underlying the deletion is known as Non-Allelic Homologous Recombination (NAHR). When chromosomes pair up at meiosis, the chromosomes align strongly at regions of high sequence identity – like buttons and buttonholes on a shirt. In NAHR a mismatch occurs rather akin to missing out one of the buttons when buttoning up a shirt front and the intervening section of DNA is not copied into the chromosome 22 in the egg or sperm. When the egg is fertilised, the fertilised egg will have one normal chromosome 22 and one deleted chromosome 22. The particular genomic architecture of chromosome 22 means that 22q11.2 is one of the regions of the genome most prone to this mismatching process.

When an individual is diagnosed with 22q11DS, analysis for the microdeletion (e.g. by genomic array, FISH or MLPA) should be offered to both parents [B].

### 3.1.1 Unaffected parents of a child with a *de novo* deletion

The chance of recurrence in a future pregnancy, or in existing siblings, is very low. It is likely to be of the order of <1%. The risk is higher than in the general population because of the possibility of germline mosaicism (where the 22q11.2del affected not a single egg or sperm, but a cluster of germ cells) in one of the parents. Sibling recurrence has been reported, but is rare[3] [C].

### 3.2 Affected parent

An individual with 22q11DS has a 50/50 chance of transmitting the condition to their offspring in any pregnancy. The high intrafamilial variability of 22q11DS, from mild cognitive impairment to severe life-threatening congenital anomalies, should be emphasised[4] [B]. In view of the high risk of transmission, discussion may include the possibility of prenatal diagnosis[5] and preimplantation genetic diagnosis (PGD) where available.

### 3.3 Prenatal diagnosis

Prenatal diagnosis of 22q11DS requires invasive testing by chorionic villus sampling (CVS) at 10-12 weeks gestation with a miscarriage risk of ~1%, or by amniocentesis at 15-16 weeks gestation with a miscarriage risk of 0.5-1%. This will determine whether or not the fetus has 22q11.2del, but will not give an indication of how mildly or how severely the child might be affected, or about what body systems will be involved. Detailed ultrasound scanning of the fetal heart (fetal echocardiography) at ~16 and 20 weeks gestation may be very helpful in determining whether a significant congenital heart defect is present [D]. However, ultrasound scanning cannot identify cognitive, behavioural, endocrinological or immunological problems. It is also not possible to identify velopharyngeal insufficiency, and cleft palate is extremely difficult to identify by ultrasound scan even by the most experienced fetal medicine specialists.

### 3.4 Pregnancy

### 3.4.1 22q11DS identified during pregnancy

The couple should be offered [D]:

- Fetal echocardiography
- Genetic counselling (including testing parents for 22q11.2del)
- Expert review of the newborn infant by a senior paediatrician to include cardiac assessment and assessment of calcium and immune function.

### 3.4.2 Management of pregnancy in a woman with 22q11DS [D]

This requires careful communication and coordination between the patient, her general practitioner, her obstetrician and clinical geneticist. Priorities include:

- Assessment of the cardiac status of the mother if she is known to have congenital heart disease or if she is not known for certain to have a structurally normal heart
- Assessment of the endocrine status of the mother especially for hypoparathyroidism or hypothyroidism

- Genetic counselling to discuss the 50/50 risk to the pregnancy and to offer prenatal diagnosis and/or fetal echocardiography
- Arranging for expert review of the newborn infant by a senior paediatrician to include cardiac assessment and assessment of calcium and immune function – unless prenatal diagnosis demonstrates that the baby has not inherited the 22q11DS deletion.

**Helen Firth**

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# 4. Cardiac Abnormalities

## 4.1 Introduction

The incidence of congenital heart disease is less than 1% in the general population, with conotruncal cardiac malformations accounting for approximately 50% of congenital heart defects in newborn infants. Conotruncal abnormalities affect the outflow portion of the heart (e.g. truncus arteriosus, tetralogy of Fallot, interrupted aortic arch) and are particularly common in 22q11DS.

Chromosome 22q11.2 deletions and, recently, hemizygosity for several genes on chromosome 22q11.2 have been reported to be present in the majority of patients with DiGeorge, velo-cardiofacial and conotruncal anomaly face syndromes and the Cayler cardio-facial syndrome[1-4] suggesting that these syndromes represent a spectrum of phenotypic expression of the deletion [B]. These disorders most frequently occur *de novo* and are relatively common (>1 in 6,000 live births)[5]. Mutation of the *TBX1* gene has recently been suggested as a major determinant of the syndrome[6], causing impaired development of the cardiac outflow tract and resulting in conotruncal mal-formations[7]. As has been shown by Kirby and Le Douarin et al., depleting the heart of cells derived from occipital neural crest may result in aorto-pulmonary septal defects[8;9]. Although the exact role of the neural crest cells that migrate into the tunica media of the visceral arch arteries during conotruncal formation remains obscure[8], it appears that there is an important gene connected with the development of the arterial trunk and pulmonary arteries in the 22q11.2 region.

The cardiac defects commonly seen in these disorders therefore derive either from the conotruncus, the embryonic aortic arches or the ventricular septum and consist of abnormal aortic arch laterality and branching such as right aortic arch or type B Interrupted Aortic Arch (IAA) (30-45%), Ventricular Septal Defect (VSD), Tetralogy of Fallot (ToF) or Pulmonary Atresia-Ventricular Septal Defect (PA-VSD) (12.5%), and Truncus Arteriosus (TA) (14-25%)[7;10] [B]. Some phenotypic differences have been shown between patients with and without the 22q11.2del[11;12].

## 4.2 Clinical manifestations and presentation

Clinical manifestation of the cardiac condition is dependent on the type of cardiac anomaly and the timing of the diagnosis. Recently McElhinney et al.[13] reported 125 patients who presented with conotruncal malformations. They found that 10% of these patients had 22q11.2del. Anatomical features which were associated significantly with the gene deletion were abnormal aortic arch and discontinuous pulmonary arteries (45%).

Many children with 22q11DS have cardiac defects which cause cyanosis; the infants have lowered oxygen saturations unresponsive to oxygen therapy. The degree of desaturation is dependent on the level and degree of mixing of oxygenated and deoxygenated blood, relative resistances between pulmonary and systemic circulations, size and development of the pulmonary arteries and the presence or absence of major aorto-pulmonary connections (MAPCAs); the smaller the pulmonary arteries in the absence of MAPCAs, the more cyanosed the infant. Chessa et al.[14] showed in their study that the morphological features of ToF and PA-VSD appear to be different in patients with and without 22q11.2del. They were able to describe a 'specific' phenotype of PA-VSD in 22q11DS characterised by major aorto-pulmonary connections with complex loop morphology originating from the descending aorta. However, they could not find an easy differentiating factor if MAPCAs were absent, nor could they establish a correlation between the 22q11.2del status of the patient and the size of the pulmonary arteries. Goldmuntz et al.[15] reported that the frequency of 22q11DS was higher in patients with anomalies of the pulmonary arteries but, again, the size of the pulmonary arteries was not a distinguishing factor.

These studies were all performed postnatally. However, with increasing advances in fetal cardiology it is now possible to detect the majority of these heart defects by 18-20 weeks of gestation, therefore allowing for appropriate antenatal counselling and advice before the baby is born[16] [B]. Therefore it is now recommended that high risk pregnancies are screened by assessing the fetal heart in more detail [D]. This would involve referral to a fetal cardiologist for detailed assessment of the cardiac anatomy. Positive family history in a first degree relative of congenital heart disease

and known chromosomal deletions or abnormalities are considered to fall into the 'high risk pregnancy' category[17].

### 4.3 Ventricular Septal Defect (VSD)

#### 4.3.1 Background

VSD is the commonest congenital heart defect. It occurs in 1.5 to 3.5 per 1,000 live births. They occur in any portion of the inter-ventricular septum and may on occasion be multiple.

#### 4.3.2 Presentation

Infants usually present early in life with a murmur or failure to thrive. The severity of symptoms depends on the functional size of the defect.

#### 4.3.3 Investigation

The diagnosis is made by echocardiography. Chest X-ray and ECG help guide the need for and timing of intervention.

#### 4.3.4 Management

If the defect is large and associated with significant shunting across the interventricular septum, surgical closure should be performed when medical therapy alone is inadequate for appropriate growth and development of the child. Symptoms may be controlled by diuretics +/- ACE inhibitor. Most defects are small and may not need medication. With time, many smaller defects close spontaneously, while other small defects may be haemodynamically insignificant and not warrant intervention. Some defects may be suitable for transcather approach once the child is of adequate size. Defects which are located in the subaortic area may cause deformity of the aortic valve and patients may therefore present with, or develop, aortic incompetence. Such defects should be closed, even if functionally small, to prevent secondary damage to the aortic valve.

### 4.4 Tetralogy of Fallot (ToF)

#### 4.4.1 Background

ToF is the commonest cyanotic heart defect. It occurs in 3 to 6 per 10,000 births and represents 5-7% of congenital heart defects. It consists of four elements; VSD, overriding aorta, (sub) pulmonary stenosis and right ventricular hypertrophy. Historically a variation on this morphology has been described called Tetralogy of Fallot with absent pulmonary valve. This is now termed absent pulmonary valve syndrome as, instead of the infundibular stenosis found in Tetralogy of Fallot, the pulmonary valve annulus is small with no effective valve thereby allowing significant pulmonary regurgitation. This causes dramatic pulmonary artery dilatation during fetal life with the result that the child's major problem is airway compression and tracheobronchomalacia.

#### 4.4.2 Presentation

The defect may be detected antenatally or may present at birth or during infancy with a murmur or significant cyanosis. The degree of cyanosis is dependent on the size of the right ventricular outflow tract (including the pulmonary arteries) and this determines the timing of presentation. Cyanotic spells (episodic, dramatic exacerbation of the degree of desaturation) are common in this condition and may be the feature of initial presentation.

#### 4.4.3 Investigation

The definitive diagnostic tool is echocardiography which allows delineation of the anatomy in great detail. Chest X-ray and ECG are useful adjuncts but neither is diagnostic.

#### 4.4.4 Management

Depending on the degree of right ventricular outflow obstruction the infant will either require surgery very early in life in order to provide adequate blood flow to the pulmonary arteries or, definitive surgery in later infancy. The precise timing of definitive surgery varies between patients and also between centres but is usually carried out at around 6-8 months. Securing adequate pulmonary blood flow early in life has traditionally been achieved by performing a Blalock-Taussig (B-T) shunt but nowadays early definitive repair even in the newborn period is routinely undertaken. However, many will require further surgery later in life as, with time, pulmonary valvar regurgitation can lead to right ventricular volume overload.

### 4.5 Pulmonary Atresia-Ventricular Septal Defect (PA-VSD)

#### 4.5.1 Background

Pulmonary atresia/VSD is rare. In this abnormality there is no right ventricular outflow and the main pulmonary artery may be completely unformed. A VSD is present and the right ventricle is usually of adequate size. There are three main types based on the degree of development and arborisation of the pulmonary arteries. In most patients there are well formed branch pulmonary arteries with a patent arterial duct supplying them. In the other group there are small but well formed branch pulmonary arteries connected to MAPCAs. In extremely rare cases, there are no central

pulmonary arteries and different segments of pulmonary arteries are supplied only by the MAPCAs.

#### 4.5.2 Presentation

If not detected antenatally, babies usually present very early in life with worsening cyanosis and difficulty feeding as pulmonary blood flow is dependent on patency of the ductus arteriosus and this vessel gradually closes naturally over the first few days of life. However, if associated with MAPCAs, the infant may not present until later in life as pulmonary perfusion is not dependent on ductal patency. Indeed, some babies have such profuse pulmonary blood flow from the MAPCAs that they present early in heart failure.

#### 4.5.3 Investigation

Echocardiography is used for diagnosis. The intracardiac morphology is delineated, as is the anatomy of the branch pulmonary arteries if these are confluent. MAPCAs are more difficult to delineate with echocardiography alone, and in this circumstance early cardiac catheterisation or Magnetic Resonance Imaging (MRI) is required.

#### 4.5.4 Management

Immediate treatment of the neonate to secure pulmonary blood flow in the face of a closing duct is prostaglandin infusion followed by surgery. This may be by means of a palliative systemic-pulmonary artery shunt, but definitive repair (VSD closure and insertion of a right ventricle to pulmonary artery conduit) can also be the initial surgical strategy depending on unit philosophy. Definitive repair is usually achievable, though this ultimately depends on the size of the pulmonary arteries. Even following definitive repair, patients will require multiple operations for conduit changes. Even when MAPCAs are present the objective of initial surgery is to preserve and support the growth of the native pulmonary artery. If this is not possible MAPCAs may need anastomosing together to create adequate pulmonary arteries (a procedure known as unifocalisation). This may be combined with either complete repair or a B-T shunt followed by later completion depending on the size and complexity of the MAPCAs.

