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][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 to strongly 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 for 22q11DS than for other individuals [D]. Since there is a great lack of research regarding the treatment of mental health problems in people with 22q11DS, often guidelines written for the general population, like the NICE guidelines, are being used.

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]. Special attention should be paid to the use of medications that can lower seizure threshold or have potential cardiac side-effects. See sections below for specific precautions with regard to clozapine (an antipsychotic medication) and methylphenidate (a stimulant medication). Precautions and specialist advice should be considered[7;8].

Dori et al. name several reasons why people with 22q11DS may have a less favourable clinical response to psychopharmacological treatment; cognitive deficits may influence their ability to report effectively and reliably on the effect and side-effects, biological factors might influence the clinical response and people with 22q11DS are more vulnerable to adverse events due to higher rates of somatic comorbidities[9].

Many of the principles that apply to people with 22q11DS, apply to them as they do to anyone who might have an intellectual disability and/or autism. In that respect we wish to refer to the recent NICE guidelines for the treatment of challenging behaviour: http://pathways.nice.org.uk/pathways/challenging-behaviour-and-learning-disabilities.

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%[10] . For 22q11DS, this percentage is higher, ranging from 60%[11;12] to 93%[13]. 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[14] and psychotic disorder[15]. 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.

We would also like to mention a paper by Ousley et al. with advice on clinical evaluation and treatment of mental health problems in people with 22q11DS[16].

9.2.1 Attention-Deficit/ Hyperactivity Disorder (ADHD)

9.2.1.1 Prevalence

The prevalence of ADHD is 5.29% in the general population[17]. However, in people with 22q11DS ADHD appears to range between 30% and 46%[11;18;19]. If you look at the different types of ADHD, the inattentive type seems to be more prevalent in people with 22q11DS[11;19]; no gender differences were found[20].

9.2.1.2 Diagnosis

ADHD is described in the 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 7. 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)[21].

9.2.1.3 Symptoms

Antshel et al.[11] 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

The treatment of ADHD in all patients starts with a behavioural approach and could be combined with medication. We would like to refer to the nice guideline: (http://pathways.nice.org.uk/pathways/attention-deficit-hyperactivity-disorder).

With regard to prescribing stimulant medication for people with 22q11DS and ADHD, there is some research. Gothelf et al.[22] 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[23] also advises to use the standard treatment protocols for ADHD in people with 22q11DS.

Green et al.[24] studied a group of 15 people with 22q11DS and ADHD and they found a significant reduction in ADHD symptoms after using methylphenidate for 6 months. They conclude that methylphenidate treatment is safe and effective in treating ADHD symptoms in children with 22q11DS. They did find an clinically significant increase in systolic blood pressure and heart rate in two children[24]. A

comprehensive cardiologic evaluation before and following initiation of stimulant medication is advised since people with 22q11DS are already at risk for cardiac problems

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[25]. In people with 22q11DS, reported prevalence rates have ranged from 14%[26] to 50%[27]. 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 3. 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[28].

The 'gold standard' for diagnosing ASD[29;30] is a combination of The Autism Diagnostic Interview - Revised[31] and the Autism Diagnostic Observation Schedule[31].

9.2.2.3 Symptoms

Symptoms mentioned in the DMS-IV are:

- impairment in using nonverbal 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.

9.2.2.4 Treatment

Many therapies have been developed to improve the symptoms of ASD in the general population, for example social-skills training,communication interventions, and medication to address co-morbid disorders such as ADD and anxiety[32]. The specific pattern of social strengths and difficulties varies for each child with 22q11DS, and a supportive approach that builds social confidence is encouraged. Specific guidance for management of ASD symptoms in 22q11DS has yet to be developed.

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%[10]. In people with 22q11DS, prevalence rates of 11% to 29% have been found[3;18].

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)[33].

9.2.3.3 Treatment

When it comes to anxiety in general. This may arise due to an interaction between a heightened propensity to anxiety and the environment that the person is in at the time. Depending on the level of any intellectual disability there are communication strategies and the principles of Applied Behavioural Analysis that should be followed (see for example https://www.autismspeaks.org/what-autism/treatment/applied-behavior-analysis-aba) for example the use of visual timetables and visual forms of communication may reduce uncertainty. There is also a lot of emphasis now place on the principles of Positive Behaviour Support (PBS) – as you can see on the BILD website: http://www.bild.org.uk/our-services/positive-behaviour-support/.

Specialist assessment prior to a trial of medication is warranted. No literature was found on the pharmacological treatment of GAD in people with 22q11DS.

The British Association for Psychopharmacology has written a guideline on the treatment of anxiety disorders in the general population. They recommend cognitive behavioural therapy (CBT) as the preferred form of psychotherapy, and advise which antidepressants and anxiolytics have proven effective in the treatment of GAD[34].

Bandelow et al. have written a summary of the World Federation of Biological Psychiatry guideline for the treatment of anxiety disorders. They also advice CBT as preferred form of psychotherapy. They name SSRIs, SNRIs and pregabalin as first-line pharmacological treatments and also mention other treatment options[35].

9.2.4 Specific phobia

9.2.4.1 Prevalence

In the general population, Kessler et al.[10] 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;11;13;18].

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. 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.[11] 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

We found no literature on the treatment of specific phobia in people with 22d11DS. Davis et al.[36] wrote a review on anxiety disorders in general in people with ID. With regard to the treatment, they concluded that more research is needed. Common psychotherapeutic anxiety interventions modified for people with ID appear to be useful, for example graded exposure and exposure and response prevention[36].

Baldwin et al. and Bandelow et al. advise psychological treatment based on exposure techniques as first-line treatment in the general public[34;35].

9.2.5 Major Depression

9.2.5.1 Prevalence

Kessler et al.[10] 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;12]. These average rates mask a specific peak in depression during the teenage years. The larger number of individuals with 22q11DS 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)[33] can be used.

9.2.5.3 Treatment

In the general population the NICE guideline on major depressive disorder advises treatment with either antidepressants or psychotherapy or a combination of the two, depending on the severity of the depression and the age of the patient (http://pathways.nice.org.uk/pathways/depression).

Janowsky and Davis[37] wrote a review on the diagnosis and treatment of depression in people with ID. They find that there is considerable evidence that the selective serotonin reuptake inhibitors are useful in the treatment of people with ID. They advise to start with a low dose and to increase the dose very slowly to avoid toxicity. They warn that SSRIs and other medications may activate symptoms such as aggression, self-injurious behaviour and destructiveness.

When choosing a pharmacological treatment Handen and Gilchrist also advice the use of SSRIs as treatment of choice over TCAs for children and adolescents with ID[38]. There is the concern that antidepressants could increase suicidality. This should be monitored after prescribing antidepressants[16].

9.2.6 Schizophrenia

9.2.6.1 Prevalence

The median lifetime prevalence of schizophrenia in the general population is 0.4%[39]. A large study looking at the prevalence of psychiatric disorders in people with 22q11DS found a prevalence of 23.5% for schizophrenia spectrum disorders in emerging adults and a prevalence of approximately 41% in participants over 25 years of age[30]. It is important to recognise that schizophrenia is a complex 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)[21] can be used for children and the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID) for adults[40].

Endocrine dysfunctions such as hypoparathyroidism and hypothyroidism could mimic psychotic features and should be checked and corrected[41].

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[42]. Several authors suggested that many people with 22q11DS experience a psychotic symptoms[14;27] and that there may be a continuum of psychotic disorders in people with 22q11DS. Bassett et al.[43] 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 risk factors for developing schizophrenia are: relatively lower verbal IQ scores, the COMT Met/Val genotype, anxiety or symptoms of depression earlier in life or experiencing psychotic symptoms earlier in life[3;27;44]

9.2.6.4 Treatment

In the general population, the symptoms of schizophrenia are often treated with anti-psychotic medication[45]. De Leon et al.[46] 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.

Research into the specific treatment of schizophrenia in people with 22q11DS is sparse. Butcher et al.[7] studied a group of 20 people with 22q11.2DS and schizophrenia who were prescribed clozapine. They found that the psychotic symptoms generally responded well to clozapine. Also the people in the 22q11.2DS group needed a significantly lower dose of clozapine. However they did find that half of the 22q11.2DS group had severe side effects, including seizures (n=8), myocarditis (n=1) and severe neutropaenia (n=3).

Verhoeven and Egger[41] report successful treatment of psychotic symptoms in patients with 22q11DS with quetiapine or clozapine. Besides medication, they stress the importance of environmental strategies matching the individuals needs.

Specialist advice is warranted when prescribing antipsychotics, especially clozapine, since they can lower seizure threshold. There is a growing literature on people with 22q11DS who use clozapine for psychotic symptoms and develop seizures[7;8;47]. Several authors advise to consider the prescription of prophylactic anticonvulsants to reduce the risk of clozapine induced seizures[7;48] and to monitor calcium levels when prescribing medication that lowers seizure threshold[16].

Also other severe side effects like movement disorders, neutropaenia and myocarditis are reported[7;49]. The general precautions and controls, like blood monitoring protocols for white blood count, that come with the prescription of clozapine should take place.

People with 22q11DS and severe cardiac anomalies are at an increased risk for arrhythmias. So when prescribing antipsychotics, psychiatrists should chose antipsychotics that are less likely to prolong the Q-T interval on the ECG and monitor the ECG closely during dose titration and thereafter[44].

The overall advice is, start low and go slow[16;38;48].

9.2.7 Obsessive Compulsive Disorder (OCD)

9.2.7.1 Prevalence

Twelve month prevalence rates in the general population are approximately 1%[10]. In people with 22q11DS this prevalence rate was measured at 4%[11], 16%[3] and 33%[13]. The larger study by Schneider et al. looking at the prevalence in different ages groups, found a prevalence ranging from 5.08% for emerging adults to 6.3% for mature adults[30].