### 4.6 Truncus Arteriosus (TA). Common Arterial Trunk

#### 4.6.1 Background

TA is a rare congenital heart disease where the embryologic structure known as the truncus arteriosus does not septate into pulmonary artery and aorta. A single artery therefore arises from the two ventricles which gives rise to both aorta and pulmonary arteries; there is also a large VSD. TA is often associated with an abnormal truncal valve which can either be stenotic or regurgitant and in about 30% of cases it is associated with a right aortic arch. There are three types (I, II, III) of TA which are distinguished by the branching pattern of the pulmonary arteries. Interruption of the aortic arch may also be present with the descending aorta supplied via an arterial duct. Coronary abnormalities often coexist.

#### 4.6.2 Presentation

The baby generally presents with a murmur and mild cyanosis at birth or with heart failure in the first few months of life as pulmonary vascular resistance falls.

#### 4.6.3 Investigation

Echocardiography will define the cardiac anatomy and is able to distinguish between the three types with a reasonable amount of certainty. Echocardiography will also be able to delineate arch morphology.

#### 4.6.4 Management

Cardiac surgery is required soon after birth to prevent pulmonary vascular damage. The defect is repaired by separating the pulmonary arteries from the arterial trunk and closing the VSD, which commits the truncus to the left ventricle. A conduit is placed between the pulmonary arteries and the right ventricle.

### 4.7 Interrupted Aortic Arch (IAA)

#### 4.7.1 Background

In IAA the aortic arch is discontinuous, usually with a physical gap but occasionally with fibrous continuity but no lumen present between the two segments. There are three types depending on where the arch is interrupted:

- type A distal to the left subclavian artery
- type B between the left common carotid and subclavian arteries
- type C between the innominate and left carotid arteries.

Anomalous origin of the right subclavian artery is also common with this abnormality. It is usually associated with other cardiac abnormalities, most frequently a VSD but occasionally TA or aortopulmonary window.

#### 4.7.2 Presentation

If not diagnosed prenatally patients often present collapsed *in extremis* following a fall in pulmonary arterial resistance or after closure of the ductus arteriosus. Occasionally, infants

present with a murmur or signs consistent with aortic coarctation if ductal patency persists to some extent.

#### 4.7.3 Investigation

The definitive diagnosis can usually be made by echocardiography though occasionally MRI scanning is also helpful. With these modalities the anatomy can be delineated in great detail. It is imperative to examine the subaortic area carefully as it can be critically small with this morphology.

#### 4.7.4 Management

As children are often brought into hospital in a state of collapse, initial management is by basic resuscitation and starting an infusion of prostin. Following this, definitive treatment is by surgery and this should be performed as soon as the child is stabilized with appropriate intensive care support and when multi organ dysfunction and metabolic derangement is corrected.. Usually the aortic arch can be reconstructed with an end-to-end anastomosis though, on occasion (particularly if associated with other cardiac abnormalities), an arch repair comprising subclavian artery turn-down with prosthetic patch enlargement (Blalock-Park operation) may be helpful to avoid compression of other structures lying underneath the aortic arch. Nowadays other cardiac abnormalities are usually corrected at the first operation. Late stenosis of the anastomosis is not uncommon but can usually be treated using transvascular techniques.

### 4.8 Recommendations

#### 4.8.1 Antenatal

- Fetal echocardiogram by a fetal cardiologist in any fetus where there is a family history of congenital heart disease in a first degree relative (i.e. mother, father, sibling)[17] [D]
- Fetal echocardiogram by a fetal cardiologist if there is evidence of familial 22q11DS (there is a 50% chance of passing on this deletion)[13] [B]
- Testing for chromosome 22q11DS in a fetus found to have a congenital heart defect commonly associated with 22q11DS (cono-truncal anomalies, posteriorly malaligned VSD or cono-septal VSD with abnormal vessel anatomy, abnormal aortic arch laterality, cervical arch and discontinuous pulmonary arteries)[13;16] [B].

#### 4.8.2 Postnatal

- Any infant/child with congenital heart disease which falls into the category of a cono-truncal malformation (e.g. ToF +/- absent pulmonary valve, TA, PA-VSD, IAA, VSD with vessel anomalies) should undergo chromosomal testing for 22q11.2del[13;15] [B]
- Any infant or child with abnormal arch laterality, cervical arch and/or discontinuous pulmonary arteries should have genetic testing[13;15]. 22q11DS is particularly associated with vascular anomalies such as right aortic arch, cervical aortic arch, aberrant right or left subclavian artery, aorto-pulmonary collaterals, and absent or discontinuous branch pulmonary arteries
- Any patient who presents with ToF or PA-VSD with or without MAPCAs should have chromosomal testing for 22q11.2del [B]
- Individuals with a cono-ventricular, posteriorly mal-aligned, or cono-septal VSD *and* anomalies of the aortic arch or branch pulmonary arteries commonly have 22q11.2del and genetic assessment of these patients should therefore be performed[13;15] [B]. However, genetic testing of patients with these types of VSD but a normal aortic arch and pulmonary arteries may be performed routinely or guided by the presence of associated non-cardiovascular features of chromosome 22q11DS [D]
- Any adult with high-risk cardiac lesions, or typical associated cardiac and extracardiac anomalies, should be offered screening after appropriate personal and genetic counselling at which the patient should be presented with the pros (screening for extracardiac manifestations, knowledge as to the potential for transmission to offspring) and cons (insurance implications) of screening[18] [B]
- Any patient who has non-cardiac manifestations of 22q11DS in addition to a cardiac defect which is not commonly associated with the syndrome, should have genetic evaluation and molecular-cytogenetic studies[18]
- Once the diagnosis is confirmed, a multi disciplinary team approach is mandatory. This should include endocrinologist, clinical geneticist, immunologists, speech and language therapist, general and community paediatrician with provision for input from clinical psychologist during the child's development.

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# 5. Endocrinology

## 5.1 Introduction

Three principal problems related to endocrinology are seen in the 22q11DS:

- hypoparathyroidism with or without symptomatic hypocalcaemia
- thyroid disease, both underactive and overactive
- short stature

Other endocrine abnormalities such as diabetes mellitus, obesity and pituitary gonadotrophin deficiency have also occasionally been described.

## 5.2 Hypoparathyroidism and hypocalcaemia

### 5.2.1 Aetiology and Epidemiology

This results from failure of normal development of the parathyroid glands. These are derived from the IIIrd and IVth pharyngeal arches, from which the other structures whose abnormalities are seen in 22q11DS are also derived.

The prevalence of hypoparathyroidism is a little difficult to determine and increases with age. This is partly because those individuals with severe cardiac anomalies may not survive and hypocalcaemia may not be identified in these subjects whilst the cardiac problems are being dealt with. In addition, the hypocalcaemia may develop with time and is more likely to become apparent during infancy and adolescence when growth rates are more rapid and the demand for calcium increases. Various estimates of the prevalence of hypocalcaemia have been made and it may be as high as sixty percent[1] [B] although most authors give a prevalence of nearer thirty percent[2-4] [B].

### 5.2.2 Clinical features

If severe hypocalcaemia is present, hypoparathyroidism presents with symptoms related to this. These include convulsions, irritability and muscle pains. Voice changes related to spasm of the vocal cords may be present in young children. However, hypocalcaemia is not always severe enough to cause such obvious symptoms although it may be present for several years before being diagnosed and, in retrospect, it may be suspected that this has been the case. If 22q11DS is known to be present, screening for hypoparathyroidism should be undertaken regularly (at least annually)[5] [C]. Conversely, any child who presents with unexplained hypoparathyroidism should be screened for 22q11DS since this is the commonest cause of isolated hypoparathyroidism in childhood.

A diagnosis of hypoparathyroidism may be missed in infancy, particularly if other problems such as cardiac abnormalities and immune deficiency are also present. If hypocalcaemia is not detected in the early months, it may become less troublesome as the child's growth rate slows and demand for calcium diminishes. If this happens, the hypoparathyroidism may not become apparent until puberty when growth rate increases again and demand for calcium rises. It may also be that the severity of the hypoparathyroidism increases with age as the capacity of the glands to secrete the hormone diminishes[6] [C]. At this stage CT scan of the brain may show the presence of calcification in the basal ganglia which indicates that hypocalcaemia has been long standing. Because PTH has a positive effect on bone formation, bone density may be reduced rendering the child more susceptible to fractures.

### 5.2.3 Diagnosis

A diagnosis of hypoparathyroidism is made by demonstrating low calcium and raised phosphate in plasma, together with inappropriately low parathyroid hormone (PTH) and normal vitamin D levels.

### 5.2.4 Treatment

Treatment usually consists of a combination of oral calcium supplements and the active vitamin D metabolite, 1α-hydroxy-colecalciferol (alfacalcidol), the aim being to maintain the plasma calcium at the lower end of the normal range in order to prevent adverse effects on the kidney which may occur if urinary calcium levels rise unduly. Although theoretically PTH would be a more logical treatment, this has only recently become available and it has to be given by injection at least twice daily and there is no current experience of its use in children in this condition. A trial of intact PTH (1-84) is currently being undertaken in adults with hypoparathyroidism.

## 5.3 Growth

Short stature is present in between one third and two thirds of patients with 22q11DS[7] [B]. The cause of this short stature is most likely to be a combination of constitutional delay of growth and a non-specific feature of the

condition. Only about ten percent of adults with 22q11DS syndrome have short stature[8] [B].

However, a small proportion of patients have documented growth hormone deficiency[7] [C] and it has been suggested that patients with 22q11DS are at an increased risk of pituitary deficiencies, particularly if abnormalities of the palate are present. Occasionally, other pituitary hormone abnormalities have also been described.

Weight is sometimes reduced in the early years, particularly if feeding problems are present, but corrects with age and, indeed, some degree of obesity may then supervene[9] [B]. Growth and development should always be monitored in children with 22q11DS and, if growth rates are slower than normal (as opposed to the child having short stature but growing at a normal rate), screening for growth hormone deficiency is justified [D]. This can initially be undertaken by measurement of IGF-1 but, if there is any doubt, growth hormone dynamic testing should be undertaken since treatment with growth hormone can then be instituted.

### 5.4 Thyroid Disease

Both hypo- and hyperthyroidism can occur in 22q11DS[10;11] [C]. Thyroid gland development is partly determined by the gene *TBX1*, mutations or deletions of which are thought to be responsible for many of the features of 22q11DS. Hypothyroidism is over represented in 22q11DS and should always be screened for [D]. The diagnosis is usually made by demonstrating a combination of a raised thyroid stimulating hormone (TSH) level associated with a low normal or low thyroxine ($FT_4$) levels in plasma.

However, a proportion of patients with 22q11DS develop an overactive thyroid gland as a result of autoimmunity[12;13] [C]. This may seem somewhat surprising in patients who are at risk of an immune deficiency, but it seems that there may be an increased risk of developing antibodies that cause either Graves' Disease or Hashimoto thyroiditis and it has been suggested that autoimmune diseases are more commonly present in 22q11DS patients[14] [C].

Treatment of hypothyroidism consists of replacing the deficient hormone with oral thyroxine. Thyrotoxicosis is treated in the usual way with antithyroid drugs (carbimazole or propyl thiouracil).

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# 6. Immunology

## 6.1 Clinical manifestations and presentation

Disorders of immunity are widely acknowledged in patients with 22q11DS, but frequently misunderstood. Thymic development may be affected, and hence T cell development impaired. The overwhelming majority of patients have normal T cell function and do not suffer from clinical consequences of T cell immunodeficiency. However, the most serious presentation is during early infancy, with a complete absence of the immune system, which very rapidly leads to severe, recurrent or persistent viral respiratory or gastrointestinal infections, which are the hallmarks of this presentation, and infants may die within the first year of life unless treated[1]. Fortunately this is a very rare presentation and fewer than 1% of patients with 22q11DS present with this[2] [C]. Opportunistic infection with organisms such as *Pneumocystis jiroveci*, and fungal infections are also recognised. Less immediately serious, but more common (affecting up to 40% of patients), are mild to moderate reduction in T lymphocyte numbers and/or specific antibody deficiency[3] [D], the latter particularly to encapsulated bacteria like *pneumococcus*[4] [C], which cause recurrent upper and, more rarely, lower respiratory tract infection. This commonly manifests in later infancy, after the first six months of life. Affected patients suffer frequent coughs, colds, ear and throat infections. Concomitant velo-pharyngeal dys-function with poor muscular co-ordination contributes to the increased frequency of upper respiratory tract infections, and these are common in this group of patients even in the absence of immunological abnormalities. More serious, but less common, manifestations include invasive infection such as pneumonia affecting up to 10% of patients[5] or, less commonly, meningitis. In many children who have reduced T lymphocyte numbers, these improve during the first few years of life, often reaching normal levels.

A more recently recognised presentation of disordered immunity in patients with 22q11DS is an increased susceptibility to autoimmune disease. It is unclear how common this presentation is, and whether it is more common in older patients, but it seems to occur at any age. Further studies are required to assess how common this complication is. Presentations include rheumatoid arthritis[6] [C], autoimmune thyroid disease[7] [C] and cytopaenias[8] [C], but other autoimmune manifestations have been described.