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 conditions, obsessive compulsive disorder. One example of a semi-stuctured interview useful for people with ID is the Mood and Anxiety Semi-Structured Interview (MASS)[33].

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[13].

9.2.7.4 Treatment

In the general population OCD is often treated with either medication (serotonin reuptake inhibitors - SSRIs) or with cognitive behavioural therapy[50;51]. One study looking at OCD in four people with 22q11DS found a mean rate of improvement of 35% in the 4 patients treated with fluoxetine (30-60 mg/day)[13]. Only one patient reported a side effect: transient abdominal discomfort.

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References

1. Baker K, Vorstman JA. Is there a core neuropsychiatricphenotype in 22q11.2 deletion syndrome? Current opinion in neurology 2012;25(2):131-7. doi: 10.1097/WCO.0b013e328352dd58 [published Online First: 2012/03/08]
2. Hercher L, Bruenner G. Living with a child at risk for psychotic illness: the experience of parents coping with 22q11 deletion syndrome: an exploratory study. American journal of medical genetics Part A 2008;146a(18):2355-60. doi: 10.1002/ajmg.a.32466 [published Online First: 2008/08/14]
3. Green T, Gothelf D, Glaser B, et al. Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. Journal of the American Academy of Child and Adolescent Psychiatry 2009;48(11):1060-8. doi: 10.1097/CHI.0b013e3181b76683 [published Online First: 2009/10/03]
4. Antshel KM, Shprintzen R, Fremont W, et al. Cognitive and psychiatric predictors to psychosis in velocardiofacial syndrome: a 3-year follow-up study. Journal of the American Academy of Child and Adolescent Psychiatry 2010;49(4):333-44. [published Online First: 2010/04/23]
5. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. American journal of medical genetics Part A 2005;138(4):307-13. doi: 10.1002/ajmg.a.30984 [published Online First: 2005/10/07]
6. Beaton EA, Simon TJ. How might stress contribute to increased risk for schizophrenia in children with chromosome 22q11.2 deletion syndrome? Journal of neurodevelopmental disorders 2011;3(1):68-75. doi: 10.1007/s11689-010-9069-9 [published Online First: 2011/04/09]
7. Butcher NJ, Fung WL, Fitzpatrick L, et al. Response to clozapine in a clinically identifiable subtype of schizophrenia. The British journal of psychiatry : the journal of mental science 2015;206(6):484-91. doi: 10.1192/bjp.bp.114.151837 [published Online First: 2015/03/07]
8. Gladston S, Clarke DJ. Clozapine treatment of psychosis associated with velo-cardio-facial syndrome: benefits and risks. Journal of intellectual disability research : JIDR 2005;49(Pt 7):567-70. doi: 10.1111/j.1365-2788.2005.00708.x [published Online First: 2005/06/22]
9. Dori N, Green T, Weizman A, et al. The Effectiveness and Safety of Antipsychotic and Antidepressant Medications in Individuals with 22q11.2 Deletion Syndrome. Journal of child and adolescent psychopharmacology 2015 doi: 10.1089/cap.2014.0075 [published Online First: 2015/07/02]
10. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Archives of general psychiatry 2005;62(6):617-27. doi: 10.1001/archpsyc.62.6.617 [published Online First: 2005/06/09]
11. Antshel KM, Fremont W, Roizen NJ, et al. ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. Journal of the American Academy of Child and Adolescent Psychiatry 2006;45(5):596-603. doi: 10.1097/01.chi.0000205703.25453.5a [published Online First: 2006/05/04]
12. Arnold PD, Siegel-Bartelt J, Cytrynbaum C, et al. Velo-cardio-facial syndrome: Implications of microdeletion 22q11 for schizophrenia and mood disorders. American journal of medical genetics 2001;105(4):354-62. [published Online First: 2001/05/30]
13. Gothelf D, Presburger G, Zohar AH, et al. Obsessive-compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 2004;126b(1):99-105. doi: 10.1002/ajmg.b.20124 [published Online First: 2004/03/30]
14. Baker KD, Skuse DH. Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. The British journal of psychiatry : the journal of mental science 2005;186:115-20. doi: 10.1192/bjp.186.2.115 [published Online First: 2005/02/03]
15. Gothelf D, Aviram-Goldring A, Burg M, et al. Cognition, psychosocial adjustment and coping in familial cases of velocardiofacial syndrome. Journal of neural transmission (Vienna, Austria : 1996) 2007;114(11):1495-501. doi: 10.1007/s00702-007-0766-9 [published Online First: 2007/06/09]
16. Ousley OY, Smearman E, Fernandez-Carriba S, et al. Axis I psychiatric diagnoses in adolescents and young adults with 22q11 deletion syndrome. European psychiatry : the journal of the Association of European Psychiatrists 2013;28(7):417-22. doi: 10.1016/j.eurpsy.2013.06.002 [published Online First: 2013/08/07]
17. Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. The American journal of psychiatry 2007;164(6):942-8. doi: 10.1176/ajp.2007.164.6.942 [published Online First: 2007/06/02]
18. Feinstein C, Eliez S, Blasey C, et al. Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. Biological psychiatry 2002;51(4):312-8. [published Online First: 2002/04/18]
19. Niklasson L, Rasmussen P, Oskarsdottir S, et al. Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. Research in developmental disabilities 2009;30(4):763-73. doi: 10.1016/j.ridd.2008.10.007 [published Online First: 2008/12/17]
20. Antshel KM, Faraone SV, Fremont W, et al. Comparing ADHD in velocardiofacial syndrome to idiopathic ADHD: a preliminary study. Journal of attention disorders 2007;11(1):64-73. doi: 10.1177/1087054707299397 [published Online First: 2007/07/04]
21. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry 1997;36(7):980-8. doi: 10.1097/00004583-199707000-00021 [published Online First: 1997/07/01]