## 6.2 Investigation and diagnosis

Severe T lymphocyte immunodeficiency due to thymic aplasia should be excluded in patients presenting with classical features of heart disease or hypocalcaemia in early infancy. Thymic aplasia can also occur in the absence of other classical features. Lymphocyte phenotype analysis should be performed urgently. Lymphocyte proliferative responses should be measured in those with <400 T cells/μL.

In toddlers and pre-school children, lymphocyte phenotype should be evaluated along with analysis of antibody function. Immunoglobulin levels should be measured, and the IgG antibody response to vaccine antigens, such as tetanus and *haemophilus influenzae* (Hib), should be evaluated. Inadequate responses should be repeated after further immunisation. For those with recurrent or persistent lower respiratory tract infection or clinical signs, referral to a respiratory specialist should be made for consideration of high resolution computerised tomographic imaging of the chest and an assessment of lung function.

Evidence for autoimmunity should be sought in older children and adults who have suggestive symptoms. An assessment of thyroid function, as well as a full blood count should be routinely performed. Specific symptoms may guide specific investigations including autoantibody screening.

## 6.3 Management

Children with complete 22q11DS who have very low or absent T lymphocytes should be referred urgently to a supra-regional immunology centre for further evaluation and treatment which may include haematopoietic stem cell or thymic transplantation. Management of such infants may depend on the extent of other congenital abnormalities. If erythrocyte transfusions (for cardiac surgery) are required before results are available, they should be from cytomegalovirus seronegative donors, and should be irradiated to prevent potential transfusion related graft versus host disease. Prophylactic treatment with anti-PCP, antiviral and anti-fungal agents, and immuno-globulin replacement therapy should be commenced[9].

Symptomatic partial 22q11DS patients with milder T lymphocyte defects or impaired specific antibody responses to tetanus and Hib should be seen once or twice annually in the first few years of life. Antibiotic prophylaxis may be required over the winter months, and more rarely through the summer months, for children with recurrent respiratory infections. This can usually be discontinued by the age of 5 or 6 years, if not before. For patients with breakthrough infections, or those with progressive lung disease despite antibiotic therapy, immunoglobulin replacement therapy may be considered. This should be supervised by an immunologist.

It is good practice to review patients annually thereafter for evidence of autoimmune disease. History and examination should be directed towards symptoms of autoimmunity. Investigations should be directed by the clinical picture but should include appropriate auto-antibodies thyroid function, a full blood count and film and the direct antiglobulin test.

### 6.4 Immunisation

Primary immunisations should be given to all patients without delay. For those rare patients with severe T lymphocyte immuno-deficiency there may be no benefit, but the current UK immunisation schedule includes only inactivated vaccines and is therefore safe. For the majority of children who have a CD4 T lymphocyte count above 400 cells/μL of blood, immunisation with the measles, mumps and rubella (MMR) vaccine is safe[10] [D]. All children should receive MMR. Currently in the UK, varicella use is discretionary, but is safe to give if the CD4 T lymphocyte count is above 400 cells/μL of blood. BCG immunisation is no longer routinely included in the UK schedule for teenagers, so for most patients will not raise a question. BCG should not be given to any infants with significant T lymphocyte abnormalities. For individual cases where BCG is being considered, advice should be sought from an immunologist.

### 6.5 Minimum initial immunological investigations:

- Full Blood count and differential white cell count
- Immunoglobulins (IgM, IgA, IgG,)
- Lymphocyte phenotyping (CD3, CD4, CD8, CD19 or CD20, CD16/CD56)
- Lymphocyte proliferations to phyto-haemagglutinin, if easily available and T cell counts low
- Post immunisation antibody responses to tetanus and Hib antigens.

### 6.6 Minimum follow-up immunological investigations:

- Assessment of specific antibody response to tetanus and Hib
- Full Blood count and film
- Assessment of autoantibodies, if clinically indicated, including direct antiglobulin test and thyroid antibodies
- Thyroid function tests.

### 6.7 Key immunological management decisions

- Irradiated, CMV negative blood products if immune status severely affected or unknown
- Urgent referral to specialist centre for further treatment if absent or very low T lymphocytes
- Assess immunisation status – live viral vaccines not contra-indicated unless severe immunocompromise present. (If tetanus and Hib responses are normal and CD4>400/μL, MMR should be given)
- If recurrent respiratory infection – refer to an immunologist to exclude underlying immunodeficiency
- Consider antibiotic prophylaxis if recurrent respiratory infection or evidence of poor specific antibody response to vaccine antigens
- Patients with recurrent or severe respiratory symptoms should be assessed by a respiratory paediatrician or physician.
- Regular monitoring for autoimmunity, particularly autoimmune cytopaenias and thyroid disease.

**Andy Gennery**

**Table 6.1 Characteristics of immunodeficiency**

| |
|---|
| **Severe T cell immunodeficiency (complete 22q11DS)**<br>very low or absent T cells (below the 5th percentile for age), with variable immunoglobulin production (rare, <1% of all cases). |
| **Mild or minimal T cell abnormalities (partial 22q11DS)**<br>low or normal T cell numbers, usually normal T cell proliferative responses, with variable minor immunoglobulin abnormalities, particularly low IgM levels in older children. |

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# 7. Craniofacial Manifestations

**Including the management of Communication Disorders, Cleft Palate, Velopharyngeal Incompetence (VPI) and Hearing Disorders**

## 7.1 Facial dysmorphism

The characteristic facial features of Velocardiofacial Syndrome (VCFS) are usually not evident at birth but develop in early childhood[1,2] [C]. They are pathognomonic but not diagnostic[3] [D].

The features are:

- Narrow palpebral apertures (the distance between upper and lower lid margins)
- Telecanthus (increased distance between the inner corner of the eyes)
- Wide/prominent nasal bridge and root
- Small mouth
- Round ears with deficient upper pole helix (rim of the ear)
- Prominent ears
- Long lower and mid face ('adenoidal' face)
- Hypodynamic facial features (impassive face) due to VII nerve weakness and/or hypocalcaemia
- 1% have craniosynostosis (premature fusion of the skull growth centres causing skull asymmetry).

Treatment is rarely indicated except for prominent ear correction if the child is concerned about them (and the surgery is funded by the local commissioners in England).

## 7.2 Cleft palate

### 7.2.1 Overview

Nine percent of patients with 22q11DS have an overt cleft palate and 5% will have a submucous cleft palate (SMCP) (i.e. 14% overall). A small number will also have a cleft lip and palate[4-6] [B][2;7-9] [C].

Perinatal presentation is common[1;2] [C] with the baby having problems with breast and/or bottle feeding. Nasal regurgitation of milk during feeding is the principal presentation, together with poor weight gain. If these symptoms are present, the perinatal examination of the palate must be performed by a senior paediatrician/ neonatologist who must look for, visualise with a torch and tongue depressor and record if there is:

- an overt cleft of the palate
- a bifid uvula
- a lucent zone in the midline of the palate (a grey line instead of the usual white midline). This is caused by the absence of the *levator veli palatini* in the midline so the shadow of the nasal cavity shows through the two layers of mucosa.

The examiner must feel, using a gloved little finger slid along the midline of the palate, for a notch in the posterior hard palate (instead of the usual bump of the posterior nasal spine). A common error is for the examiner to feel just behind the teeth and alveolus and not back to the hard palate/soft palate junction because this will miss all soft palate and submucous clefts.

Children with VCFS may have a weak gag reflex in addition and this should be noted. It may be a sign of possible poor velopharyngeal coordination.

If an overt cleft or an SMCP is detected the Regional Cleft Team must be called immediately. Cleft Specialist Nurses will provide assessment, feeding advice and equipment such as feeding bottles and breast pumps. Please do not try instituting a feeding regimen that is not recommended by the cleft team, and nasogastric (NG) feeding should be avoided if at all possible.

### 7.2.2 Cleft palate management

If a child with 22q11DS has an overt cleft palate they should have it repaired, and repair of a SMCP should be considered, particularly if the baby has a history of feeding problems. The technique and timing will be advised by the local cleft team, but should be completed by a year of age if at all possible to maximise speech outcomes. Cardiac and paediatric issues must take precedence, so surgery is only undertaken after the child is declared fit by the appropriate specialists. The paediatric anaesthetist will require a pre-operative echo and ECG. The child's calcium levels should

be checked pre-operatively. Antibiotics should be given peri-operatively according to local cleft and cardiac guidelines, as necessary. Post-operative feeding is often slower to return to normal in a child with 22q11DS and they may well stay an extra day in hospital as a result.

Follow up will be dictated by the regional cleft team protocol, and there are agreed standards set out by the Craniofacial Society of Great Britain and Ireland for the follow up for all children with cleft palate. In addition, children with 22q11DS should be seen for assessment in a specialist 22q11DS Clinic, where available, because these children may require a different skill mix.

### 7.2.3 Feeding

Few babies with an overt cleft will be able to breast feed because the cleft makes the nose and mouth into one cavity. The consequence of this is that the baby is unable to coordinate sucking, swallowing and breathing. In addition, the hypodynamic pharynx and other medical problems may make feeding problematic for children with 22q11DS. In the absence of an obvious cleft, referral to a Speech and Language Therapist with special expertise in paediatric swallowing problems may be required urgently to ensure that the child is safe to feed orally. If there is any doubt, a period of NG tube feeding may be required until the situation can be evaluated. It must be remembered that a child with 22q11DS and an obvious cleft (or SMCP) may ALSO have other problem with feeding and also need the help outlined above.

Notwithstanding, breastfeeding is important and many mothers will want to try. Mothers are to be encouraged to put the baby to the breast, but it should be explained that she should not necessarily expect nutritive feeding to be achieved in most instances. Any baby with 22q11DS who is establishing breastfeeding must be weighed regularly, according to local protocols, because there is no other way of monitoring how well the baby is feeding. If the baby can be heard feeding it suggests that air is being entrained together with milk. In this situation the baby will have a mixture of air and milk in the stomach, which makes them windier, and also gives the baby the sensation of having a full stomach. Feeding is often very slow because it is so inefficient and the baby becomes exhausted. The small volume of milk taken in means that, in a short time, the baby becomes hungry again and wakes. Rapidly the baby and the carers become exhausted.

When a midwife checks the feeding post-natally, often the baby will latch on and suck well but the whole feed must be watched, not just the first few minutes. The first few minutes of a feed do not make a meal!

Alternative feeding is often required and a soft bottle and an appropriate teat is best (UK National Standards – Craniofacial Society of Great Britain and Ireland). The regional cleft unit will advise the exact type of equipment appropriate for the baby and training will be given by specialist cleft nurses. All mothers should be encouraged to express and monitor the baby's weight carefully. Advice is available from all UK cleft teams. The Red Book is an invaluable communication aid for professionals, so the family must bring it to all appointments.

## 7.3 Hearing management

### 7.3.1 Overview

It is standard practice for every neonate in England to have their sensorineural hearing tested shortly after birth and children with a cleft palate are one of the groups known to be at risk of hearing loss. Sensorineural (SN) hearing loss occurs in 15% of children with 22q11DS and 75% will have Secretory Otitis Media (SOM)[10] [A][11;12] [C]. Although this figure seems very high, 60% of the 'normal' paediatric population of the South West of England will have SOM at some time (South of England unpublished audit figures). If the baby fails the neonatal screen the child will be referred to the paediatric audiology or ENT service, depending on local arrangements and brainstem testing may be required. If the early tests are failed, further testing will be performed at 8 months corrected age.

Patients with cleft palate develop SOM because the paired *levator veli palatini* (LVP) muscles in the soft palate have an abnormal origin from the Eustachian tube and may also have an abnormal mix of muscle fibre types. So, when the baby swallows, cries or

yawns, the nasopharyngeal portion of the Eustachian tube fails to open and equalise the pressure in the middle ear. If severe, SOM can lead to retraction of the tympanic membrane, even to the point of cholesteatoma formation, and to infection of the middle ear, culminating in chronic perforation of the ear.

### 7.3.2 Management of hearing problems

If SN hearing loss is present perinatally, the baby will be referred to the local ENT service and on for specialist advice.

If there is SOM, usually the primary management is "watchful waiting". Longitudinal studies by Mars et al. in Sri Lanka[13] [C], where no ENT intervention was available, have shown that the majority of ears with SOM will be dry by the age of 10[14] [C]. Grommet insertion at the time of palate repair has a low complication rate but occasionally results in multiple insertions, chronic discharge and mild high tone hearing loss as a result of the scars on the ear drum. It has not been shown to have a beneficial long-term effect on hearing, but the practice has not been subjected to study by randomised controlled trial. T tubes are known to have a higher risk of chronic perforation and discharge[15] [A][16] [C].