22. Gothelf D, Gruber R, Presburger G, et al. Methylphenidate treatment for attention-deficit/hyperactivity disorder in children and adolescents with velocardiofacial syndrome: an open-label study. The Journal of clinical psychiatry 2003;64(10):1163-9. [published Online First: 2003/12/09]

23. Murphy KC. Annotation: velo-cardio-facial syndrome. Journal of child psychology and psychiatry, and allied disciplines 2005;46(6):563-71. doi: 10.1111/j.1469-7610.2005.00408.x [published Online First: 2005/05/10]

24. Green T, Weinberger R, Diamond A, et al. The effect of methylphenidate on prefrontal cognitive functioning, inattention, and hyperactivity in velocardiofacial syndrome. Journal of child and adolescent psychopharmacology 2011;21(6):589-95. doi: 10.1089/cap.2011.0042 [published Online First: 2011/12/14]

25. Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. The Journal of clinical psychiatry 2005;66 Suppl 10:3-8. [published Online First: 2006/01/13]

26. Fine SE, Weissman A, Gerdes M, et al. Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. Journal of autism and developmental disorders 2005;35(4):461-70. doi: 10.1007/s10803-005-5036-9 [published Online First: 2005/09/01]

27. Vorstman JA, Morcus ME, Duijff SN, et al. The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. Journal of the American Academy of Child and Adolescent Psychiatry 2006;45(9):1104-13. doi: 10.1097/01.chi.0000228131.56956.c1 [published Online First: 2006/08/24]

28. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics 2004;113(5):e472-86. [published Online First: 2004/05/04]

29. Angkustsiri K, Goodlin-Jones B, Deprey L, et al. Social impairments in chromosome 22q11.2 deletion syndrome (22q11.2DS): autism spectrum disorder or a different endophenotype? Journal of autism and developmental disorders 2014;44(4):739-46. doi: 10.1007/s10803-013-1920-x [published Online First: 2013/09/21]

30. Schneider M, Debbane M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. The American journal of psychiatry 2014;171(6):627-39. doi: 10.1176/appi.ajp.2013.13070864 [published Online First: 2014/03/01]

31. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of autism and developmental disorders 1994;24(5):659-85. [published Online First: 1994/10/01]

32. Levy SE, Mandell DS, Schultz RT. Autism. Lancet 2009;374(9701):1627-38. doi: 10.1016/s0140-6736(09)61376-3 [published Online First: 2009/10/13]

33. Charlot L, Deutsch C, Hunt A, et al. Validation of the mood and anxiety semi-structured (MASS) interview for patients with intellectual disabilities. Journal of intellectual disability research : JIDR 2007;51(Pt 10):821-34. doi: 10.1111/j.1365-2788.2007.00972.x [published Online First: 2007/09/07]

34. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. Journal of psychopharmacology (Oxford, England) 2005;19(6):567-96. doi: 10.1177/0269881105059253 [published Online First: 2005/11/08]

35. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. International journal of psychiatry in clinical practice 2012;16(2):77-84. doi: 10.3109/13651501.2012.667114 [published Online First: 2012/05/01]

36. Davis E, Saeed SA, Antonacci DJ. Anxiety disorders in persons with developmental disabilities: empirically informed diagnosis and treatment. Reviews literature on anxiety disorders in DD population with practical take-home messages for the clinician. The Psychiatric quarterly 2008;79(3):249-63. doi: 10.1007/s11126-008-9081-3 [published Online First: 2008/08/30]

37. Janowsky DS, Davis JM. Diagnosis and treatment of depression in patients with mental retardation. Current psychiatry reports 2005;7(6):421-8. [published Online First: 2005/12/02]

38. Handen BL, Gilchrist R. Practitioner review: Psychopharmacology in children and adolescents with mental retardation. Journal of child psychology and psychiatry, and allied disciplines 2006;47(9):871-82. doi: 10.1111/j.1469-7610.2006.01588.x [published Online First: 2006/08/26]

39. McGrath J, Saha S, Chant D, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiologic reviews 2008;30:67-76. doi: 10.1093/epirev/mxn001 [published Online First: 2008/05/16]

40. Lobbestael J, Leurgans M, Arntz A. Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). Clinical psychology & psychotherapy 2011;18(1):75-9. doi: 10.1002/cpp.693 [published Online First: 2010/03/24]