Common practice now is to retest any child who fails a hearing test, usually after three months, and reserve grommet insertion for those with severe conductive hearing loss on repeated testing or as part of the management of repeated bouts of infection. Hearing aids are used for moderate and intermittent hearing loss. Surgery should only be undertaken on the recommendation of the paediatric audiologist and ENT surgeon associated with the regional cleft team.

In any child with cleft palate or an SMCP the adenoids **MUST NOT BE REMOVED** without prior speech investigation because the child may be rendered hypernasal as a result of the soft palate no longer being able to close to the adenoidal pad[17;18] [B].

## 7.4 Surgical management of children with cleft palate

### 7.4.1 Management of Overt Cleft Palate (CP)

The Regional Cleft Unit will advise on cleft related feeding issues, the type and timing, of palate repair. In the United Kingdom, either a Langenbeck or No Flap technique is used to repair an overt CP in most Regional Cleft Units. A form of Intra Velar Veloplasty (IVVP) is universally used.

### 7.4.2 Management of Primary Sub-Mucous Cleft Palate (SMCP)

A primary submucous cleft palate SMCP does not necessarily need repair and if an infant has established breast-feeding it may be a good indicator of future palate function and 'watchful waiting' may be appropriate. If there is a significant history of feeding problems, a palate repair is likely to be recommended. If so, a primary Furlow or 'No Flap' repair, with an IVVP, is used for most SMCP repairs in the United Kingdom in this situation.

## 7.5 Follow up of children with cleft/non-cleft speech problems

Children with VPI of any cause should be seen at 2, 3, 5, 10 and 15 years of age as a minimum. The same applies to children with 22q11DS. A perceptual speech analysis and hearing test should be performed on each occasion and video fluoroscopy and nasendoscopy used when indicated to plan treatment for VPI and to assess its outcome (UK National Standards for Cleft Lip and Palate – Craniofacial Society of Great Britain and Ireland).

## 7.6 Speech, language and communication issues

### 7.6.1 General considerations

Difficulties with communication are extremely common in 22q11DS (it has been suggested to be as high as 90%) and every person with this condition is at risk from birth through to adulthood. The communication profile for this condition is both varied and complex and, as such, assessment and management must be tailored to the individual. The profile may be syndrome specific and it co-occurs with other features such as learning difficulties, recurrent otitis media and hearing loss, behavioural difficulties including Autistic

Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) and palatal/velopharyngeal anomalies.

### 7.6.2 Language development

In an infant with 22q11DS both expressive and receptive language may be slower to develop than normal. Reported features include:

- Quiet Baby - delayed, limited or absent babble[9] [B]
- Delayed vocabulary development[19] [C]
- Understanding of language shows a mild-moderate delay with expressive language more significantly affected[20] [C]
- Language impaired beyond cognitive skills[6] [C]
- Pre-school child shows particular deficits in expressive language[20;21] [C]
- Often a rapid increase in vocabulary and expressive language between the ages of 3 and 4 years[9] [B]
- Use of gesture may be a strength - in advance of verbal expressive language[4] [C].

### 7.6.3 Language assessments for young children:

Language assessment can be undertaken in this age group using:

- Preschool Language Scale, Fourth Edition (PLS-4UK)[22] which assesses young children's receptive and expressive language from birth to 6.11 years using UK norms
- Clinical Evaluation of Language Fundamentals - Preschool 2 UK[23] which measures a broad range of receptive and expressive language skills broken down into 7 norm-referenced subtests. It is used for the diagnosis and classification of language disorders in young children. Age range 3-6 years.

### 7.6.4 Language assessment in school aged children

In the school-aged child the language profile changes and the gap between receptive and expressive language is less marked[24] [B]. Specific language impairment has been found in up to 40% of school-aged children with 22q11DS[6;9] [B,C]. Specific areas of difficulty persist, most notably:

- Working memory (verbal memory): difficulty with dealing with more complex information especially involving long sentences, sequences of information, directions, stories etc.
- Reasoning/abstract thinking: difficulties in putting information together to draw conclusions/problem solve. Expressions are often understood literally e.g. 'Pull your socks up'. Subtle messages and implied meanings are missed, as are the meaning of jokes, sarcasm and irony
- Non-verbal understanding: difficulty in using signals such as facial expression, tone of voice, posture etc. to inform understanding which can result in social communication difficulties
- Difficulty with using and understanding concepts, vocabulary, syntax and with word finding[6] [C]
- Language used tends to be terse and concrete[4] [C] and lacking in grammatical complexity although few actual grammatical errors may be made[25] [C].

There may be areas of strength, in particular:

- Verbal rote memory/rote learning
- Concrete thinking
- Decoding
- Reading. However, ability in reading may mask reading comprehension issues. The child may be better at 'learning to read' than 'reading to learn'.

Referral to speech and language therapy services should be made early after diagnosis in order that early intervention programmes can be initiated[26] [C]. However, ongoing monitoring of language and communication skills is also imperative. In the early years the child may seem to cope with the relatively straight forward and concrete linguistic demands of schooling but may begin to fall behind their peers as these demands become more complex, requiring reasoning and abstraction skills which are beyond their capabilities. Language deficits may become more apparent during the middle school years as it at this time that language is used for learning and concepts are more abstract[23] [D]. Language deficits may become more apparent during these later school years and these can persist into adulthood. Highlighting specific difficulties and incorporating them within the child's

Individual Educational Programme (IEP) helps the school staff to be aware of the child's areas of difficulty.

### 7.6.5 Language assessments

- Clinical Evaluation of Language Fundamentals Fourth Edition UK (CELF 4 UK)[27] gives a Total language Score and Receptive and Expressive Language Scores looking at structure, content memory and working memory. Age range 5 years – 16 years 11 months
- Action Picture Test – Revised Edition[28] assesses levels of information content and grammatical usage from short sentence answers to specified questions. Age range 3-8 years
- The Bus story - A test of Narrative Speech[29] assesses age level of consecutive speech looking at information content, grammatical usage and sentence length whilst re-telling a story. Age range 3-8 years.

Many other language assessments are available and would be appropriate for use with this age group.

### 7.6.6 Social communication

Difficulties in the area of social communication are common and become more apparent in the later school years and adolescence. This may present as:

- difficulties in interpreting changes in tone, meaning and facial expressions
- difficulties understanding jokes, irony and sarcasm
- extremes in social interaction from over shyness to over familiarity[30] [C]
- reduced social initiation[30] [C]
- peer relationship difficulties.

### 7.6.7 Speech

Significant speech problems are associated with 22q11DS[9] [B]. In many cases these are associated with palatal anomalies including overt cleft palate, submucous cleft palate (classic or occult) and velopharyngeal dysfunction (where the soft palate is unable to make contact with the posterior pharyngeal wall appropriately during speech, resulting in hypernasality and/or increased nasal airflow). [See section on cleft palate for more information].

Speech disorders associated with 22q11DS have been shown to be more severe and more complex in nature than those who have a similar history of clefting and/or velopharyngeal dysfunction (VPD) for speech without the presence of 22q11DS[19;31] [B,C].

Dyspraxic features of speech are now more widely reported[32] [C] and can have a marked impact on the development of sounds and there may be a voice disorder due to VPI and/or vocal cord dysfunction[33;34] [D,C]. Although the speech may be similar to those with non-syndromic cleft palate or VPD, children with 22q11DS have been shown to have more impaired articulation skills, regardless of the presence of a cleft[31;35;36] [B,D,D]. There has, however, been limited research on causal factors and factors which may contribute to the increased severity of speech difficulty in 22q11 DS. Suggested causal factors include:

- hypodynamic velopharynx[31;37] [B,C]
- hypoplastic palatal muscle with unusual fatty tissue[38]
- a developmental deformity of the occipital bone and upper cervical spine (platybasia) resulting in an increased basal angle of the skull and an enlarged VP gap[7;39] [B,B]
- adenoid hypoplasia[40] [C]
- increased prevalence of upper airway asymmetry including asymmetrical palate closure and abnormal vocal cord size/motion[41] [C]
- neuroanatomical anomalies[42-44] [D,B,C] including laryngeal web
- neurological, including VIIth cranial nerve weakness and poor oromotor coordination, which can lead to drooling and problems eating lumpy foods.

A longitudinal study[19] [C] comparing the speech of 4 children with 22q11Ds with nonsyndromic children with a palatal cleft found:

- a smaller repertoire of consonant types
- a higher predominance of glottal stops
- a lower frequency of consonant use
- a higher rate of VPD

in the 22q11DS cohort and this seems to be a typical finding, but there is paucity of research using larger subject numbers.

Common features of speech where there is velopharyngeal dysfunction include:

- hypernasal resonance(nasal tone)
- missing oral consonants e.g. p, b, s, f, ch
- oral consonants weak/nasalised
- oral consonants replaced by nasals i.e. m, n
- nasal emission (air escaping down nose during speech)
- nasal turbulence (a friction sound in nose due to air escape)
- quiet voice/abnormal voice quality.

Where there is evidence of velopharyngeal dysfunction, the patient should be referred to the Regional Cleft Team who will assess the palate function and explore possible treatment options with the patient and family. Those options may involve speech therapy alone or perhaps surgery together with speech therapy. Investigation of palate function may need to be delayed if the patient's language development is significantly delayed, if they have poor attention skill or they are not able to cooperate.

Therapy involves direct teaching of new speech targets with frequent repetition and opportunities to practise new skills. The child will need tangible rewards to remain motivated. Therapy may need to be both intensive and prolonged to achieve success with support from both home and school.

Signing (e.g. Makaton) can be employed as a support to verbal communication. There is a debate as to whether signing delays speech acquisition or if it gives the child a mechanism for communication and reduces frustration. No comparison has been made between the different philosophies[53] [C].

#### 7.6.8 Speech assessment

Speech assessment is most usually undertaken using:

- GOS.SP.ASS[45]. This is a speech sample elicitation assessment for children with a cleft palate or velopharyngeal dysfunction which assesses airflow, resonance, intelligibility and cleft speech characteristics based on spontaneous speech and sentence repetition
- Diagnostic Evaluation of Articulation and Phonology (DEAP)[46] which detects and differentiates between articulation prob-lems, delayed phonology and consistent versus inconsistent phonological disorders using National UK norms.

Other tests of articulation and phonology are available.

Due to the complex, multifactorial nature of speech and communication difficulties in 22q11DS it is imperative that a referral is made for assessment at an early stage, but the need for ongoing monitoring and intervention is likely as the child gets older due to the changing communication profile. With increasing age, social communication difficulties may well come to the fore with consequent difficulties for the child in relating to peers along with emerging deficits in higher level language functioning. Often a Statement of Educational Need is required to allow schools to put in place the required resources and to enable the child to access the curriculum fully.

### 7.7 Management of cleft/non-cleft VPI

Management may be complicated, over and above issues associated with cleft palate by multiple factors in children with 22q11DS and no secondary management should be undertaken with out a full multi-disciplinary assessment of the patient (usually a child).

There is no consensus on the surgical procedure of choice for management of VPI, let alone in 22q11DS. Various procedures have been advocated for the patient with 22q11DS ranging from primary palate repair, secondary re-repair often combined with a posterior pharyngeal flaps and/or a sphincter pharyngoplasty.

Success rates are hard to assess as the series are universally small and either retrospective or uncontrolled cohort studies[54-59] [C]. None the less, it is agreed that surgery or prosthetic management will be required for VPI because it cannot be cured by Speech Therapy. The size of the residual gap between the velum and posterior pharyngeal wall, or basisphenoid, at maximal velar excursion tends to influence the surgeon as to what approach to take.

The recent trend in the United Kingdom has been for patients who have previously been treated for a cleft palate (overt or SMCP) to undergo a Furlow Re-

Repair or a Palate Re-Repair with IVVP. This approach is best suited to a small residual VP gap, but may still be beneficial in larger gaps because the increased range of palatal movement means that any subsequent pharyngeal procedure need not be as extensive. As yet, although clearly common sense, there is no literature to back the philosophy [D].

Techniques to change the pharynx are of 2 broad types:

- **Sphincter Pharyngoplasty**
  Hynes or Orticochoea pharyngoplasty (or modifications) are theoretically more suited for patients with coronal pattern of VP closure
- **Pharyngeal Flap**
  A posterior, superiorly or inferiorly, based flap is usually used in the United Kingdom and is theoretically more suited to patients with sphincteric or sagittal VP closure.

There is, as yet, no evidence that attempting to match the pattern of closure with the operation chosen to correct VPI is any better than using a single technique[7;39;60;61] [C]. It remains impossible to tailor the treatment accurately to fit the velopharyngeal gap and, even if closure is anatomically possible on suction testing at the end of a procedure, a functional deficit may persist due to intrinsic hypotonicity and incoordination.

Residual hypernasality and nasal escape is common in children with 22q11DS, but this is better than rendering a child with congenital heart disease over closed, exposing them to the risk of developing *cor pulmonale*.

### 7.8 Post-operative management after oropharyngeal surgery

Children with 22q11DS often remain in hospital for one to two days longer than non-syndromic children after pharyngeal or palatal surgery. They are often reluctant to swallow liquids and solids of any sort or consistency, including medication. Warning the family about this before surgery is important and explaining to the child the importance of drinking and taking the medication in reducing discomfort is essential. This behaviour seems to be unique to children with 22q11DS[48] [C]. It is known that children between 4 and 6 years may have psychological consequences of being in hospital such as wetting and night terrors and it is advisable, if possible, to avoid this time period for non-essential surgery in children with 22q11DS. Any psychological sequelae and loss of confidence or trust in the cleft team may have an additional adverse impact on the child's ability to work with the speech and language therapist after surgery.

It is better to have mild VPI than to have over closure which can lead to snoring, habitual mouth breathing, difficulties with nose blowing and with eating and swallowing and, potentially, sleep apnoea which can be severe enough to produce right heart strain leading to *cor pulmonale*, which must be avoided if the child has had cardiac surgery. Some children develop mixed nasal resonance where the gap is too small for normal nasal resonance but where the pharynx is too hypodynamic to close the residual gap.

### 7.9 Prosthetic management of VPI

Some children with 22q11DS will have a severely hypodynamic pharynx and palate, and they may also have medially displaced carotids, residual cardiac problems or other medical or psychological problems that effectively preclude surgery for VPI. In this group, prosthetic management of VPI may be appropriate on risk/benefit analysis. The benefit of an appliance is that it can be removed at night and for eating, so avoiding lifelong hyponasality from an over closed pharynx. Unfortunately, prosthetic management of VPI in children in the deciduous dentition is problematic due to difficulty in retention and, in some children with 22q11DS, it may be especially difficult due to poor compliance. To wait for the secondary dentition to hold an appliance in place means that a child will have abnormal speech during their formative years.

Unfortunately, for these reasons, obturation may not be very successful in the management of children with 22q11DS and VPI. There is little published on the use of prostheses in these patients.

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# 8. General paediatric problems

## 8.1 Breathing problems

Causes include laryngomalacia, tracheomalacia (2%), or laryngeal web (1%), usually symptomatic from birth. Later onset occurs in hypocalcaemia, and acid spillage from gastro-oesophageal reflux disease (GORD). Bronchomalacia and vascular rings may present as wheeze or breathlessness.

Aspiration presents with cough or choking during feeds; silent aspiration may present as recurrent infections or wheeze. A dysphagia assessment, sometimes with videofluoroscopy (VF), is required. Frank aspiration on VF with all thicknesses mandates nasogastric (NG) tube feeding; if thin fluids only, add thickeners in milk, and weaning foods.

## 8.2 Feeding

Feeding difficulties are common up to 3 years of age, may be multifactorial, including dysphagia due to inco-ordinate muscles, submucous cleft palate, or secondary to cardiac and respiratory related breathlessness. Severe early weight loss often occurs[1] [D]. GORD is frequently associated. Periodic, forceful vomiting suggests malrotation.

Management includes nutrition and feeding support, sometimes completion of feeds by NG, and occasionally gastrostomy.

## 8.3 Constipation

Muscle hypotonia and dysynergy of the gut predispose to constipation. Exclude hypothyroidism, consider Hirschsprung's disease, anteriorly placed anus, and anal stenosis. Encourage adequate food intake in infancy and, at older ages, exercise, fluid and fibre. Consider regular laxatives.

## 8.4 Growth

Undernutrition in infancy is followed by catch up growth in childhood, a risk of overweight in adolescence and below average adult height.. Consider hypothyroidism, growth hormone deficiency, coeliac disease, gut malrotations, and Hirschsprung's disease as their prevalence is increased.

## 8.5 Musculoskeletal abnormalities

Limb abnormalities include supernumerary digits, talipes equinovarus and Sprengel's shoulder. Scoliosis (3%) occurs in infancy from hemivertebrae and in adolescence from hypotonia. Increased prevalence of patella dislocation occurs in adolescence. Ligamentous laxity, flat foot, and tight heel cords are common. Whether these are causally linked with commonly occurring and mobility limiting leg pains is uncertain.

## 8.6 Neurological aspects

Non-progressive dyspraxia and clumsiness occurs in 94%[2] [D]. Differentiate hypocalcaemia from epileptic seizures (6%). Polymicrogyria, seen on MRI, occur with increased frequency in the latter, especially when cerebral palsy is present. Cervical vertebral malformations are common[3], but neurological sequelae rare. Evaluate when symptomatic cord compression or nerve entrapment occurs.

## 8.7 Sleep disturbance

Restless legs, nocturnal leg pains, and 'growing pains' may disturb sleep. Treatment is symptomatic. Obstructive sleep apnoea may occur post pharyngoplasty, requiring early ENT assessment.

## 8.8 Genitourinary abnormalities

Refer persistent undescended testes (6%) beyond one year and hypospadias (8%). Generally, renal anomalies (36%) are asymptomatic[4] [D].

## 8.9 Ears and hearing

Hearing impairment due to recurrent serous and infective otitis media is common; sensorineural impairment is usually mild to moderate, unilateral, affecting 15%[5] [D].

## 8.10 Eyes

Conjunctivitis is common. Moderate hypermetropia is the commonest refractive error[6] [D]. Corrective glasses may improve spatial awareness and reading.

## 8.11 Autoimmune

Differentiate juvenile idiopathic arthritis from commoner 'limb pains'. Raynaud's phenomenon, idiopathic thrombocytopaenia, Evan's haemolytic anaemia, autoimmune neutropaenia, aplastic anaemia, Graves' disease and hypothyroidism, vitiligo, and coeliac disease have increased prevalence in 22q11DS.

## 8.12 Teeth and gums

**Alex Habel**

Tooth enamel defects and caries are increased, mandating good dental care[7] [D].

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# 9. Psychiatric illness

## 9.1 Introduction

### 9.1.1 General principles

Psychiatric symptoms are common in the general population, especially in individuals with intellectual disability. Emotional and behavioural disturbances are often transient or mild, but can also be persistent, severe and disruptive to day-to-day life.

Research studies and clinical experience consistently show that individuals with 22q11DS carry an elevated susceptibility to psychiatric symptoms, at every age investigated [B] (reviewed by Baker and Vorstman 2012[1]).

This aspect of 22q11DS can cause a great deal of worry for individuals and families[2]. A balance needs to be struck between awareness of vulnerability and early access to support if and when problems arise, without awareness of risk itself becoming a source of stress and anxiety.

With timely recognition of problems and appropriate interventions (which may take several forms including alterations to environment, psychological support, as well as medication in some situations), symptoms can usually be managed so that they are less distressing and do not limit an individual's activities, achievements and relationships.

### 9.1.2 Symptoms and diagnoses

Emotional and behavioural symptoms that may be experienced by individuals with 22q11DS are diverse, and affect each individual in a unique way. 'Diagnoses' are simply patterns of symptoms which indicate the specific support a person might need at a particular time.

Sometimes an individual experiences symptoms from a number of different diagnostic categories at the same time (known as co-morbidity). At other times an individual may have just one or two symptoms, not fitting a particular diagnostic pattern, but still causing disruption to a person's day-to-day life and therefore benefiting from support. These complexities can be confusing and frustrating.

The types of symptoms that can occur change at different ages, because of the normal process of emotional and behavioural development [B]. This means that different diagnoses may be considered over time within an individual's life, and are rarely present in the same form continuously. The diagnoses that may be considered for an individual with 22q11DS are not different from individuals without 22q11DS at the same age[3].

Research studies that have followed up a relatively large number of children and teenagers with 22q11DS over time have found that individuals with more symptoms at a younger age tend to continue to have more symptoms as they get older[4]. But this is not always the case - sometimes problems can be quite severe during childhood but then improve; for other individuals, major symptoms can appear later in adolescence or adulthood 'out of the blue'. Importantly, there is currently no evidence that any specific symptom or group of symptoms is strongly predictive of later problems [C].

### 9.1.3 Interactions between psychiatric symptoms and other aspects of 22q11DS

There is no evidence at present that psychiatric symptoms are more likely to affect an individual with 22q11DS who has any particular physical features of the syndrome[5]. Nor is psychiatric illness more common among individuals with either severe or milder intellectual disability [C].

Clinical experience indicates that consideration of physical factors is important when assessing psychiatric symptoms in 22q11DS. Treating hypocalcaemia and monitoring endocrine function may have an impact, as will assessment of diet and any restrictions to physical activity. On-going monitoring of medical factors is important, although is not a substitute for considering interventions specifically targeted to help manage psychiatric symptoms [D].

### 9.1.4 Pathways to referral

Different approaches are advocated for investigating psychiatric symptoms over time in a child or adult with 22q11DS, and there is no evidence at present strongly to support any one model. One approach is to offer regular surveillance at different ages for all patients. This could take the form of detailed specialist assessment by a psychiatrist or psychologist. Another more practical form of surveillance is for any medical individual conducting a general health review for an individual with 22q11DS to remember to ask some basic questions about emotional, behavioural and social well-being. This enquiry should be considered an important

part of multi-disciplinary support for individuals with 22q11DS, whether or not taking place in a dedicated clinic setting [D].

What features should trigger referral for mental health assessment for a child or adult with 22q11DS? In general terms, if an individual or family is concerned about any distressing or disruptive symptom, they should feel able to discuss it openly and request support. Sometimes a simple chat with a GP or paediatrician may help to put an emotional symptom into perspective, and consider whether it is a problem or within the range of fluctuating psychological function that is part of normal life. If a non-specialist professional is uncertain whether or not to refer, they should discuss the situation with a mental health professional before making a decision [D].

A key trigger for referral is deterioration in function, for example withdrawal from normal activities, seeming unhappy, afraid or disorientated, or acting in a way that is out of character for the individual. People experiencing psychiatric symptoms often find it difficult to explain what they are feeling, and this may be especially true in 22q11DS.

Clinical experience has shown that individuals with 22q11DS sometimes show marked deteriorations during times of change in their lives, and may require more support than other individuals in adjusting to change[6]. For other individuals, however, deteriorations occur without any obvious changing factor in the person's life.

Whether or not there is a clear triggering factor, seeking advice and support at an early stage is preferable. Evidence from the general population shows that problems treated earlier are more likely to respond effectively to intervention [A].

### 9.1.5 Assessment

Methods of assessment used by psychiatrists and psychologists vary, from detailed discussion of symptoms (clinical history-taking), to structured interviews and questionnaires, to observation in different settings. There is no essential part of this process and no specific methods recommended for 22q11DS, other than appropriate methods for age, development and communication abilities.

It is important to ask children, teenagers and adults with 22q11DS about their own symptoms (in a sensitive manner appropriate to their age and understanding), as well as seeking information from parents, carers and teachers [D].

Repeated assessments across time by the same professional are often helpful to determine how best to support an individual and to monitor responses to interventions [D].

### 9.1.6 Interventions

Treatment of psychiatric symptoms in 22q11DS always requires an individually-tailored approach.

There is no evidence that any particular treatments (medications or psychological approaches) are more effective or more dangerous for 22q11DS than for other individuals [D].

However, potential side-effects must be very carefully considered, and caution exercised in light of the individual's medical history and known features of the syndrome [D].

Consideration should be given to the on-going vulnerability of individuals with 22q11DS to psychiatric symptoms, which is different from individuals without 22q11DS, and therefore may require longer term follow-up and on-going support to prevent symptoms returning [D].

A health professional considering treatments for psychiatric disorders in this syndrome who does not have previous experience of 22q11DS should consider seeking advice from an expert who does have such experience, in order to maximise the benefit and reduce risks [D]. However, it is probably more important to have easily-accessible local support (with specialist advice) than for treatment to be managed at a distance.

## 9.2 Specific psychiatric disorders

The 12-month prevalence of psychiatric disorders in the general population is around 26%[7]. For 22q11DS, this percentage is higher, ranging from 60%[8;9] to 93%[10]. When comparing the prevalence of psychiatric disorders in the population of people with 22q11DS with the prevalence in the group of people with general intellectual disabilities (ID), more individuals with 22q11DS had a diagnosis of attention-deficit/hyperactivity disorder (ADHD), anxiety disorder, mood disorder[11] and psychotic disorder[12]. In this section we describe some of the psychiatric diagnoses commonly experienced by individuals with 22q11DS in more detail, organised according to the age at which each diagnosis is commonly observed.

### 9.2.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

#### 9.2.1.1 Prevalence

The prevalence of ADHD is 5.29% in the general population[13]. However, in people with 22q11DS ADHD appears to range between 30% and 46%[8;14;15]. If you look at the different types of ADHD, the inattentive type seems to be more prevalent in people with 22q11DS[8;15]; no gender differences were found[16].