41. Verhoeven WM, Egger JI. Atypical Antipsychotics and Relapsing Psychoses in 22q11.2 Deletion Syndrome: A Long-term Evaluation of 28 Patients. Pharmacopsychiatry 2015;48(3):104-10. doi: 10.1055/s-0034-1398612 [published Online First: 2015/02/06]

42. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Archives of general psychiatry 1999;56(10):940-5. [published Online First: 1999/10/26]

43. Bassett AS, Chow EW, AbdelMalik P, et al. The schizophrenia phenotype in 22q11 deletion syndrome. The American journal of psychiatry 2003;160(9):1580-6. doi: 10.1176/appi.ajp.160.9.1580 [published Online First: 2003/08/29]

44. Gothelf D, Feinstein C, Thompson T, et al. Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. The American journal of psychiatry 2007;164(4):663-9. doi: 10.1176/ajp.2007.164.4.663 [published Online First: 2007/04/04]

45. van Os J, Kapur S. Schizophrenia. Lancet 2009;374(9690):635-45. doi: 10.1016/s0140-6736(09)60995-8 [published Online First: 2009/08/25]

46. de Leon J, Greenlee B, Barber J, et al. Practical guidelines for the use of new generation antipsychotic drugs (except clozapine) in adult individuals with intellectual disabilities. Research in developmental disabilities 2009;30(4):613-69. doi: 10.1016/j.ridd.2008.10.010 [published Online First: 2008/12/17]

47. Yacoub A, Aybar M. Response to clozapine in psychosis associated with velo-cardio-facial syndrome. Psychiatry (Edgmont (Pa : Township)) 2007;4(5):14. [published Online First: 2007/05/01]

48. Fung WL, McEvilly R, Fong J, et al. Elevated prevalence of generalized anxiety disorder in adults with 22q11.2 deletion syndrome. The American journal of psychiatry 2010;167(8):998. doi: 10.1176/appi.ajp.2010.09101463 [published Online First: 2010/08/10]

49. Boot E, Butcher NJ, van Amelsvoort TA, et al. Movement disorders and other motor abnormalities in adults with 22q11.2 deletion syndrome. American journal of medical genetics Part A 2015;167a(3):639-45. doi: 10.1002/ajmg.a.36928 [published Online First: 2015/02/17]

50. Kordon A, Kahl KG, Broocks A, et al. Clinical outcome in patients with obsessive-compulsive disorder after discontinuation of SRI treatment: results from a two-year follow-up. European archives of psychiatry and clinical neuroscience 2005;255(1):48-50. doi: 10.1007/s00406-004-0533-y [published Online First: 2004/11/13]

51. Simpson HB, Fallon BA. Obsessive-compulsive disorder: an overview. Journal of psychiatric practice 2000;6(1):3-17. [published Online First: 2005/07/02]

10. Learning and education

10.1 Understanding the impact of 22q11DS on learning and education

In view of the fact that there is a wide range of abilities in the 22q11DS population 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. Of these, a significant number will require an Education, Health and Care plan (EHC), which has replaced the Statement of Special Educational Needs (SEN), with some benefiting from a special school environment. Most children 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 across the lifespan. Therefore, matching the individual profile to the services available is essential[1]. The information gathered should be used to understand children's difficulties and generalisations about their behaviour or educational achievements should not be made. Formal assessment, through the administration of selective tests designed to tap specific areas of cognition, is therefore important in order to identify strengths and weaknesses. This facilitates a thorough understanding of the complexity of the learning profiles with a recognition that early and on-going intervention is essential in order to ensure that children reach their academic potential.

10.2 Style of learning and social skills

Kok and Solmon (1995)[2] found that children with 22q11DS tend to have an orderly, analytical learning style, preferring logical explanations and specific instructions rather than a more abstract 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. Problems in social communication are often noted, with young children often being described as shy or over-friendly, with some exhibiting symptoms similar to those with social and communication disorders[3]. From adolescence onwards, problems relating to peers may become more evident with young people experiencing difficulties in interpreting humour, abstract language and subtle non-verbal communication[4]. These difficulties may be further compounded by problems in recognising emotions in others, such as through facial expression[5] and by deficits in their own facial expressiveness due to low facial muscle tone. They may struggle to ask for help and tend to await instructions. For these children, their difficulties may not to be identified until secondary school, suggesting that they may have already spent some time struggling to access the curriculum. Frustration and previous failure in learning may engender a reduction in levels of confidence, self-esteem and motivation.

10.3 Behaviour

There does not seem to be one single pattern of behaviour seen in children and young people with 22q11DS. For this reason, it is important that children with the condition are understood as individuals with their own unique personalities and their own life experiences. However, as mentioned above, overall the research has shown that children with the condition tend to be quieter, more sensitive, possibly due to difficulties with speech early on and have problems with communicating in social situations. However, they may also be more strong willed, independent and impulsive. For some children and young people, these types of behaviours may become more marked throughout childhood and adolescence and put them at increased risk of mental health problems later in life[6]. It is crucial that there is an accurate assessment of these complexities and an agreement between the family and teaching staff as to the abilities and cognitive strengths and needs of these individuals. There also needs to be recognition of the importance of reducing levels of stress and anxiety as much as possible[7] and the calming effects of familiarity and predictability[8].