#### 9.2.1.2 Diagnosis

ADHD is described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as a pattern of inattention and/or hyperactivity-impulsivity that is persistent for at least six months. Compared to other people with the same level of development, this pattern must be displayed more frequently and be more severe. Impairment because of these symptoms must be seen in at least two settings and it must cause interference on social, occupational or academic functioning. Besides that, the disturbance should occur not only during a period of pervasive developmental disorder, schizophrenia or another psychotic disorder but should also be more likely to be caused by another psychiatric disorder. Some of the impairment causing symptoms must have been present before the age of seven years. There are three subtypes of ADHD:

- the combined subtype, with symptoms of hyperactivity-impulsivity and inattention
- the inattentive type, with predominantly symptoms of inattention
- the hyperactive-impulsive type with predominantly symptoms of hyperactivity-impulsivity.

A questionnaire that can be used for the assessment is the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL)[17].

#### 9.2.1.3 Symptoms

Antshel et al.[16] found that inattentive symptoms were more common in a group of people with 22q11DS and ADHD compared to a group of people with idiopathic ADHD. When looking at individual symptoms, children with 22q11DS and ADHD were more likely to exhibit the following symptoms:

- fail to give close attention to details and make careless mistakes in schoolwork
- not seem to listen when spoken to directly
- not follow through on instructions and fail to finish schoolwork or chores
- avoid, dislike, or are reluctant to engage in tasks that require sustained mental effort.

They also found that children with 22q11DS and ADHD had significantly higher scores on the Child Behaviour Checklist scales of somatisation, social problems, thought problems and internalising problems compared to children with idiopathic ADHD.

#### 9.2.1.4 Treatment

Pearson et al.[18] found that methylphenidate improved both behavioural and cognitive performance in children with ID and ADHD, but this was contra-indicated in children with 22q11DS because it might not be effective or would aggravate psychotic illness. However, Gothelf et al.[19] performed a pilot study in which they administered methylphenidate 0.3 mg/kg once daily to participants with 22q11DS and ADHD and found that the low dose was generally effective and well tolerated. Murphy[20] also advises to use the standard treatment protocols for ADHD in people with 22q11DS.

### 9.2.2 Autism Spectrum Disorders (ASD)

#### 9.2.2.1 Prevalence

In the general population prevalence rates are 0.13% for autism, 0.03% for Asperger, and .002% for childhood disintegrative disorder[21]. In people with 22q11DS, reported prevalence rates have ranged from 14%[22] to 50%[23]. The social communication difficulties experienced by individuals with 22q11DS may differ in some respects from individuals with autism in the general population, and research is ongoing to understand this aspect of the syndrome in more detail.

#### 9.2.2.2 Diagnosis

Autism spectrum disorders are characterised by a triad of impairment in social interaction and in communication and a restricted repetitive and stereotyped pattern of behaviour, interests and activities. There is an impairment in functioning in either social interactions or language (the way it is used in social communication) or symbolic of fantasy play before the age of three years. These symptoms should not be caused by Rett's disorder or childhood development disorder. There are five disorders within the autism spectrum:

- autistic disorder
- Asperger disorder
- disintegrative disorder

- pervasive developmental disorder not otherwise specified
- Rett disorder[24].

The Autism Diagnostic Interview - Revised is one of the questionnaires that can be used to make a diagnosis[25].

#### 9.2.2.3 Symptoms

Symptoms mentioned in the DMS-IV are:

- impairment in using non-verbal behaviour
- not succeeding in making relationships with people of the same intellectual level
- lack of sharing pleasures and activities with others
- lack of social or emotional reciprocity
- delay or lack in the development of verbal language
- impairment in the ability to start or sustain a conversation
- stereotypical and repetitive use of language
- use of idiosyncratic language
- lack of varied, spontaneous fantasy play or social imitative play
- strong preoccupation with one of more stereotyped patterns of interest
- adherence to specific non-functional routines or rituals
- stereotyped and repetitive motor mannerisms
- preoccupation with parts of objects.

Vorstman et al.[23] suggested that the symptoms of ASD in people with 22q11DS could in fact be prodromal features of psychosis, but the relationship between social communication impairments during childhood and later psychiatric difficulties remains unclear at present.

#### 9.2.2.4 Treatment

Many therapies have been developed to improve the symptoms of ASD, for example social-skills training to improve social skills, communication intervention to improve communication and medication to address co-morbid disorders such as ADD and anxiety[26]. The specific pattern of social strengths and difficulties varies for each child with 22q11DS, and a supportive approach that builds social confidence is encouraged.

### 9.2.3 Generalised Anxiety Disorder (GAD)

#### 9.2.3.1 Prevalence

In the general population the twelve month prevalence for GAD is 3.1%[7]. In people with 22q11DS, prevalence rates of 11% to 29% have been found[3;14]. Anxieties may be present at any age, and are often a persistent feature during late childhood and adolescence.

#### 9.2.3.2 Diagnosis and Symptoms

People with GAD suffer from excessive anxiety and worries about a number of activities which they find difficult to control. These worries and feelings of anxiety occur more than half the time during a period of at least six months. In adults the worries and anxiety cause at least three of the following symptoms (and in children one):

- a feeling of restlessness or of feeling keyed up or on edge
- being easily fatigued
- difficulties concentrating or mind going blank
- irritability
- muscle tension
- sleep disturbance.

These worries should not be caused by another mental disorder, like another anxiety disorder or post-traumatic stress disorder, or by substance abuse or a general medical condition. Because of the worries, anxiety and physical symptoms, there is a clinically significant distress or impairment in important areas of functioning, such as social or occupational functioning. The disturbance does not only occur during a mood disorder, psychotic disorder or pervasive developmental disorder. For assessing whether someone fulfils the criteria of the DSM-IV for generalised anxiety disorder, one can, for example, use the Mood and Anxiety Semi-Structured Interview (MASS)[27].

#### 9.2.3.3 Treatment

The International Consensus Group on Depression and Anxiety[28] wrote a consensus statement on generalised anxiety disorder. With regard to treatment they recommend cognitive behavioural therapy as the preferred form of psychotherapy. When GAD is comorbid with a depression, medication is increasingly indicated. SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) or a nonsedating tricyclic antidepressant (TCA) are recommended as the first-line treatment for GAD. Specialist assessment prior to a trial of medication is warranted.

### 9.2.4 Specific phobia

#### 9.2.4.1 Prevalence

In the general population, Kessler et al.[7] found a 12-month prevalence of specific phobia of 8.7%. People with 22q11DS have a prevalence of specific phobia ranging from 23% to 61%[3;8;10;14].

#### 9.2.4.2 Diagnosis and symptoms

A specific phobia is described in the DSM-IV as a marked and persistent fear towards a thing or event. The fear is not reasonable or the fear is greater than may be expected. It is cued by either the presence or the anticipation of this thing or event. And when there is exposure to the stimulus, the person reacts with an immediate response of anxiety. In adults, people with a specific phobia acknowledge that the fear is excessive or not reasonable; children do not recognise this. People try to avoid the stimulus or they endure it with distress or anxiety. The person's normal routine, occupational or academic functioning, or social activities or relationships are disturbed by the phobia, or the person is distressed about having it. When the person is younger than 18, the phobia must be present for at least six months. To assess specific phobias, the Mood and Anxiety Semi-Structured (MASS) interview can be used, which has been tested and approved for people with Intellectual Disabilities (ID)[27]. There a five types of phobias:

- the animal type
- the natural environment type
- the blood-injection-injury type
- the situational type
- the 'other' type.

Antshel et al.[8] found most children with 22q11DS who had a specific phobia had fear of the dark, fears of the natural environment type (fear of lightning/thunder) and the animal type.

#### 9.2.4.3 Treatment

Davis et al.[29] reviewed anxiety disorders in people with ID. With regard to the treatment, they concluded that more research is needed. For now, there is some evidence that the antidepressants, buspirone and risperidone can be used. Again, be aware of the side effects, especially when using them in combination with antidepressants, since there are cases described in which they induced psychosis or mania[30]. Common anxiety interventions modified for people with ID appear to be useful for psychosocial intervention, for example graded exposure and exposure and response prevention[29].

### 9.2.5 Major Depression

#### 9.2.5.1 Prevalence

Kessler et al.[7] found a twelve month prevalence of major depression in 6.7% in the general population. In the 22q11DS population, prevalence rates of 6% to 20% are found for depression[3;9]. These average rates mask a specific peak in depression during the teenage years, and the larger number of individuals with 22q11DS who may have symptoms of depression not meeting standard diagnostic criteria, which can occur in isolation or in parallel with symptoms of another psychiatric diagnosis.

#### 9.2.5.2 Diagnosis and symptoms

A depression is a period of at least two weeks in which a person experiences at least five of the following symptoms:

- depressed mood
- loss of interest or pleasure
- weight loss or weight gain
- insomnia or hypersomnia
- psychomotor retardation or agitation
- fatigue or loss of energy
- feelings of worthlessness or guilt
- diminished ability to think or concentrate or indecisiveness
- recurrent thoughts of death or suicidal ideas.

Of these symptoms, either the first or the second has to be present. There is a change in functioning compared to the period before these symptoms started. They cause significant distress or impairment in important areas of functioning, such as social or occupational areas. The symptoms should not be the consequence of a medical disorder or substance misuse or bereavement. In children and adolescents their mood can be irritable instead of depressed and children might fail to make weight gains. To assess whether some patients fulfil the criteria of the DMS-IV for major depression an instrument like the Mood and Anxiety Semi-Structured Interview (MASS)[27] can be used.

#### 9.2.5.3 Treatment

In the general population the international consensus statement on major depressive disorder[31] advises treatment with either antidepressants or psychotherapy or a combination of the two, depending on the severity of the depression. As for the antidepressants, the international consensus

statement on major depressive disorder advises to use the newer agents, like serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or norepinephrine-dopamine-reuptake inhibitors (NDRIs), because of their better tolerability and safety profiles.

### 9.2.6 Schizophrenia

#### 9.2.6.1 Prevalence

The median lifetime prevalence of schizophrenia in the general population is 0.4%[32]. One study looking at a population of fifty adults with 22q11DS found a point-prevalence figure of 24%[33], and this finding has been consistently replicated in several further studies around the world. It is important to recognise that schizophrenia is a very broad diagnosis, including many different symptoms which can affect each individual in a different way, with symptoms that can change over time and that can be effectively managed with specialist support.

#### 9.2.6.2 Diagnosis

Schizophrenia is described by the DSM-IV as a mental disorder in which a person experiences two of the following symptoms for one month during a significant part of the time:

- delusions
- hallucinations
- disorganised speech
- grossly disorganised or catatonic behaviour
- negative symptoms like apathy or social withdrawal.

The level of social or occupational functioning or functioning on other major areas are below the level at which the person performed before the symptoms started. They must exist for at least six months and schizoaffective disorder, mood disorder, medical conditions and substance use must be ruled out as a cause of the symptoms. To assess whether a person qualifies for the diagnosis the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL)[17] can be used for children and the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID) for adults[34].

#### 9.2.6.3 Symptoms

One study found that people with 22q11DS and schizophrenia had fewer negative symptoms and a later onset of schizophrenia than people without 22q11DS[33]. Several authors suggested that many people with 22q11DS experience psychotic symptoms[11;23] and that there may be a continuum of psychotic disorders in people with 22q11DS. Bassett et al.[35] compared two groups of people with schizophrenia: one group with 22q11DS and one group without 22q11DS. The group of people with 22q11DS showed more poor impulse control, uncooperativeness and hostility.

Risk factors for developing a psychotic disorder in 22q11DS remain a topic of research. Some authors have found that individuals are more likely to develop schizophrenia if they have relatively lower verbal IQ scores[3;12,23] or experience psychotic symptoms earlier in life. However other studies, including a longitudinal study of repeatedly assessing the same children at several timepoints, highlights that anxiety, and depression may be more strongly associated with later development of schizophrenia.

#### 9.2.6.4 Treatment

In the general population, the symptoms of schizophrenia are often treated with anti-psychotic medications[36]. Research into specific treatment of schizophrenia in people with 22q11DS is sparse. Handen and Gilchrist[37] concluded that risperidone has the greatest research in safety and efficacy in children and adolescents with ID. De Leon et al.[38] have written a guideline for the use of new generation antipsychotics (excluding clozapine) for adults with ID. They concluded that there is little research on their use in people with ID, but they do give guidelines for the use of aripiprazole, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone in people with ID. Specialist advice is warranted.

### 9.2.7 Obsessive Compulsive Disorder (OCD)

#### 9.2.7.1 Prevalence

Twelve month prevalence rates in the general population are approximately 1%[7]. In people with 22q11DS this prevalence rate was measured at 4%[8], 16 %[3] and 33%[10].

#### 9.2.7.2 Diagnosis

Obsessive compulsive disorder is described in the DSM-IV criteria as a disorder in which a person has either compulsions or obsessions. These obsessions or compulsions either take up a least one hour a day, or cause clinically important suffering or interfere with the daily routine and occupational or social functioning or relationships. The adult who has these obsessions or compulsions recognises that they are not reasonable or that they are excessive. The obsessions and compulsions should not be

related to another mental disorder, medical disorder or substance use. There are many questionnaires developed to assess whether people fulfil the criteria for, amongst other disorders, obsessive compulsive disorder. One example of a semi-stuctured interview useful for people with ID is the Mood and Anxiety Semi-Structured Interview (MASS)[27].