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 problems with visuospatial tasks, deficits in working memory and impaired numerical processing functions required for most mathematical tasks[9] This is known as '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[10].

Research in this area has made the link between these mathematical difficulties and unusual cognitive processing in the spatio-temporal domain. Basic abilities required to carry out simple addition and subtraction are dependent on these underlying cognitive processes. De Smedt et al.[11] found that children aged 6 to 12 years with 22q11DS were adept at reading numbers accurately and were able to retrieve number-facts, whilst experiencing difficulties in understanding number-magnitude, identifying and ignoring irrelevant information in story problems, and accurately multiplying with more than single digit numbers. These weaknesses in mathematics seem to relate to wider issues and difficulties in the areas of abstract reasoning, converting language into mathematical expressions, telling time, using money and problem solving[2].

10.4.2 Memory

Memory may be both a strength and weakness in children and young people with 22q11DS. Rote verbal memory, which is the ability to repeat back a list of verbally presented items after a delay, is typically a strength for those with 22q11DS[12]. Complex memory tasks may present more difficulties. Research has shown that children with 22q11DS struggle with recalling verbal information contained in long sequences such as directions, sentences or stories. They also struggle to remember complex visual spatial forms such as locating dots on a grid. In contrast, they may have an ability to learn and retain verbal information which has been taught though experience and, as such, they can, for example, offer definitions of words and remember general facts with no difficulty[13]. Another area of weakness may be working memory[14] which is the ability simultaneously to store and process information. This in turn may impact on the ability to complete everyday tasks successfully and solve problems due to difficulties in integrating and assembling information into a meaningful structure.

10.4.3 Executive function

Executive functions are a set of high level cognitive abilities which are responsible for controlling and regulating emotional, social and behavioural functions[15]. These are necessary for goal-directed behaviours, encompassing the ability to initiate and stop actions, monitor and change behaviour as required 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[16] that for children and young people with 22q11DS the 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. These executive function difficulties may be linked to altered pre-frontal cortical structures during maturation which is a burgeoning area of neuropsychiatric research[17].

10.5 Motor skills

Some children with 22q11DS have low muscle tone, otherwise known as hypotonia, alongside delays in motor development[18]. This can have an impact on gross and fine motor skills, particularly in tasks which require quick movement or reactions[9]. Children have been noted to have difficulties performing tasks which require dexterity and careful control of movements such as holding a pencil or handling scissors. Problems in these areas may affect the ability of children to perform many tasks in the classroom with speed and accuracy, particularly writing[18], and should be taken into account in educational settings.

10.6 Language

Children with 22q11DS are often slow to develop complex vocabulary and grammar. In some cases, they use a limited range of words and remain concrete in their use of speech. They tend to have more advanced verbal than nonverbal skills with well-developed 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 the receptive language skills[19], with the latter often requiring more complex and abstract thinking. These relative strengths in expressive skills may mask deficits in receptive understanding in the classroom and may result in a subsequent tendency for teachers and others to be unaware of the need for speech and language assessment and therapy[9] and multi-modal ways of communicating.

10.7 Reading, writing and spelling

Rote-reading and spelling have been noted to be relative strengths with many children doing

well early on in their school lives when learning to read. However, it is common for them to struggle more when they are expected to learn from what they read, and may demonstrate problems in understanding, recalling facts, selecting relevant details and drawing conclusions. This is thought to be due to the shift from learning skills which are basic and concrete to mastering more abstract, integrated concepts[9]. In addition, they can find it difficult to copy down text, as this requires co-ordination, the complex use of motor skills, memory and language functions and the ability to hold the information in mind in the short-term. Recent longitudinal research is also indicating that there may be a change in the profile of skills from primary school age onwards[20], with a decline in reading comprehension and an increase in word reading abilities over time.

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 have a striking profile of peaks and troughs and, as stated previously, demonstrate strengths on verbal tasks and impairment in the more performance based domains. These profiles may in turn be indicative of a non-verbal learning disorder[19] and seem to be true for the majority, although not for all children[21].

Conclusion

In conclusion, it is important that those who are working with children and young people affected by 22q11DS have the opportunity to acquaint themselves with the types of approaches which have been found to be of benefit. These approaches are based on those used in other conditions such as autism and attention deficit and hyperactivity disorder. Whilst these approaches may be appropriate, it is essential that all those involved are also aware of the additional functional and medical needs of individuals affected by 22q11 deletion syndrome[22].

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References

1. Kok LL,.Solman RT. Velocardiofacial syndrome: learning difficulties and intervention. J Med Genet. 1995; 32: 612-8.
2. Kates, W. What can functional brain imaging tell us about cognition and emotion in VCFS? Presentation at the 12th Annual International Scientific Meeting, Strasbourg, France. 2006.
3. Swillen A, Vandeputte L, Cracco J, Maes B, Ghesquiere P, Devriendt K et al. Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): evidence for a nonverbal learning disability? Child Neuropsychol. 1999; 5: 230-41.
4. Prasad SE, Howley S, Murphey KC. Psychiatric disorders in people with 22q11.2 Deletion Syndrome: A population-based prevalence study in Ireland. Journal of Intellectual Disability: Research 2008; 14: 26-34.
5. Gerdes M. Infants and preschoolers with a 22q11.2 Deletion: Developmental Challenges. Faces of Sunshine: A handbook for parents and professionals., pp 74-81. West Berlin, NJ: Cardinal Business Forms and Systems Inc, 2000.
6. Cutler-Landsman D, Simon TJ, Kates W. Introduction to the education and the neurocognitive profile. In Cutler-Landsman D, ed. Educating Children with Velo-Cardio-Facial Syndrome, pp 15-37. San Diego: Plural Publishing, 2007.
7. Simon TJ. A new account of the neurocognitive foundations of impairments in space, time, and number processing in children with 22q11 deletion syndrome. Developmental Disabilities Research Reviews 2008; 14: 52-8.
8. De Smedt B, Swillen A, Devriendt K, Fryns JP, Verschaffel L, Ghesquiere P. Mathematical disabilities in young primary school children with velo-cardio-facial syndrome. Genet.Couns. 2006; 17: 259-80.
9. Sobin C, Kiley-Brabeck K, Daniels S, Khuri J, Taylor L, Blundell M et al. Neuropsychological characteristics of children with the 22q11 Deletion Syndrome: a descriptive analysis. Child Neuropsychol. 2005; 11: 39-53.
10. Woodin MF, Moss EM. The 22q11.2 deletion: Neuropsychological presentation, profiles and practical suggestions. Faces of Sunshine: A handbook for parents and professionals., West Berlin, NJ: Cardinal Business Forms and Systems Inc., 2000.
11. Kates WR, Krauss BR, AbdulSabur N, Colgan D, Antshel KM, Higgins AM et al. The neural correlates of non-spatial working memory in velocardiofacial syndrome (22q11.2 deletion syndrome). Neuropsychologia 2007; 45: 2863-73.
12. Woodin M, Wang PP, Aleman D, McDonald-McGinn D, Zackai E, Moss E. Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion. Genet.Med 2001; 3: 34-9.
13. Van Aken K, De Smedt B, Van Roie A, Gewillig M, Devriendt K, Fryns JP et al. Motor development in school-aged children with 22q11 deletion (velocardiofacial/DiGeorge syndrome). Dev.Med Child Neurol. 2007; 49: 210-3.
14. Glaser B, Mumme DL, Blasey C, Morris MA, Dahoun SP, Antonarakis SE et al. Language skills in children with velocardiofacial syndrome (deletion 22q11.2). J Pediatr 2002; 140: 753-8.
15. Campbell L, Swillen A. The cognitive spectrum in velo-cardio-facial syndrome. In Murphy KC, Scramble PJ, eds. Velo-Cardio-Facial Syndrome: A Model for Understanding Microdeletion Disorders, pp 147-64. Cambridge, UK: Cambridge University Press, 2005.

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

1. Sedláčková E. Insufficiency of palatolaryngeal passage as a developmental disorder. Cas.Lek.Cesk. 1955; 94: 1304-7.

Appendix 1: Multi-system features

Common features[1]	Relevant age groups					Less Common but significant features[2]	Management[3]	Specialties commonly involved (in addtion to GP, paediatrician, general medicine)
	Prenatal	**Infant**	**Child**	**Teen**	**Adult**			
Genetics • Dysmorphic features (>90% of cases) • Multiple congenital anomalies • Learning disability/mental retardation/Familial delay • Polyhydramnios (16%)	✓	✓	✓	✓	✓	• Fetal loss or infant death	• Genetic counselling • Medical Management	• Medical genetics; • Obstetrics and gynaecology
Cardiovascular anomalies (conotruncal/other) (75%) • Requiring surgery (30-40%)	✓	✓	✓	✓	✓	• Vascular ring • Dilated aortic root • Prolonged QT interval	• Monitor Calcium level • Irradiated blood products	• Cardiovascular surgery • Cardiology
Palatal and related anomalies (75%) • Hypernasal speech (crying) and/or nasal regurgitation (>90%) • Velopharyngeal insufficiency ± submucous cleft palate (overt cleft palate/cleft lip is less common) • Chronic otitis media • Sensorineural and/or conductive hearing loss (30%)	✓	✓	✓	✓	✓	• Laryngeal web • Tracheo-oesophageal fistula • Oesophageal atresia • Preauricular tags/pits* • Microtia/anotia*	• Speech therapy • Palatal surgery	• Speech pathology • Cleft Palate Team • Otorhinolaryngology • Audiology • Radiology
Immune-related[5] • Recurrent infections (35%-40%) • Impaired T-cell function • Humoral defects • Autoimmune diseases		✓	✓	✓	✓	• IgA deficiency • (0.5-1%) Severe immunodeficiency	• Special protocol[5]	• Immunology • Rheumatology • Otolaryngology • Allergy