#### 9.2.7.3 Symptoms

Symptoms of OCD in people with 22q11DS include contamination, aggressive obsessions, worries about somatic problems, hoarding, asking repetitive questions and cleaning[10].

#### 9.2.7.4 Treatment

In the general population OCD is often treated with either medication (SSRIs) or with cognitive behavioural therapy[39;40]. One study looking at OCD in people with 22q11DS found a mean rate of improvement in 35% of the cases when treated with fluoxetine (30-60 mg/day)[10]. Only one patient reported a side effect: transient abdominal discomfort.

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# 10. Learning and education

## 10.1 Understanding the impact of 22q11DS on learning and education

There is a wide range of abilities in the 22q11DS population and it is essential that each child is assessed individually. Whilst many children benefit from being placed in mainstream school, the vast majority will require educational support at some point. There is also a significant number who will require a statement of educational need (SEN) and some who will benefit from a special school environment.

Most children do tend to have difficulties in similar areas but it is important to remember that 22q11DS is a syndrome and that there remains a significant variability in the presentation and severity of symptoms. The information gathered should be used to understand a child's difficulties and not to generalise about their behaviour or educational achievement. Formal assessment through the administration of selective tests designed to tap specific areas of cognition is therefore important to identify strengths and weaknesses and understand the complexity of their learning profile. Early intervention is also essential to ensure children reach their academic potential.

## 10.2 Style of learning and social skills

Kok and Solmon[1] [C] found that children with 22q11DS tend to have an orderly, analytical learning style, preferring logical explanations and specific instructions rather than an imaginative approach. Children also prefer focussing on one thing at a time and seem to respond well to interactive computer based programmes. Early on in school, children tend to be non-assertive and compliant. They may struggle to ask for help and tend to await instructions. It is common, therefore, for these children not to get identified until secondary school, suggesting that they may have already spent some time struggling to access the curriculum. Frustration and previous failure in learning can cause a loss of confidence and low self esteem which in turn can affect motivation. Problems in social communication are often noted in these children. It is common for young children to be described as shy or over friendly, with some exhibiting symptoms of autism[2] [C]. From adolescence, problems relating to peers may become more evident and young people often experience difficulties in interpreting humour, abstract language and subtle nonverbal communication[3] [C].

## 10.3 Behaviour

There does not seem to be one single pattern of behaviour with children and young people with 22q11DS. It is important that children with the condition are understood as individuals with their own unique personality and their own life experiences.

Research has shown that some children with the condition tend to be quieter and more sensitive, possibly due to difficulties with speech early on and difficulties communicating in social situations. Others, however, can be more strong willed, independent and impulsive. For some children and young people, these types of behaviours can become more marked throughout childhood and adolescence and put them at increased risk of mental health problems later in life[4] [C]. However, there is a significant number of children and young people who do not develop these difficulties.

Research has also shown that children are generally more at ease in familiar situations and with people they know well[5] [D]. They have no problems expressing a wide range of emotions although they may not always show all of their facial emotions because of low facial muscle tone.

## 10.4 Cognitive abilities

### 10.4.1 Mathematics

Mathematics is typically the first area in which children's difficulties become apparent. This is due to children's difficulties with visuo-spatial tasks, deficits in working memory and impaired numerical processing functions required for most mathematical tasks[6] [C]. This is called *Spatial Acalculia* and is characterised by deficits in the spatial representation of numerical information. Common problems have been described in terms of alignment errors in column arithmetic, number omission, misreading arithmetic operation signs and difficulties with place values and decimals[7] [D]. Research in this area has made the link between these mathematical difficulties and unusual cognitive processing in the spatiotemporal domain. Basic abilities required to carry out simple addition and subtraction are dependent upon these underlying cognitive processes.

De Smedt et al.[8] [C] found that children aged 6 to 12 years with 22q11DS could read numbers accurately and could retrieve number facts, but had difficulty with understanding number magnitude, identifying and ignoring irrelevant information in story problems, and accurately multiplying with more than single-digit numbers.

These weaknesses in maths seem to be relevant to wider issues and difficulties in the areas of abstract reasoning, converting language into mathematical expressions, telling time, using money and problem solving[1] [C].

### 10.4.2 Memory

Memory can be both a strength and a weakness for children and young people with 22q11DS[6] [C].

Rote verbal memory, which is the ability to repeat back after a delay a list of verbally presented items, is typically a strength for those with 22q11DS (e.g.[9]) [C].

Complex memory tasks can present more difficulties. Research has shown that children with 22q11DS struggle with recalling verbal information contained in long sequences like directions, sentences or stories. They also struggle to remember complex visual spatial forms (e.g. location of dots on a grid). In contrast, they have an ability to learn and retain verbal information that has been taught to them though experience and, as such, they can, for example, offer definitions of words and remember general facts with no difficulty [10] [C].

Another area of weakness is working memory[11] [C]. This is the ability simultaneously to store and process information. This in turn can impact on the ability successfully to complete everyday tasks, as well as on general problem solving as children are unable to integrate information and assemble it into a meaningful structure.

### 10.4.3 Executive function

Executive functions are a set of high level cognitive abilities that are responsible for controlling and regulating emotional and behavioural functions. They are necessary for goal directed behaviour, encompassing the ability to initiate and stop actions, to monitor and change behaviour as needed and to plan future behaviour when faced with novel situations and tasks. These cognitive abilities enable us to anticipate outcomes and adapt to change.

As children develop into adolescents, they become more dependent on executive functions to help them develop independence and the ability to organise themselves with less adult support. Research has shown[12] [C] that for children and young people with 22q11DS their executive functions are typically less well developed than those of their peers. They often have difficulties problem-solving and applying information that they have learned in new situations. In some cases, children remain concrete in their thinking as they grow older and may find it difficult to think in more abstract ways about ideas and concepts.

## 10.5 Motor skills

Some children with 22q11DS have low muscle tone. This can have an impact on gross and fine motor skills, especially in tasks that require quick movement or reactions[6] [C]. Children have been noted to have difficulties performing tasks that require dexterity and careful control of movements such as holding a pencil or handling scissors. Problems in this area can affect the ability of children to perform many tasks in the classroom with speed and accuracy, especially writing[13] [C].

## 10.6 Language

Children with 22q11DS are often slow to develop language and complex grammar. In some cases, they use a limited range of words and remain concrete in their use of speech. They tend to have better verbal than nonverbal skills with good expressive language, especially if they have had speech therapy and successful surgical intervention to improve the palate function. Many researchers have found these expressive language skills to be stronger than their receptive language skills[14] [C], which often require more complex and abstract thinking. With good expressive skills, these receptive skills can easily be masked in the classroom and it is common for teachers to not recognise the need for language intervention[6] [C].

## 10.7 Reading, writing and spelling

Reading and spelling has been noted as a relative strength for children with 22q11DS. Many children do well early in their school life when they are learning to read. However, it is common for them to struggle more when they are expected to learn from what they read, showing problems with understanding, recalling facts, picking out relevant details and drawing conclusions. This is thought to be due to the shift from learning skills that are basic and concrete to mastering more abstract, integrated concepts[6] [C].

In addition, they can find it very difficult to copy down text, as this requires coordination and the ability to hold the information in mind in the short-term and thus the complex use of motor skills, memory and language functions.

## 10.8 Intelligence

Research into the intelligence of children with 22q11DS has suggested that their general IQ scores tend to be below average for their particular age group. However, these children tend to demonstrate a striking profile of peaks and troughs with strengths on verbal tasks and impairment on performance–based tasks. This profile is indicative of a non-verbal learning disorder[14] [C] and seems to be true for most, though not all children[15] [C].

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# 11. Transition to adult care

Generally, young people undergo transition to adult care between the ages of 16-19 years depending on a combination of the medical issues involved, psychosocial maturity of the individual and local opportunities for ongoing MDT service provision. Whilst at the moment there are no consensus guidelines for the standards of care for children transitioning from paediatric to adult services, or indeed for the care of young adults suffering chronic diseases from childhood, it is increasingly recognised that this patient cohort is particularly vulnerable and both the Royal College of Paediatrics and Child Health (RCPCH) and the Royal College of Physicians (RCP) are involved in the development of Quality Standards to support the commissioning of services for young people with conditions such as 22q11DS to continue to receive expert MDT care through early adult life.

As part of preparing for transition, some generic principles should be followed. Transition is a process rather than a single point in time event and, whilst adolescence is defined as young people aged 10-19 years, the transition from adolescence to adulthood may continue until the age of about 25 years. As such, young adults with chronic diseases of childhood represent a particularly vulnerable group. A comprehensive understanding of the physical, psychosocial and educational aspects of the patient's condition and a detailed evaluation of the patients clinical care needs are therefore required to determine the most appropriate mechanism of transition and to ensure that transition is successful.

Transition is often a time of considerable anxiety for the family and requires preparation both for the patient, their families and the medical teams involved in their care. Children who have been diagnosed with 22q11DS may be looked after by a single paediatrician within one of a number of specialties as outlined above or, due to the complexity of their syndrome, may be receiving multidisciplinary care at the time of transition from paediatric to adult services. When preparing for transition, the complexity of the care package requirement should be taken into account by all teams involved in the care of the patient, and the patient and their family should be involved in evaluating the best clinical care delivery package to ensure continued attendance.

The process of transition varies between centres. In a number of centres, transition clinics have been established within paediatric services where the patient and their family will meet the receiving clinical team within which a doctor and nurse may have been identified with a particular interest in transition and the care of young adults. This may be a one stop clinic or be provided as a regular drop-in service for the patient more gradually to get to know the receiving team. A number of paediatric specialties have generated their own transition guidelines and there is a generic training module produced by the RCPCH for those with a particular interest in adolescent and young people's health. The RCP has recently generated a Young Adults and Adolescents steering group to evaluate care and services for patients who are progressing from childhood into adult care such that the specific health needs of young adults are recognised, and guidelines for training, clinical governance and standards of care may be generated to facilitate appropriate commissioning of clinical service for the care of this patient cohort.

**Helen Baxendale**

# Historical postscript

Although mainly of historical interest, it seems likely that some of the very earliest descriptions of the DiGeorge/Shprintzen/Velocardiofacial phenotype were made by Dr Eva Sedláčková, an otolaryngologist from Prague, who published her observations of a series of 26 children with palatal, facial, lip, jaw, ear, phalangeal, heart, speech and mental defects in 1955[1]. The cold war political situation in Europe at that time along with the relative obscurity arising from publishing these vignettes in her native Czech (in the face of English language domination of the medical and scientific literature) meant that Dr Sedláčková's pioneering work has not (then or now) received the recognition or profile which it probably deserves. In a small way, this footnote acknowledges her contribution and her early, if little known, place in the chronicle of 22q11 deletion syndrome.

**Richard Herriot**

**Reference**

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# Appendix 1: Multi-system features

| Common features[1] | Relevant age groups | | | | | Less Common but significant features[2] | Management[3] | Specialties commonly involved (in addition to GP, paediatrician, general medicine) |
|---|---|---|---|---|---|---|---|---|
| | Prenatal | Infant | Child | Teen | Adult | | | |
| **Genetics**<br>• Dysmorphic features (>90% of cases)<br>• Multiple congenital anomalies<br>• Learning disability/mental retardation/Familial delay<br>• Polyhydramnios (16%) | ✓ | ✓ | ✓ | ✓ | ✓ | • Fetal loss or infant death | • Genetic counselling<br>• Medical Management | • Medical genetics;<br>• Obstetrics and gynaecology |
| **Cardiovascular anomalies** (conotruncal/other) (75%)<br>• Requiring surgery (30-40%) | ✓ | ✓ | ✓ | ✓ | ✓ | • Vascular ring<br>• Dilated aortic root<br>• Prolonged QT interval | • Monitor Calcium level<br>• Irradiated blood products | • Cardiovascular surgery<br>• Cardiology |
| **Palatal and related anomalies** (75%)<br>• Hypernasal speech (crying) and/or nasal regurgitation (>90%)<br>• Velopharyngeal insufficiency ± submucous cleft palate (overt cleft palate/cleft lip is less common)<br>• Chronic otitis media<br>• Sensorineural and/or conductive hearing loss (30%) | ✓ | ✓ | ✓ | ✓ | ✓ | • Laryngeal web<br>• Tracheo-esophageal fistula<br>• Oesophageal atresia<br>• Preauricular tags/pits*<br>• Microtia/anotia* | • Speech therapy<br>• Palatal surgery | • Speech pathology<br>• Cleft Palate Team<br>• Otorhinolaryngology<br>• Audiology<br>• Radiology |