								• Respiratory
Endocrine disorders • Hypocalcaemia and/or hypoparathyroidism (>60%) • Hypothyroidism (20%), hyperthyroidism (5%) • Failure to thrive • Obesity (35%)		✓	✓	✓	✓	• Growth Hormone Deficiency • Type 2 diabetes	• Vitamin D and calcium supplement[n] • Growth Hormone • Dietary/exercise counselling	• Endocrinology • Dietitian
Gastroenterology/Dysphagia (35%) • Failure to thrive • GORD • Dysmotility • Constipation • Cholelithiasis (20% adults, occasional in others) • Umbilical hernia	✓	✓	✓	✓	✓	• Imperforate anus • Intestinal malrotation • Hirschsprung's • Diaphragmatic hernia	• Tube feeding • Medical interventions appropriate therapist support/drugs) • Surgical interventions (e.g. gastrostomy, Nissen)	• Gastroenterology • General Surgery • Feeding Team • Speech Pathology • Occup[l] Therapy • Physiotherapy • Radiology • Respiratory
Genitourinary abnormalities • Structural urinary tract anomaly (31%) • Dysfunctional voiding (11%) • Unilateral renal agenesis (10%) • Multicystic dysplastic kidneys (10%) • Inguinal hernia	✓	✓	✓	✓	✓	• Echogenic/ hypoplastic kidneys • Duplex kidney • Hydronephrosis • Hypospadias • Cryptorchidism • Absent uterus • Nephrocalcinosis	• Surveillance • Medical management • Surgical repair • Transplant	• Renal ultrasound • Urology • Nephrology • Gynaecology • Radiology
Skeletal • Scoliosis (18%; 18% of them requiring surgery)/thoracic butterfly vertebrae • Cervical spine anomalies • Idiopathic leg pains • Sacral sinus	✓	✓	✓	✓	✓	• Cervical cord compression • Craniosynostosis	• Radiographs	• Orthopaedics • Neurosurgery • Radiology • General Surgery • Hand Surgery

						• Upper extremity pre- and post-axial polydactyly • Lower extremity post-axial polydactyly		
Haematology/Oncology • Thrombocytopaenia (30%) • Splenomegaly (10%)		✓	✓	✓	✓	• Bernard-Soulier • Autoimmune neutropaenia • Leukaemia • Lymphoma • Hepatoblastoma	• Surveillance	• Haematology
Neurologic • Recurrent hypocalcaemic seizures (40%) • Unprovoked epilepsy (5%)		✓	✓	✓	✓	• Polymicrogyria • Cerebellar abnormalities • Neural tube defects • Abdominal migraines	• Calcium, magnesium levels • EEG • MRI	• Neurology
Growth and development • Motor and/or speech delay (>90%) • Learning disabilities (>90%); mental retardation (~35%)		✓	✓	✓	✓		• Early intervention • Sign language • Educational supports • Vocational counselling	• Developmental paediatrics • Speech language pathology • Occupational therapy • Neuropsychology

Neuropsychiatric disorders • Psychiatric illness (60%) • Childhood disorders (e.g. attention-deficit, obsessive-compulsive, autism/ autism spectrum disorders) • Anxiety and depressive disorders • Schizophrenia and other psychotic disorders (>20%)		✓	✓	✓	✓			• Psychiatry
Multi-system medical & surgical history • Non-infectious respiratory disease (10-20%) • Seborrhoea or dermatitis (35%); severe acne (25%) • Patella dislocation (10%) • Dental problems - enamel hypoplasia/chronic caries (common) • Varicose veins (10% of adults)		✓	✓	✓	✓	• Fetal loss or infant death		• Respiratory/ Anaesthesia • Dermatology • Rheumatology • Orthopaedics • Dentistry • 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	●					●
Echocardiogram	●					
Development[6]	●	●	●			
School performance				●	●	
Socialisation/functioning	●	●	●	●	●	●
Psychiatric/emotional/behavioural[7]	●		●	●	●	●

[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.

[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).

Systems review	●	●	●	●	●	●
Deletion studies of parents	●					
Genetic counselling[8]	●				●	●

[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 • Small food portions may help • 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 • Availability of small intubation equipment
Narrow lumens (e.g. airway, spinal canal, ear canals)	• May need smaller sized intubation equipment • 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
Hypocalcaemia worsening factors (e.g. alcohol, pop (fizzy drinks), pancreatitis)	• Minimise alcohol and pop intake • Extra caution with pancreatitis • 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 • Investigate low calcium and magnesium levels and ensure adequate treatment • 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 • 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 • Routine measures, including hydration, exercise, fibre, bowel routine, judicious use of laxatives.
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 • Psychiatric diseases • Seizure diatheses • Social situation.

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