| Common features[1] | Relevant age groups | | | | | Less Common but significant features[2] | Management[3] | Specialties commonly involved (in addition to GP, paediatrician, general medicine) |
|---|---|---|---|---|---|---|---|---|
| | **Prenatal** | **Infant** | **Child** | **Teen** | **Adult** | | | |
| **Immune-related[5]**<br>• Recurrent infections (35%-40%)<br>• Impaired T-cell function<br>• Humoral defects<br>• Autoimmune diseases | | ✓ | ✓ | ✓ | ✓ | • IgA deficiency<br>• (0.5-1%) Severe immunodeficiency | • Special protocol[5] | • Immunology<br>• Rheumatology<br>• Otolaryngology<br>• Allergy<br>• Respiratory |
| **Endocrine disorders**<br>• Hypocalcaemia and/or hypoparathyroidism (>60%)<br>• Hypothyroidism (20%), hyperthyroidism (5%)<br>• Failure to thrive<br>• Obesity (35%) | | ✓ | ✓ | ✓ | ✓ | • Growth Hormone Deficiency<br>• Type 2 diabetes | • Vitamin D and calcium supplementation<br>• Growth Hormone<br>• Dietary/exercise counselling | • Endocrinology<br>• Dietitian |
| **Gastroenterology/Dysphagia** (35%)<br>• Failure to thrive<br>• GORD<br>• Dysmotility<br>• Constipation<br>• Cholelithiasis (20% adults, occasional in others)<br>• Umbilical hernia | ✓ | ✓ | ✓ | ✓ | ✓ | • Imperforate anus<br>• Intestinal malrotation<br>• Hirschsprung's<br>• Diaphragmatic hernia | • Tube feeding<br>• Medical interventions appropriate therapist support/drugs)<br>• Surgical interventions (e.g. gastrostomy, Nissen) | • Gastroenterology<br>• General Surgery<br>• Feeding Team<br>• Speech Pathology<br>• Occup[1] Therapy<br>• Physiotherapy<br>• Radiology<br>• Respiratory |

| Common features[1] | Relevant age groups | | | | | Less Common but significant features[2] | Management[3] | Specialties commonly involved (in addition to GP, paediatrician, general medicine) |
|---|---|---|---|---|---|---|---|---|
| | Prenatal | Infant | Child | Teen | Adult | | | |
| **Genitourinary abnormalities**<br>• Structural urinary tract anomaly (31%)<br>• Dysfunctional voiding (11%)<br>• Unilateral renal agenesis (10%)<br>• Multicystic dysplastic kidneys (10%)<br>• Inguinal hernia | ✓ | ✓ | ✓ | ✓ | ✓ | • Echogenic/ hypoplastic kidneys<br>• Duplex kidney<br>• Hydronephrosis<br>• Hypospadias<br>• Cryptorchidism<br>• Absent uterus<br>• Nephrocalcinosis | • Surveillance<br>• Medical management<br>• Surgical repair<br>• Transplant | • Renal ultrasound<br>• Urology<br>• Nephrology<br>• Gynaecology<br>• Radiology |
| **Ophthalmology**<br>• Strabismus (15%)<br>• Posterior Embyrotoxin<br>• Tortuous Retinal vessels | | ✓ | ✓ | | | • Scleracornea<br>• Coloboma<br>• Ptosis | • Eye exam | • Ophthalmology |
| **Skeletal**<br>• Scoliosis (18%; 18% of them requiring surgery)/thoracic butterfly vertebrae<br>• Cervical spine anomalies<br>• Idiopathic leg pains<br>• Sacral sinus | ✓ | ✓ | ✓ | ✓ | ✓ | • Cervical cord compression<br>• Craniosynostosis<br>• Upper extremity pre- and post-axial polydactyly<br>• Lower extremity post-axial polydactyly | • Radiographs | • Orthopaedics<br>• Neurosurgery<br>• Radiology<br>• General Surgery<br>• Hand Surgery |

| Common features[1] | Relevant age groups | | | | | Less Common but significant features[2] | Management[3] | Specialties commonly involved (in addition to GP, paediatrician, general medicine) |
|---|---|---|---|---|---|---|---|---|
| | Prenatal | Infant | Child | Teen | Adult | | | |
| **Haematology/Oncology**<br>• Thrombocytopaenia (30%)<br>• Splenomegaly (10%) | | ✓ | ✓ | ✓ | ✓ | • Bernard-Soulier<br>• Autoimmune neutropaenia<br>• Leukaemia<br>• Lymphoma<br>• Hepatoblastoma | • Surveillance | • Haematology |
| **Neurologic**<br>• Recurrent hypocalcaemic seizures (40%)<br>• Unprovoked epilepsy (5%) | | ✓ | ✓ | ✓ | ✓ | • Polymicrogyria<br>• Cerebellar abnormalities<br>• Neural tube defects<br>• Abdominal migraines | • Calcium, magnesium levels<br>• EEG<br>• MRI | • Neurology |
| **Growth and development**<br>• Motor and/or speech delay (>90%)<br>• Learning disabilities (>90%); mental retardation (~35%) | | ✓ | ✓ | ✓ | ✓ | | • Early intervention<br>• Sign language<br>• Educational supports<br>• Vocational counselling | • Developmental paediatrics<br>• Speech language pathology<br>• Occupational therapy<br>• Neuropsychology |

| Common features[1] | Relevant age groups | | | | | Less Common but significant features[2] | Management[3] | Specialties commonly involved (in addition to GP, paediatrician, general medicine) |
|---|---|---|---|---|---|---|---|---|
| | Prenatal | Infant | Child | Teen | Adult | | | |
| **Neuropsychiatric disorders**<br>• Psychiatric illness (60%)<br>• Childhood disorders (e.g. attention-deficit, obsessive-compulsive, autism/ autism spectrum disorders)<br>• Anxiety and depressive disorders<br>• Schizophrenia and other psychotic disorders (>20%) | | ✓ | ✓ | ✓ | ✓ | | | • Psychiatry |
| **Multi-system medical & surgical history**<br>• Non-infectious respiratory disease (10-20%)<br>• Seborrhoea or dermatitis (35%); severe acne (25%)<br>• Patella dislocation (10%)<br>• Dental problems - enamel hypoplasia/chronic caries (common)<br>• Varicose veins (10% of adults) | | ✓ | ✓ | ✓ | ✓ | • Fetal loss or infant death | | • Respiratory/ Anaesthesia<br>• Dermatology<br>• Rheumatology<br>• Orthopaedics<br>• Dentistry<br>• Vascular surgery |

[1] Rates are estimates only of lifetime prevalence of features for 22q11DS and will vary depending on how cases are ascertained and age of the patient.
[2] A selected (and to some extent arbitrary) set of rarer features of note in 22q11DS, emphasising those needing active treatment.
[3] Standard investigations and management according to involved condition(s).
[4] Characteristic facial features include long narrow face, malar flatness, hooded eyelids, tubular nose with bulbous tip, hypoplastic *alae nasae*, nasal dimple or crease, small mouth, small protuberant ears with thick overfolded/crumpled helices, and asymmetric crying facies.
[5] Infants only: Minimise infectious exposures; initially withhold live vaccines; CMV-negative irradiated blood products; Influenza immunisations; RSV prophylaxis.

# Appendix 2. Recommended assessments

| Assessment | At diagnosis | Infancy (0-12mo) | Preschool (1-5yr) | School Age (6-11yr) | Adolescence (12-18yr) | Adult (>18yr) |
|---|---|---|---|---|---|---|
| Ionised calcium, PTH[1] | ● | ● | ● | ● | ● | ● |
| TSH (annual) | ● | | ● | ● | ● | ● |
| FBC and differential (annual) | ● | ● | ● | ● | ● | ● |
| Immunologic evaluation[2] | ● | | ●[3] | | | |
| Ophthalmology | ● | | ● | | | |
| Evaluate palate[4] | ● | ● | ● | | | |
| Audiology | ● | ● | ● | | | ● |
| Cervical spine (>age 4) | | | ●[5] | | | |
| Scoliosis exam | ● | | ● | | ● | |
| Dental evaluation | | | ● | ● | ● | ● |
| Renal ultrasound | ● | | | | | |
| ECG | ● | | | | | ● |

[1] In infancy test calcium levels every 3-6 months, every 5 years through childhood and every 1-2 years thereafter; thyroid studies annually. Check calcium pre- and postoperatively, and regularly in pregnancy.
[2] In addition to FBC with differential, in **Newborn:** flow cytometry and **age 9-12 months (prior to live vaccines):** flow cytometry, immunoglobulins, T-cell function.
[3] Evaluate immune function prior to administering live vaccines (see above).
[4] In **infancy**: visualise palate and evaluate for feeding problems, nasal regurgitation; in **toddlers-adult:** evaluate nasal speech quality.
[5] Cervical spine films to detect anomalies: Anterior/Posterior, Lateral, Extension, Open Mouth, Skull base views. Expert opinion is divided about the advisability of routine x-rays. Symptoms of cord compression are an indication for urgent neurological referral.

| | | | | | | |
|---|---|---|---|---|---|---|
| Echocardiogram | ● | | | | | |
| Development[6] | ● | ● | ● | | | |
| School performance | | | | ● | ● | |
| Socialisation/functioning | ● | ● | ● | ● | ● | ● |
| Psychiatric/emotional/behavioural[7] | ● | | ● | ● | ● | ● |
| Systems review | ● | ● | ● | ● | ● | ● |
| Deletion studies of parents | ● | | | | | |
| Genetic counselling[8] | ● | | | | ● | ● |

[6] Motor and speech/language delays are common; rapid referral to Early Intervention for any delays can help to optimise outcomes.
[7] Vigilance for changes in behaviour, emotional state and thinking, including hallucinations and delusions; in teens and adults, assessment would include at-risk behaviours (sexual activity, alcohol/drug use, etc).
[8] See text for details.

## Appendix 3: Important cautions and considerations

| Feature | Management suggestions |
|---|---|
| Aspiration pneumonia | • Suctioning and chest physiotherapy may be necessary as preventions<br>• Small food portions may help<br>• Tube feeding frequently necessary |
| Autonomic dysfunction | • Careful monitoring peri-operative and post-operative and at times of major biological stress (e.g. infections, major medical crises) and provision of necessary support |
| Surgical complications of all types at a somewhat elevated likelihood compared to other patients (bleeding, atelectasis, seizures, difficult intubation). | • Careful monitoring peri-operative and post-operative, including ionised calcium, oxygen levels<br>• Availability of small intubation equipment |
| Narrow lumens (e.g. airway, spinal canal, ear canals) | • May need smaller sized intubation equipment<br>• Often need regular ear syringing to maximise hearing |
| Aberrant anatomy (anywhere) | • Preparatory investigations and consideration prior to surgery |
| Aberrant vascular anatomy | • Consider magnetic resonance angiography before pharyngoplasty |
| Adenoidectomy may worsen velopharyngeal incompetence (VPI) | • Consider risk/benefit |
| Posterior Pharyngeal Flap performed for VPI may cause sleep apnoea | • Consider risk/benefit |
| Hypocalcaemia risk elevated at times of biological stress (e.g. surgery, infection, burn, peripartum, puberty) | • Monitoring of ionised calcium levels and consideration of increased dose of vitamin D and/or calcium supplementation |

| Feature | Management suggestions |
|---|---|
| Hypocalcaemia worsening factors (e.g. alcohol, pop (fizzy drinks), pancreatitis) | • Minimise alcohol and pop intake<br>• Extra caution with pancreatitis<br>• Monitor calcium levels more closely. |
| Hypocalcaemia treatment may cause nephrocalcinosis | • Carefully monitor therapy |
| Seizure diathesis | • Consider myoclonic, absence or generalised seizures with apparent clumsiness/tripping, poor concentration or falls, respectively<br>• Investigate low calcium and magnesium levels and ensure adequate treatment<br>• Consider anticonvulsants as adjunctive medications for other medications that often lower the seizure threshold (e.g. clozapine, other antipsychotic medications) |
| Sensitivity to caffeine | • Reduce caffeine intake, especially cola drinks and coffee<br>• Consider as a contributory factor to anxiety and/or agitation and/or tremor |
| Developmental delays common in all aspects of development, structural and functional | • Anticipating a slower trajectory and changing capabilities over time, with necessary supports provided, can help reduce frustrations and maximise function |
| Increased need for sleep | • Regular, early bedtime and more hours of sleep than other same aged individuals can help reduce irritability and improve learning and functioning |
| Increased need for structure, routine, certainty, sameness | • Environmental adjustments to improve stability and limit changes can help reduce anxiety and frustration |
| Constipation | • Consider with verbal and especially non-verbal patients as a cause of agitation and/or pain<br>• Routine measures, including hydration, exercise, fibre, bowel routine, judicious use of laxatives. |

| Feature | Management suggestions |
|---|---|
| Tendency to form cysts of all types (renal, choledochal, brain, spinal cord syringomyelia) | • Routine renal US, others as symptoms/signs indicate. |
| Pregnancy complications | • Biological stressor for the individual in the context of their associated features and risks, e.g. hypocalcemia, adult congenital heart disease<br>• Psychiatric diseases<br>• Seizure diatheses<br>• Social situation. |

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